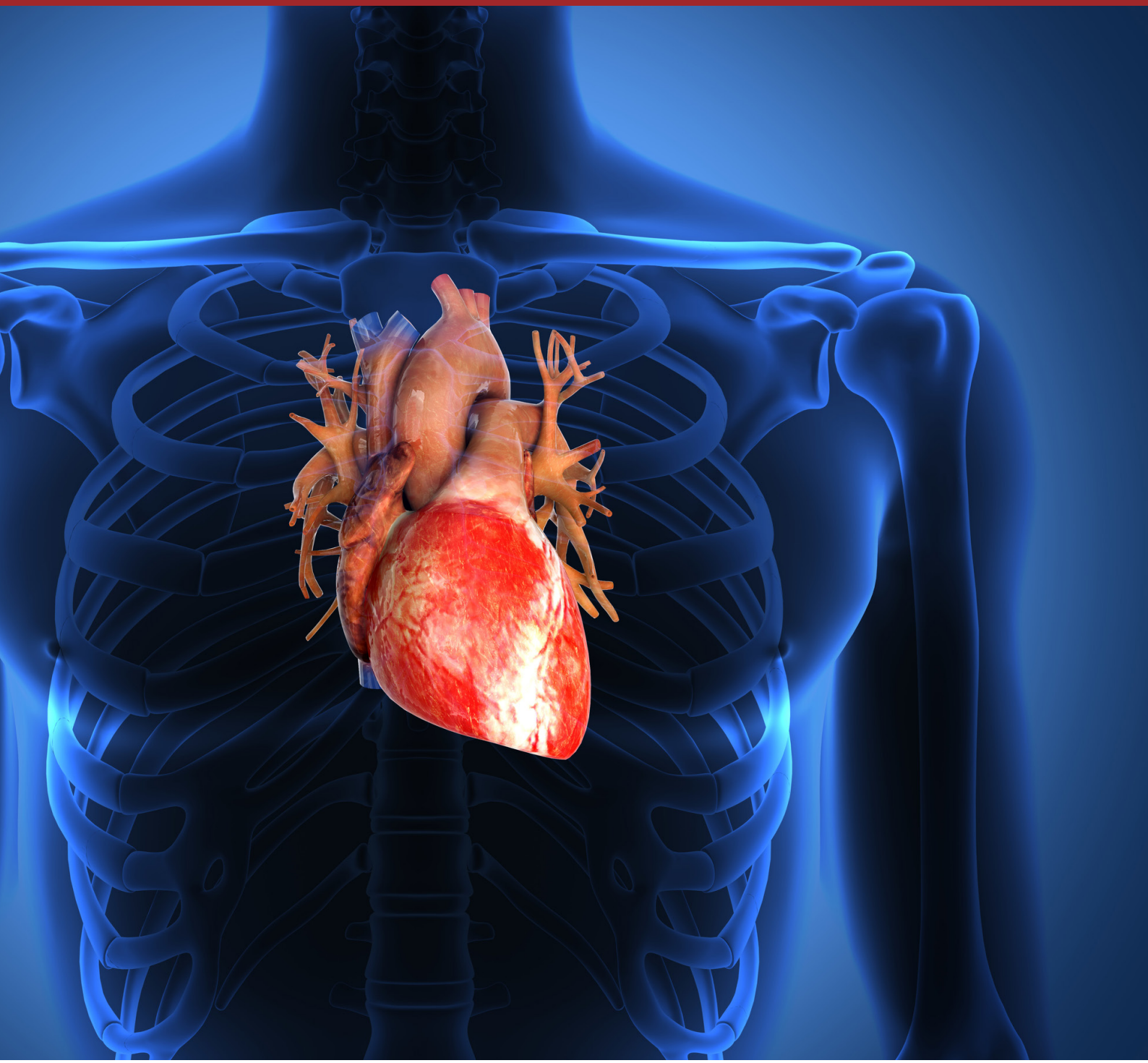
123Library

FOUNDATION YEARS JOURNAL

FEBRUARY 2018

Volume 12, Issue 2: **Cardiology & Oncology**



123Library

www.123Library.org

Sharing **more** knowledge



Contact us on
0207 253 4363
or email
sales@123library.org
for a
FREE TRIAL

What is 123Library?

123Library is a fast growing and innovative eBook and **digital content provider for libraries** in the field of healthcare.

What are the benefits for your library?

1. FULL FLEXIBILITY ✔
2. KNOWLEDGE ✔
3. CUSTOMER CARE ✔
4. NO HASSLES ✔
5. FULL SECURITY ✔
6. GET FEEDBACK ✔
7. SUPPORT ✔
8. EASE OF USE ✔
9. SAVING MONEY ✔

Benefit today, visit **www.123Library.org**

123Library

FOUNDATION YEARS JOURNAL 2018

Volume 12

Foundation years journal

Foundation Years Journal is an international peer-viewed journal which seeks to be the pre-eminent journal in the field of patient safety and clinical practice for Foundation Years' doctors and educators. The Journal welcomes papers on any aspect of health care and medical education which will be of benefit to doctors in the Foundation training grade in the UK or international equivalents.

Editor in chief

Publisher's office

Sophie Wood (Managing Editors)
123 Library, 72 Harley Street, London, W1G 7HG
Tel: +44 (0)207 253 4363 | Email: sophiewood@123doc.com

Editorial board

FOUNDATION YEARS JOURNAL 2018

Volume 12

Foundation years journal

Foundation Years Journal is the ONLY journal for Foundation Years, doctors and educators, specifically written according to the MMC curriculum. It focuses on one or two medical specialties per month and each issue delivers practical and informative articles tailored to the needs of junior doctors. The Journal closely follows the Foundation Years syllabus to provide the best educational value for junior doctors. In addition to good clinical and acute care articles, assessment questions give junior doctors the chance to gauge their learning. Each issue provides comprehensive clinical cases for trainees as well as practical teaching assessments for educators. Readers will benefit from:

- **MMC CURRICULAR-BASED CONTENT** to enhance understanding of the core competencies required from future leading doctors.
- **FOCUS ON SPECIALTY-SPECIFIC CLINICAL CASES** each month to form broad subject coverage.
- **ADDITIONAL IN-DEPTH** good clinical and acute care articles aligned with the case-based discussion assessments.
- **TRAINING GUIDE FOR FOUNDATION YEAR (FY)** educators with proposed clinical cases for teaching sessions.
- **PRACTICAL & INFORMATIVE** articles written by senior doctors & consultants.
- **EXTRA REVISION** with comprehensive assessment. Questions & Picture Quiz.

Financial statement

The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources, and authors are not paid. The decision to accept or refuse an article for publication in the Foundation Years Journal is free from financial considerations and is solely the responsibility of the Editorial Panel and Editor-in-Chief.

Conflict of interest

The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors" **(https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Animal & human rights

When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent

123library recognises patients' right to privacy. We require Authors to maintain patients' anonymity and to obtain consent to report investigations involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Guidelines for authors

The Guideline for Authors can be found on our website at: **https://www.123library.org/ejournals/foundation-years-journal.**

How to order foundation years journal

Orders for subscriptions should be made by email **(subscriptions@123doc.com)** or with a credit card through the 123 Library website **(www.123library.org).** Or by returning the subscription form included in the Journal to:

123Doc Education
72 Harley Street, London, W1G 7HG

Order online www.123library.org

Order by email subscriptions@123doc.com

Order by phone 0203 0313 866

How to advertise in foundation years journal

Advertising orders and enquiries can be sent to sabine@123doc.com.

Tel: +44 (0)207 253 4363.

Photocopying

Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission of the publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale and all forms of document delivery.

Electronic storage or usage

Permission of the publisher is required to store or use electronically any material contained in this Journal, including any article or part of an article. Except as outlined above, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the publisher.

Notice

No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein.

Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

A CASE OF CARDIAC AMYLOID

LA Allen, EHM Edwards, Z Yousef

Abstract

Cardiac amyloidosis is the commonest cause of restrictive cardiomyopathy in the United Kingdom. It is associated with high levels of morbidity and mortality, and often presents late, when significant organ damage has already occurred.

We present a case of a 54-year-old gentleman who presented with worsening dyspnoea and reduced exercise tolerance. The combination of his electrocardiogram and echocardiogram were suggestive of cardiac amyloid. We discuss the cardiac and extra-cardiac manifestations of the disease, along with an approach to investigation and management.

Case History

A 54 year old gentleman of Cypriot descent, with no significant past medical history presented with a 4 month history of fatigue and dyspnoea. There was no history of chest pain, palpitations or syncope. There was no significant family history. He lived alone, worked full-time as a hair-stylist, had never smoked, and drank minimal alcohol.

On examination there were signs of right heart failure, including an elevated jugular venous pressure, profound peripheral oedema to the thighs, and non-tender hepatomegaly. On auscultation of his chest, fine bi-basal crepitations were audible. His pulse was regular and his heart sounds normal.

Baseline electrocardiogram demonstrated sinus rhythm with small voltage complexes in the limb leads and deep 'S' waves in the anterior precordial leads.

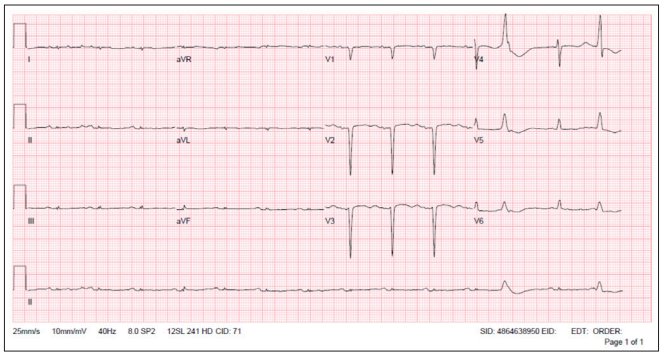


Figure 1: Electrocardiogram showing sinus rhythm with small voltage complexes in the limb leads and deep 'S' waves in the anterior precordial leads.

Conduction intervals were normal. Chest radiograph demonstrated cardiomegaly with a small right-sided pleural effusion. An echocardiogram demonstrated severe left ventricular systolic dysfunction with an ejection fraction of 30 to 35%.

On close examination of the left ventricle, the echocardiogram also revealed moderate antero-septal hypertrophy, with mild hypertrophy of the posterior wall of the left ventricle. Moderate diastolic dysfunction was also noted, in addition to mild mitral regurgitation, and a small rim of pericardial fluid. The echocardiographic appearances were felt to be suggestive of amyloidosis.

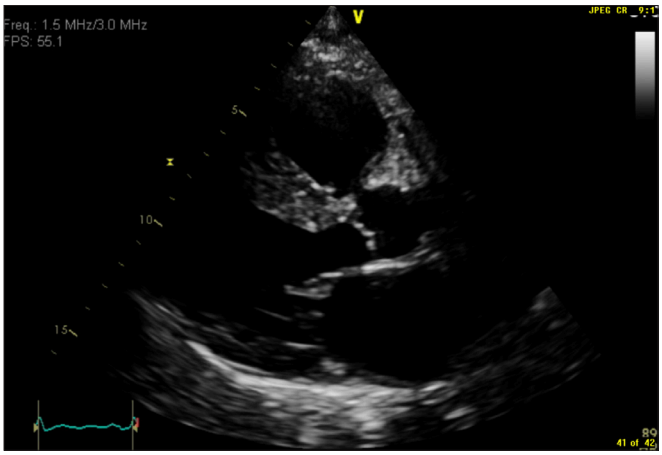


Figure 2: Echocardiogram showing antero-septal hypertrophy.

He was treated with intravenous furosemide with good effect. Cardiac magnetic resonance imaging was performed, demonstrating bi-ventricular systolic dysfunction with moderate left ventricular systolic dysfunction. No focal myocardial abnormality was seen, but late 4D sequences showed patchy intra-mural delayed enhancement, consistent with a diffuse infiltrate pathology, possibly amyloidosis.

Further investigations were undertaken to support our clinical diagnosis of amyloidosis. A serum paraprotein band of IgG lambda type was detected at a concentration of 4.0 g/L. Urine Bence Jones testing revealed a Lambda band to be present (<0.1 g/l). Serum free light chain testing revealed elevated serum free light chains (kappa light chains 22 mg/L, lambda light chains 503 mg/L) with a reduced kappa to lamba ratio (0.044).

Bone marrow trephine biopsy revealed hypocellularity (20 to 30 %) with tri-lineage haematopoiesis with maturation. There were no obvious large focal infiltrates of plasma cells. Bone marrow aspirate revealed no obvious abnormality but immune-phenotyping was requested and results are awaited. Results obtained thus far were felt to be sufficient to confirm a diagnosis of AL amyloidosis.

A CASE OF CARDIAC AMYLOID

LA Allen, EHM Edwards, Z Yousef

Further investigations to evaluate extra-cardiac manifestations were performed. Renal function was impaired (urea 7.4 mmol/L; creatinine 102 micromol/litre; estimated glomerular filtration rate 66 ml/min/1.73m^2), and urine dipstick revealed microscopic proteinuria.

Ultrasound of the renal tract demonstrated bilaterally enlarged kidneys, surrounded by concentric hyperechoic soft tissue abnormality with a clear interface between the abnormality and normal renal tissue. Computed tomography imaging showed soft tissue to be surrounding and indenting both kidneys and proximal ureters, suggestive of amyloid.

A percutaneous cardiac biopsy was undertaken. Fragments of endomyocardial tissue with extensive perivascular and interstitial infiltration by an eosinophilic acellular material were obtained. These demonstrated apple-green bi-refringence on polarisation of Congo-Red eosinophilia and stained violet-blue on Masson's trichome. In summary, the features were consistent with cardiac amyloidosis.

He was referred to the National Amyloidosis Centre in London, and the team there are now providing shared care in conjunction with his local Cardiology and Haematology teams. He has commenced chemotherapy (Cyclophosphamide, Velacade, Dexamethasone.)

Discussion

Amyloidosis is a systemic disorder caused by the accumulation of amyloid fibrils. Amyloid fibrils consist of normally soluble proteins which have become insoluble due to mis-folding resulting in the formation of beta pleated sheets (1). Cardiac amyloid results from deposition of amyloid fibrils in the endomyocardium, the conduction pathway and/or the coronary vessels. Cardiac involvement is the main predictor of poor outcomes in amyloidosis (2).

Cardiac amyloidosis is the commonest cause of restrictive cardiomyopathy in the United Kingdom (3). It typically presents with features of progressive biventricular diastolic dysfunction, with features of right ventricular failure predominating initially. Over time, systolic biventricular dysfunction ensues (4,5).

Evaluation of cardiac amyloidosis includes a baseline electrocardiogram, which classically demonstrates low QRS voltages. Other features may include poor R wave progression and/or conduction deficits (6).

Echocardiogram is a useful non-invasive tool in diagnosing and monitoring cardiac amyloid. Diastolic dysfunction may be an early hallmark. Over time thickened right and left ventricular myocardium develops, often with preserved left ventricle cavity size.

Ventricular myocardial thickening develops, due to myocyte infiltration, rather than myocyte hypertrophy, and is most marked in the basal area. Another typical feature includes a diffuse hyper-refractile "granular/sparkling" appearance (7-9). The combination of an increased ventricular mass on echocardiogram in the absence of high electrocardiogram voltages is extremely helpful in differentiating infiltrative processes from conditions like hypertensive cardiomyopathy.

Causes of Left Ventricular Hypertrophy		
Commonest causes	***Common causes***	Important to identify other features of end-organ damage e.g retinopathy. Secondary causes of hypertension may be identified in around 15% of cases.
	Aortic Stenosis	Echocardiography allows formal assessment of severity (based on trans-aortic valve gradient and valve area).
	Obesity	This is a reversible cause of left ventricular hypertrophy.
	Physiological	Individuals who undertake high level endurance training may develop reversible left ventricular hypertrophy.
Sarcomere protein disease	Hypertrophic Cardiomyopathy	Leading cause of sudden cardiac death in young adults. Diastolic dysfunction predominates.
Infiltrative processes	Amyloidosis	Leading cause of restrictive cardiomyopathy in the UK.
	Haemochromatosis	Important to assess for other features of end-organ damage e.g. diabetes, liver cirrhosis.
Metabolic disorders	Fabry's disease	X-linked recessive lysosomal storage disease caused by alpha Galactosidase A deficiency, amenable to enzyme replacement therapy.

Table 1: Differentials of left ventricular hypertrophy (10).

Cardiac magnetic resonance imaging is increasingly accessible in the evaluation of heart failure, and adds to the diagnostic work-up. Global sub-endocardial late-gadolinum enhancement is not only highly characteristic of cardiac amyloid, but also correlates with prognosis (11-13).

Biochemical testing can also help predict prognosis. Elevated B-Natriuretic Peptic (BNP) is a sensitive marker of cardiac involvement in amyloidosis (14). A significant fall in BNP concentrations after starting treatment is associated with better long-term outcomes (15). BNP is renally cleared, and must be interpreted cautiously when there is renal involvement. Troponin can also be useful in predicting prognosis (14).

However, the current gold-standard diagnostic investigation of cardiac amyloid is endomyocardial biopsy. Congo-red staining of tissue samples results in pathognomonic apple-green birefringence under polarised light microscopy. Immunohistochemistry identifies the type of amyloid fibrils deposited, which helps guide treatment (16,17).

A CASE OF CARDIAC AMYLOID

LA Allen, EHM Edwards, Z Yousef

Once a diagnosis of cardiac amyloid is established, it is important to classify the underlying mechanism. In this case, AL amyloidosis was diagnosed. AL amyloidosis is typically associated with underlying plasma cell dyscrasias which lead to excessive production and deposition of immunoglobulin light chains (18). Serum immunoglobulins, protein electrophoresis and serum free light chain testing are therefore appropriate. Bone marrow biopsy may also be considered. Other forms of amyloidosis are described in table (2).

AL Amyloidosis	Typically associated with plasma cells dyscrasias leading to overproduction and deposition of immunoglobulin light chains.
AA Amyloidosis	Typically a complication of chronic inflammatory diseases e.g. rheumatoid arthritis. Due to excessive production and deposition of amyloid A protein, which is an acute phase reactant[18].
Senile amyloidosis	Evidence of senile amyloidosis is found in around 25% of post mortems undertaken in individuals over age 80. More common in males. Typically confined to the heart. Clinical course usually more benign than other forms of amyloid.
Familial	Caused by inherited mutations. Commonest protein affected is transthyretin[19].

Table 2: Causes of Amyloidosis.

Since amyloidosis is a systemic disease, investigations should also aim to identify extra-cardiac organ involvement. The commonest organ affected is the kidney, resulting in nephrotic syndrome (5). Renal function should be monitored, and the extent of nephropathy quantified with 24-hour urine collection for creatinine clearance and protein excretion. Autonomic neuropathy may lead to troublesome symptoms which include postural hypotension and diarrhoea. Other symptoms may occur as a result of soft tissue infiltration e.g. carpal tunnel syndrome, macroglossia (5).

Treatment of cardiac amyloid may be targeted as follows:

1. Therapy to suppress amyloid production and/or deposition

2. Supportive heart failure treatment

3. and in selected patients, consideration of cardiac transplantation

Therapy targeting the underlying aetiology of amyloidosis varies according to the underlying cause. Chemotherapy is the mainstay of therapy in the setting of AL amyloidosis (20). In recent years, drugs which specifically target amyloid fibril formation and deposition have been developed e.g. Tafamidis and Diflunisal, which are licensed for use in some forms of hereditary amyloidosis. Both are anti-inflammatory medications which help enhance the stability of the normal soluble structure of proteins which misfold in amyloidosis (18,21).

Heart failure pharmacotherapy requires a measured approach. Whilst diuretics are helpful, it is essential to maintain adequate ventricular filling pressures. There is little evidence for the use of angiotensin-converting enzyme inhibitors in cardiac amyloidosis, and they are often poorly-tolerated, especially if there is renal impairment or postural hypotension.

Similarly, evidence for the use of beta-blockers is limited, and in some cases their negatively chronotropic effect can worsen cardiac output. Due to its complexity, the management of patients with cardiac amyloidosis should be undertaken by specialist heart failure teams. A small group of patients may be suitable for cardiac transplant (20).

In conclusion, cardiac amyloidosis is the commonest cause of restrictive cardiomyopathy in the United Kingdom. It should be considered in adults presenting with unexplained heart failure with an echocardiogram demonstrating increased wall thickness with a non-dilated left ventricular cavity with bi-atrial dilatation, particularly when associated with low voltage on electrocardiography.

Further investigations should aim to confirm amyloid deposition, assess the extent of cardiac involvement, identify the cause of amyloidosis, and assess extra-cardiac organ involvement. Treatment should be undertaken by specialist teams, and involves targeting the underlying cause of amyloid whilst also delivering supportive heart failure treatment.

- Heart failure is a heterogenous clinical syndrome. In cases of unexplained heart failure, cardiac amyloidosis should be considered as part of the differential diagnosis.

- Referral to specialist teams, including the UK National Amyloidosis Centre (NAC) in selected cases, is an important part of a patient's care pathway. In addition to affirming a patient's diagnosis and tailoring treatment, specialist teams can provide important support for patients and families.

Best of 5 MCQs: Test Yourself

1. Which one of the following is not considered a cause of left ventricular hypertrophy?

a. Fabry's disease

b. Hypertensive heart disease

c. Kawasaki Disease

d. Aortic stenosis

e. Hypertrophic cardiomyopathy

A CASE OF CARDIAC AMYLOID

LA Allen, EHM Edwards, Z Yousef

2. Fibrils of serum amyloid A are implicated in the pathogenesis of which of the following diseases

a. Age-related systemic amyloidosis

b. Dialysis-related amyloidosis

c. AA amyloidosis

d. AL amyloidosis

e. Cerebral amyloid angiopathy

3. Which organ is most commonly affected in primary amyloidosis?

a. Kidney

b. Heart

c. Gut

d. Nerves

e. Skin

4. A positive stain with which of the following is specific for amyloid?

a. Methenamine silver stain

b. Congo red stain

c. Periodic Acid Schif stain

d. Alizarin red stain

e. Ziehl-Neelsen stain

5. A post mortem undertaken in an 88-year-old male with no previous history of cardiac failure demonstrates amyloid deposition in the heart. No amyloid deposition was noticed elsewhere in the body. What is the most likely diagnosis?

a. AL amyloidosis

b. AA amyloidosis

c. Familial amyloid cardiomyopathy

d. Senile cardiac amyloidosis

e. Dialysis associated amyloidosis

Answers

Q1. Answer = C

Hypertensive heart disease, aortic stenosis, hypertrophic cardiomyopathy and Fabry's disease should all be included as differentials of left ventricular hypertrophy. Left ventricular hypertrophy usually results from high-pressure ventricular states.

Q2. Answer = C

Deposition of serum amyloid A fibrilis is seen in AA amyloidosis as a result of chronic inflammation. Serum amyloid A is an acute-phase reactant.

Q3. Answer = A

The kidney is the organ most likely to be affected by systemic amyloidosis. Renal involvement typically leads to proteinuria and nephrotic syndrome. All of the other organs may also be affected. Cardiac involvement classically leads to a restrictive cardiomyopathy.

Q4. Answer = B

Amyloid deposits typically stain positively with Congo Red staining. Apple green bi-refrinegnce is classical when viewed under polarised light microscopy.

Q5. Answer = D

Senile cardiac amyloidosis is relatively common, with evidence of cardiac amyloid deposition found in around 25% of post mortems undertaken in individuals over the age of 80. It is more common in males than in females. It is often asymptomatic and found incidentally at post mortem.

A CASE OF CARDIAC AMYLOID

LA Allen, EHM Edwards, Z Yousef

Authors

Dr Lowri A Allen
Senior House Officer
Department of Cardiology
University Hospital of Wales, Cardiff.

Dr Elinor Edwards
Senior House Officer
Department of Cardiology
University Hospital of Wales, Cardiff.
elinor.edwards@doctors.org.uk

Professor Z Yousef
Consultant Cardiologist
Department of Cardiology
University Hospital of Wales, Cardiff.
zaheer.yousef@wales.nhs.uk

Corresponding Author

Dr Lowri A Allen
allenla7@cardiff.ac.uk.

References

1. Merlini G, Bellotti V. Molecular Mechanisms of Amyloidosis. NEJM 2003, 349:583-96.

2. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, Falk RH. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998, 91: 141-157.

3. Nihoyannopoulos P, Dawson D. Restrictive cardiomyopathies. Eur J Echocardiogr 2009, 8:iii23-iii33.

4. Chew C, Ziady GM, Raphael MJ, Oakley CM. The functional defect in amyloid heart disease: the "stiff heart" syndrome. Am J Cardiol 1975, 36: 438-444.

5. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995, 32:45-59.

6. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol 2005, 95:535-537.

7. Falk RH, Plehn JF, Deering T, Schick EC, Boinary P, Rubinow A, Skinner M, Cohen AS. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. AM J Cardiol 1987, 59: 418-422.

8. Cueto-Garcia L, Reeder GS, Kyle RA, Wood DL, Seward JB, Naessens J, Offord MS, Greipp PR, Edwards WD, Tajik AJ. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. J Am Coll Cardiol 1985, 6:737-743.

9. Cacciapuoti F. The role of echocardiography in the non-invasive diagnosis of cardiac amyloidosis. J Echocardiogr 2015, 13:84-9.

10. Yousef Z, Elliott PM, Cecchi F, Escoubet B, Linhart A, Monserrat L, Namdar M, Weidemann F. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. Eur Heart J 2013; 34:802-808.

11. Maceira AM, Joshi K, Prasad SK, Moon JC, Perugini E, Harding I, Sheppard MN, Poole-Wilson PA, Hawkins PN, Pennell DJ. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005, 111:186-193.

12. Maceira AM, Prasad SK, Hawkins PN, Roughton M, Pennell DJ. Cardiovascular magnetic resonance and prognosis in cardiac amyloidosis. J Cardiovasc Magn Reson 2008, 10:54.

13. Peterzan MA, Rider OJ, Anderson LJ. The role of cardiovascular magnetic resonance imaging in heart failure. Card Fail Rev 2016, 2:115-122.

14. Bellavia D, Pellikka PA, Al-Zahrani HB, Abraham TP, Dispenzieri A, Miyazaki C, Lacy M, Scott CG, Oh JK, Miller FA. Independent predictors of survival in primary systemic (AI) amyloidosis, including cardiac biomarkers and left ventricular strain imaging: an observational cohort study. J Am Soc Echocardiogr 2010; 23: 643-652.

15. Palladini G, Barassi A, Klersy C, Pacciolla R, Milani P, Sarais G, Perlini S, Albertini R, Russo P, Foli A, Bragotti LZ, Obici L, Moratti R, Meizi d;Eril GV, Merlini G. The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-pro BNP) after chemotherapy best predicts survival in AL amyloidosis. Blood 2010, 116:3426-3430.

16. Pellikka PA, Holmes DR, Edwards WD, Nishimura RA, Tajik AJ, Kyle RA. Endomyocardial biopsy in 30 patients with primary amyloidosis and suspected cardiac involvement. Arch Intern Med 1988, 148: 662-666.

17. Howie AJ, Brewer DB. Optical properties of amyloid stained by Congo red: History and mechanisms. Micron 2009, 40:285-301.

18. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in Cardiac Amyloidosis: A review. J Am Heart Assoc 2012, 1:e00364.

19. Ng Belinda, Connors LH, Davidoff R. Senile Systemic Amyloidosis presenting with heart failure; a comparison with light chain-associated amyloidosis. Arch Intern Med 2005, 165: 1425-1429.

20. Wechalkar AD, Gillmore JD, Bird J, Cabenagh J, Hawkins S, Kazmi M, Lachmann HJ, Hawkins PN, Pratt G, and on behalf of the BCSH Committee. Guidelines on the management of AL amyloidosis. Br J Haematol 2014, 2 186-206.

21. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. Amyloid. 2006; 13:236-249.

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

AN INCIDENTAL FINDING REQUIRING URGENT MANAGEMENT - A YOUNG MALE WITH ATRIAL MYXOMA

J Kersey, L Floyd, A Khan

Abstract

A 50-year-old gentleman presented with a one-hour episode of chest pain. Echocardiogram as outpatient revealed a large atrial myxoma and referral was made to cardiothoracic surgeons. This case demonstrates a rare, high-risk aetiology of chest pain. We will discuss the risks of myxoma and the urgency of treatment.

Case History

A 50-year-old male presented to accident and emergency unit following an hour-long episode of non-radiating central chest pain. The pain was described as if a concrete brick was on his chest and was associated with shortness of breath and nausea. This was on a background of intermittent chest pains for two weeks. Examination was unremarkable with no additional heart sounds on auscultation, and ECG showed sinus rhythm.

His past medical history included type II diabetes mellitus, well controlled hypertension and at the time he was under vascular surgeons due to features suggestive of peripheral arterial occlusive disease. His other cardiac risk factors were being a smoker and a positive family history, his father received a bypass graft aged 40. The patient was discharged following negative repeat troponins with referral to the rapid access chest pain clinic (RACP).

When seen in RACP the initial impression was that his symptoms were attributable to angina pectoris. He was started on once daily aspirin 75mg and atorvastatin 20mg with an outpatient, echocardiogram and myocardial perfusion scan to look for any areas of ischaemia.

Two months later the outpatient echocardiogram demonstrated ejection fraction of >55%, no significant valvular disease and good biventricular systolic function. There was a large echogenic pedunculated mass in the left atrium measuring approx. 4.7 x 2.3cm attached to the interatrial septum consistent with a myxoma.

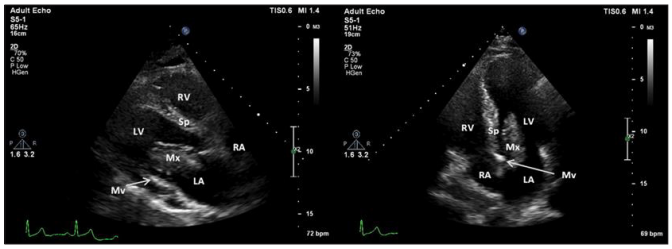


Figure 1: Two views from transthoracic echocardiogram displaying the myxoma, the image on the right hand side clearly shows the myxoma entering the left ventricle.

Key: LA – Left Atrium. RA - Right Atrium. LV - Left Ventricle. RV - Right Ventricle.

Sp - Intraventricular septum. Mv - Mitral valve outlet. Mx - Atrial Myxoma.

Despite being fixed to the wall the mass was found to move in synchrony with the anterior mitral leaflet to such a degree that it crossed through the valve and into the left ventricle. There was however no evidence of stenosis or significant regurgitation. The images were immediately reviewed and the patient was called back to be seen in clinic the following day.

A multidisciplinary discussion occurred in which the cardiothoracic surgeons at a tertiary centre organised surgical excision as soon as possible. Pre-surgical investigations, including transoesphageal echocardiogram and angiogram were planned for the following week. Angiogram found a discrete 70% mid vessel lesion in the left anterior descending, the remaining coronaries were unobstructed.

He underwent surgery 3 weeks later with successful removal of the intra-atrial mass. Histology of the excised mass was reported as an irregular gelatinous mass of 50 x 35 x 25mm, with no clear base or resection margin and a haemorrhagic cut surface. The report concluded the features as consistent with a cardiac myxoma. The patient was seen in clinic 2 months after his surgery and has had no further episodes of chest pain.

Discussion

Tumours arising from the myocardium are extremely rare with incidence rates reported to be approximately 0.056% (1). The most common form of primary cardiac tumour is a myxoma which are benign tumours of the mesenchymal connective tissue within the heart. Myxomas are most commonly found in the atria, with 75% in the left atrium compared to 20% in the right atrium (2).

Myxomas most commonly present sporadically and often in patients aged between 30-60 years (3). Whilst there are no well-established risk factors, women are more likely than men to develop them and there is evidence to suggest approximately 10% can be attributed a hereditary pattern usually associated with carney complex (4).

The presentation is often of syncope and dyspnoea, secondary to valvular obstruction, or chest pain, secondary to coronary artery emboli. However in lots of cases the symptoms are often non-specific with complaints of pyrexia, fatigue, weight loss or clubbing (5).

The symptoms of an atrial myxoma are classically attributed to triad of:

- *Embolic events*
- *Mass effect causing obstruction of the mitral valve outlet*
- *Constitutional symptoms due to the production of interleukin-6 from the tumour (6)*

AN INCIDENTAL FINDING REQUIRING URGENT MANAGEMENT - A YOUNG MALE WITH ATRIAL MYXOMA

J Kersey, L Floyd, A Khan

It is because of the non-specificity of symptoms that diagnosis can often be delayed or be attributed to atherosclerotic disease (6). This can be catastrophic as a large myxoma can quickly lead to sudden cardiac death due to obstruction of the valvular tract (7).

An important point from this case is the use of echocardiogram in patients who present with chest pain. Echocardiogram is the most sensitive investigation for detection of atrial myxoma with transthoracic reported to have a sensitivity of 95% and transoesophageal echocardiogram, 100% sensitivity (6).

ECG is a first line investigation for any patient presenting with chest pain to detect ischaemic changes. With atrial myxoma the most commonly reported finding is atrial fibrillation and or corresponding hypertrophy. However, left atrial hypertrophy on an ECG has been reported to occur in only 33% of cases (8).

Patients may present with cardiac murmurs This is usually either a mitral stenosis or what is described as a 'tumour plop', a low pitched sound in diastole caused by tumour passing into the left ventricle and hitting the wall (8). There were no additional heart sounds reported on examination in our patient.

It is important that once identified these patients are discussed with cardiothoracic teams as early as possible as there is little that can be done in the interim between surgery to reduce the risk of sudden cardiac death. This is of much relevance to the case discussed here as it was noted from the report that the myxoma was highly mobile, passing into the left ventricle during ventricular diastole. This put the patient at high risk of complete mitral valve obstruction which can lead to sudden cardiac death.

Once identified and removed surgically prognosis is good. The presence of multiple myxomas is very rare at identification as is the chance of reoccurrence. The most common post op complication is atrial fibrillation with a reported incidence of 22%, only 2.4% of these remain permanent (9).

Comparing pre-op risk of sudden cardiac death and post-operative prognosis illustrates clearly the reason for urgency of surgery. Patients can then be referred to cardiac rehabilitation programmes.

Learning Points

- *Atrial myxoma can present with a myriad of non-specific symptoms.*

- *Echocardiogram is an important investigation in the setting of chest pain believed to be of cardiac origin and should not be delayed because of a belief that the pain is not ischemic in origin such as normal troponins and no changes on ECG.*

- *Atrial myxoma is a high risk cardiac condition caused by a benign growth which can lead to sudden cardiac death. Treatment is with surgical resection; the prognosis is good and reoccurrence rates are low. Cases should therefore be discussed early on with cardiothoracic surgeons. Effective communication is important in relaying the urgency of this to the patient.*

MCQs

1. The three mechanisms by which an atrial myxoma produces symptoms are:

a. Systemic Emboli, interleukin-6 production, mitral valve obstruction

b. Systemic Emboli, mitral regurgitation , heart failure

c. Heart failure, mitral valve obstruction, bacterial colonisation

d. Bacterial colonisation, systemic emboli, mitral regurgitation

e. Mitral regurgitation, heart failure, interleukin-6 production

2. Which is the best imaging modality for diagnosing an atrial myxoma?

a. Transthoracic echocardiogram

b. Non contrast CT scan

c. Transoesophageal echocardiogram

d. Chest X-Ray

e. CT angiogram

AN INCIDENTAL FINDING REQUIRING URGENT MANAGEMENT - A YOUNG MALE WITH ATRIAL MYXOMA

J Kersey, L Floyd, A Khan

Answers

Q1. Correct answer is a)

Systemic Emboli, interleukin-6 production, mitral valve obstruction. Whilst heart failure can be a presentation of cardiac myxoma this is usually as a result of mitral valve obstruction.

There is no evidence to suggest bacterial colonisation in these patients unless they have any other predisposing risk factors.

Q2. Correct answer is c)

Transoesophageal echocardiogram. Whilst large myxomas may be visible on CXR and on CT scans, echocardiograms are a very quick and effective way of diagnosing atrial myxoma. The majority of atrial myxomas are picked up on transthoracic echocardiogram however transoesophageal echocardiogram has 100% sensitivity (6).

Authors

Dr James Kersey
FY1
Tameside General Hospital
Fountain Street
Ashton-Under-Lyne
OL6 9RW

Dr Lauren Floyd
CT2 Core Medical Trainee
Tameside General Hospital
Fountain Street
Ashton-Under-Lyne
OL6 9RW

Dr Aftab Khan
Consultant Cardiologist
Tameside General Hospital
Fountain Street
Ashton-Under-Lyne
OL6 9RW
aftab.khan@tgh.nhs.uk

Corresponding Author

Dr James Kersey
j.g.kersey@doctors.org.uk

References

1. Lam KY, Dickens P, Chan AC. Tumours of the heart. A 20-year experience with a review of 12, 485 consecutive autopsies. Arch Pathol Lab Med. 1993 Oct;117(10):1027-31

2. Lammy S, Velu PP. Massive atrial myxoma: surgical treatment for an incidentaloma causing dyspnoea. Scott Med J. 2013 Nov;58(4):e21-3. doi: 10.1177/0036933013508047.

3. Layton Susie, Ripley David P, Bellenger Nick G. Left atrial myxoma BMJ 2013; 347 :f4430

4. Iami Y, Taketani T, Maemura K, Takeda N, Harada T, Noiri T, et al. Genetic analysis in a patient with recurrent cardiac myxoma and endocrinopathy. Circ J. 2005 Aug;69(8):994-5.

5. British Heart Foundation. Atrial Myxoma - British Heart Foundation. https://www.bhf.org.uk/publications/heart-conditions/medical-information-sheets/atrial-myxoma (accessed 22 December 2017).

6. Kaneko T, Walkes JC, Tsai FW. Left atrial myxoma in a child with unique presentation: chest pain. Pediatr Cardiol. 2011 Feb;32(2):230-1. doi: 10.1007/s00246-010-9847-x

7. Pergolini A, Zampi G, Sbaraglia F, Musumeci F. Left atrial myxoma: two sides of the same coin. J Cardiovasc Med (Hagerstown). 2015 Jan;16(2):74-6. doi: 10.2459/JCM.0b013e3283621c75

8. Pinede L, Duhaut P, Loire R. Clinical presentation of left atrial cardiac myxoma. A series of 112 consecutive cases. Medicine (Baltimore). 2001 May;80(3):159-72.

9. Vroomen M, Houthuizen P, Khamooshian A, Soliman Hamad MA, van Straten AH. Long-term follow-up of 82 patients after surgical excision of atrial myxomas. Interact Cardiovasc Thorac Surg. 2015 Aug;21(2):183-8. doi: 10.1093/icvts/ivv125

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

A CASE OF AORTIC DISSECTION PRESENTING AS MYOCARDIAL INFARCTION

A Marinakis, P Calvert

Abstract

A 47-year-old gentleman was admitted with diagnosis of myocardial infarction (MI).

He underwent a coronary angiogram which revealed unobstructed coronary arteries, though intravascular ultrasound (IVUS) showed a right coronary artery (RCA) dissection. Subsequent computed tomography (CT) confirmed an extensive type A aortic dissection with the presence of a right adrenal mass.

Patient underwent an aorta interposition including coronary artery bypass graft (CABG), and followed a postoperative recovery in intensive care unit with further investigations of the adrenal mass.

Case History

A 47-year-old gentleman presented via the primary percutaneous coronary intervention (PPCI) service, complaining of a sudden onset of crushing pain on his left shoulder radiating to the lower chest. Pain was associated with sweating and nausea.

His past medical history involved smoking and malignant hypertension, poorly controlled on amlodipine and losartan. There was also long history of hypertension in the family.

Electrocardiogram (ECG) from ambulance showed ST segment elevation in leads II, III and aVF with ST depression in V1 – V4. Provisional diagnosis of inferior-posterior ST elevation myocardial infarction (STEMI) was made and patient was immediately started on treatment for acute coronary syndrome.

On arrival he was alert and orientated, haemodynamically stable with blood pressure of 180/90 mmHg and no evidence of end – organ hypo perfusion. He was verbally consented and transferred to the catheter laboratory for PPCI.

Left heart catheterisation of the left coronary artery showed no lesions in the left main stem (LMS), left anterior descending (LAD) or circumflex (Cx) respectively.

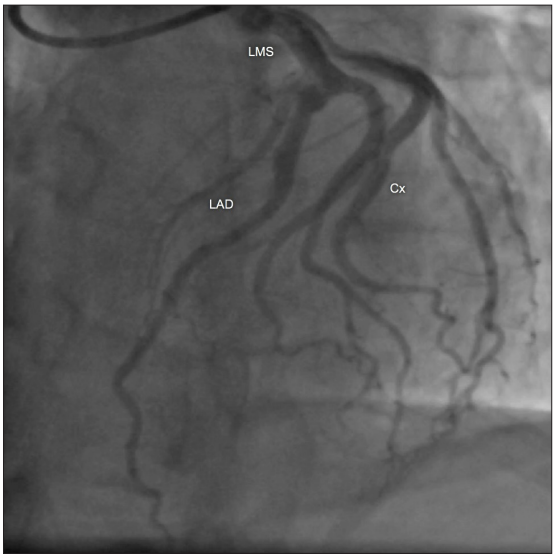


Figure 1: LAO cranial view, left coronary angiogram. Normal filling of main and distal branches.

LAO, Left anterior oblique; LMS, Left main stem; Cx, circumflex; LAD, Left anterior descending.

Right coronary artery (RCA) was equally unobstructed with no presence of atherosclerotic plaques. There was only a ''smooth stenosis'' delaying the filling of the vessel and its distal branches.

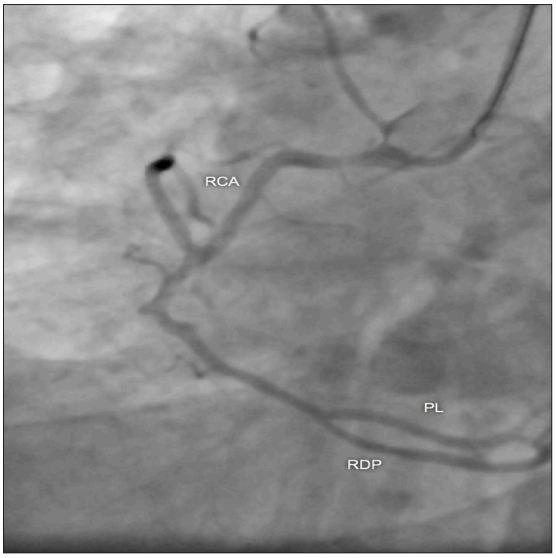


Figure 2: AP view of the RCA. There are no atherosclerotic plaques, though a smooth stenosis gives an impression of "string –vessel" with delayed filling of its distal branches.

AP, anterior posterior; RCA, right coronary artery; PL, posterolateral branch; RDP/PDA, posterior descending artery

A CASE OF AORTIC DISSECTION PRESENTING AS MYOCARDIAL INFARCTION

A Marinakis, P Calvert

Smooth stenosis of the RCA warranted visualisation with intravascular ultrasound (IVUS). The IVUS in the RCA confirmed a coronary artery dissection with a dynamically increasing false lumen compressing externally the true one.

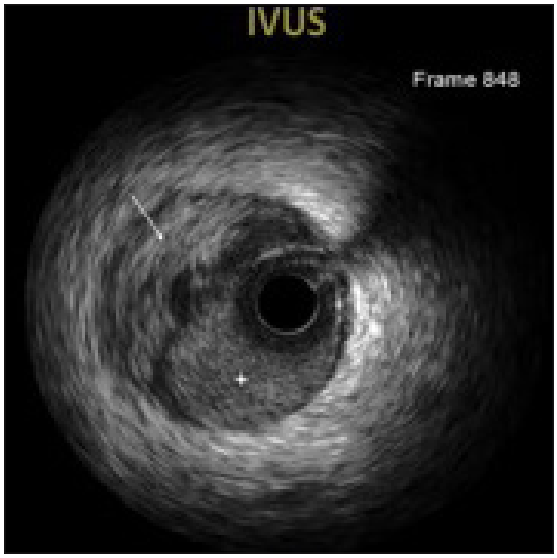


Figure 3: IVUS showing RCA dissection. The IVUS catheter is in the true lumen (asterisk) of the vessel. The white arrow points to the false lumen, which is separated by the true lumen with the intimal flap.

IVUS, Intravascular ultrasound;
RCA, Right coronary artery

On further questioning during procedure, patient revealed transient loss of sensation in his left leg, coinciding with the onset of chest pain and associated symptoms. Based on the new evidence, working diagnosis was heading towards a life-threatening condition of type A aortic dissection with involvement of RCA, and possible extension to lower limbs.

Provided that there was delayed but normal flow in the right coronary artery, decision was made not to proceed immediately with PCI, as intervening in a spontaneous coronary dissection would involve a high risk of worsening and extending the dissection. Normal flow provided time for transfer for Computed tomography (CT) and prompt escalation to critical care and cardiothoracic team.

Systolic blood procedure (SBP) was above 160mmHg and patient was started on labetalol and glyceryl trinitrate (GTN) infusion.

CT Thorax with contrast confirmed the diagnosis of an acute type A dissection

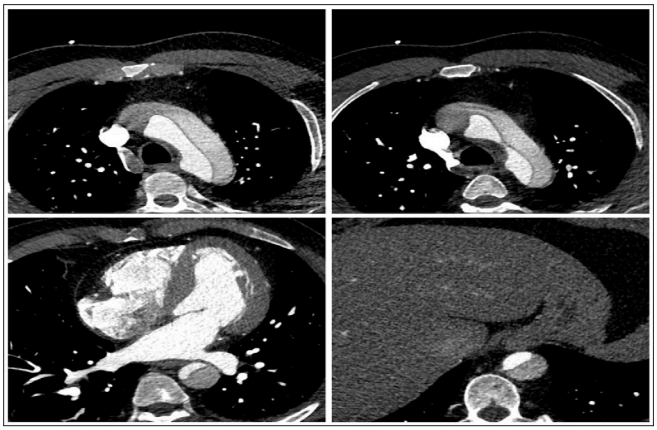


Figure 4: CT Thorax with contrast. The true lumen of the aorta and its branches show high attenuation from contrast as they descend down to the thorax. The dissecting flap surrounds externally the ascending and descending aorta at the level of aortic arch (top images). The dissection extends to the descending and thoracic aorta up to the level of the diaphragm (bottom right image).

The entry point of the dissection flap was starting from the aortic root involving both the non – coronary cusp and coronary sinus. High attenuation at the level of the RCA ostium suggested intramural haematoma and likely RCA dissection due to the retrograde progression of the aortic dissection. There were no signs of pericardial collection. On the unenhanced CT scan the aortic dissection was reaching the level of common femoral arteries.

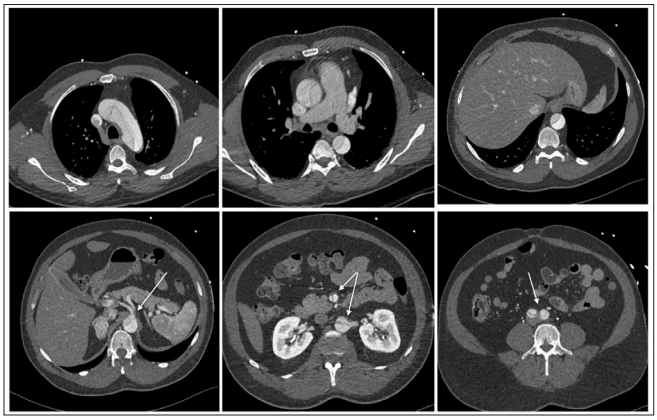


Figure 5: Unenhanced CT Aorta. Compared to the previous views there is higher attenuation on the false lumen. The first three top images portray the dissection on three different levels inside the thorax. The bottom left image shows the coeliac trunk arising from the true lumen of the abdominal aorta. The middle bottom depicts the single SMA dissection and the left renal artery arising from the false lumen, while the bottom right image shows the extension of the dissection beyond the iliac bifurcation, ultimately reaching the common femoral arteries. CT, Computed tomography; SMA, superior mesenteric artery.

A CASE OF AORTIC DISSECTION PRESENTING AS MYOCARDIAL INFARCTION

A Marinakis, P Calvert

There was a single dissection of the superior mesenteric artery (SMA) while the left renal artery was arising from the false lumen of the dissected abdominal aorta. Along with the vascular abnormalities there was a 22mm mass on the right adrenal gland, which raised suspicion of pheochromocytoma.

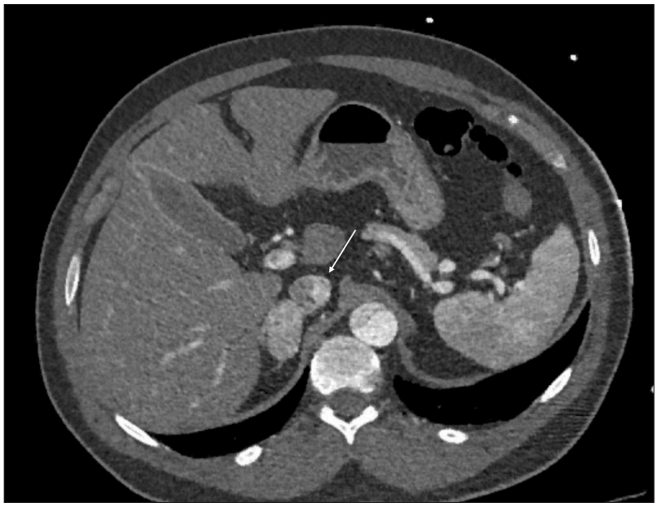


Figure 6: Unenhanced CT white arrow shows the mass in the right adrenal gland. CT, Computed Tomography.

Patient was immediately transferred to theatre. Peri-operative transoesophageal echo (TOE) revealed the dissection flap and confirmed a mild aortic regurgitation with preserved ejection fraction. (Figure 7 - 8).

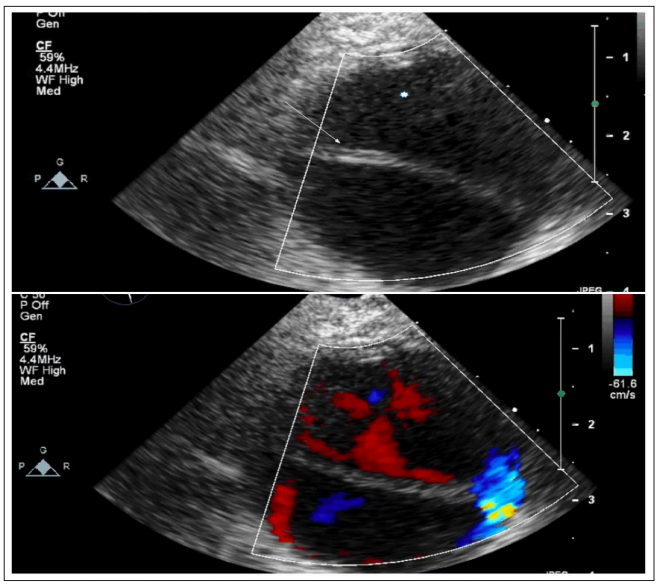


Figure 7: Shot axis view(SAX) of descending aorta on TOE. The arrow shows the intimal flap and the asterisk the false lumen. TOE, Transoesophangeal echocardiogram.

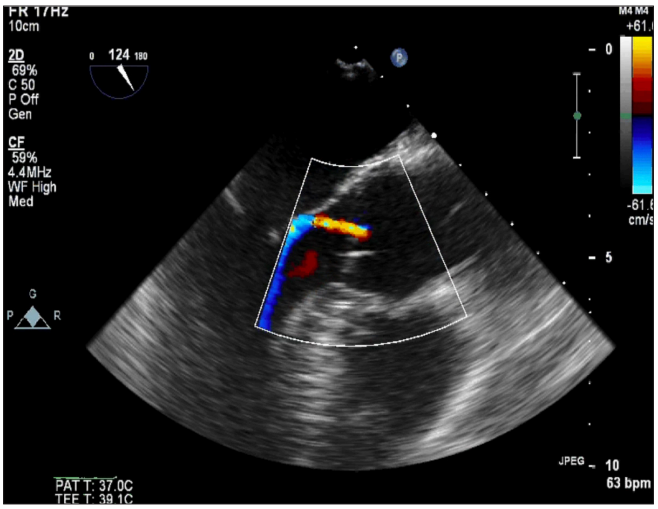


Figure 8: TOE: ME LAX view of left ventricle and aortic valve. There is trace of mild aortic regurgitation with intact aortic leaflets. TOE, transoesophageal echo; ME LAX, mid-oesophageal long axis.

The ascending aorta was excised at the level of the sino-tubular junction and replaced by a 26 mm Hemashield graft. The right saphenous vein was harvested to anastomose the Hemashield graft with the RCA distally to its dissection. Subsequently, the patient spent an uneventful recovery in CCU where he followed further investigations of his adrenal mass.

Biopsy of the excised aorta showed no signs of arteritis or connective tissue disease.

Urine and plasma metanephrines were borderline increased and could not account for a diagnosis of pheochromocytoma. Renin, aldosterone and cortisol levels were equally within normal range. Repeat CT showed no post-operative complications and no increase in the size of the mass.

The case was discussed in the multidisciplinary team and the lesion was deemed benign(Incidentaloma) with main risk factor the strong family history of hypertension. Patient was referred after discharge to clinical pharmacology for long term control of his hypertension.

A CASE OF AORTIC DISSECTION PRESENTING AS MYOCARDIAL INFARCTION

A Marinakis, P Calvert

Discussion

This was an acute type A dissection presented as inferior STEMI, and despite the complexity, critical decisions led to the optimal patient outcome. A targeted clinical history led to suspicion of the underlying condition promptly as chest pain with neurological symptoms should always raise suspicion of aortic dissection until proven otherwise.

From an interventional perspective, there is always room for discussion in terms of when to intervene in coronary artery dissection. In case of spontaneous coronary artery dissection (SCAD) the general consensus is in favour of conservative management.

The "watchful waiting" strategy is indicated unless patient has ongoing ischemia, where PCI or CABG should be considered (1). In our case the RCA dissection was due to obliteration of coronary ostium from a retrograde progression of the aortic dissection. Therefore, the right step was to visualise the whole aorta first, and decide subsequently for further management.(2)

Lab monitoring with products such as troponin and d-dimmers may be indicated if diagnosis is less clear. On our patient CT of whole aorta revealed the underlying pathology therefore urgent surgical intervention was the safest approach.

Questions

1. In an aortic dissection, in which layer of the aortic wall does the propagation of the false lumen occur?

a. endothelium

b. tunica intima

c. tunica media

d. tunica adventitia (externa)

e. internal elastic membrane

2. Which of the following types of aortic dissection can be managed medically?

a. acute type A dissection

b. acute (distal) type B with vital organ compromise

c. uncomplicated type B dissection

d. Dissection in Marfan Syndrome

e. none of the above

3. What is the first line investigation for aortic dissection?

a. CT aorta with contrast

b. Transthoracic echocardiogram

c. Transoesophageal echocardiogram

d. Chest x-ray

e. Magnetic resonance imaging (MRI)

4. What is the mortality rate the first 24h of an acute (not ruptured) aortic dissection?

a. 1% per hour

b. 5% per hour

c. 10% per hour

d. 15% per hour

e. 20% per hour

5. Which of the following conditions could present with an acute aortic dissection?

a. renal failure

b. cardiac tamponade

c. cerebrovascular accident

d. hoarseness

e. all the above

A CASE OF AORTIC DISSECTION PRESENTING AS MYOCARDIAL INFARCTION

A Marinakis, P Calvert

Answears

1. C

The aortic wall consists of three: tunica intima, tunica media and tunica adventitia. The endothelium is the first layer of cells that separate the lumen from the tunica intima and the internal elastic membrane separates the intima from the media.

In most cases the aortic dissection starts from a tear the intima, however the progression of the blood flow and the false lumen occurs towards the media. There are cases where aortic dissection may occur without the initial tear however the false lumen is always within the media layer. (2)

2. C

Acute type A is invariably managed surgically (2). It relies on the attending team to decide whether to treat with endovascular or surgical repair of a type B with impending rupture that threatens organ perfusion. A stable type B aortic dissection can be managed with long term tight BP control.

3. A

The gold standard is CT aorta with contrast. It has sensitivity and specificity 96% and can demonstrate involvement of distal branches. TOE is indicated if CT is not available or if patient is haemodynamically unstable as it can detect AR and pericardial effusion.

4. A

Mortality rate of aortic dissection is 1% per hour the first 24h (2) which makes timely diagnosis essential. In case of a rupture mortality reaches 90%.

5. E

Signs will be dependent on the progression of the false lumen and the arterial branches involved. In case of retrograde progression and rupture in the pericardial cavity we may notice fulminant pericardial tamponade. If carotids are externally compressed patient may experience CVA or acute renal failure on compression of renal artery. In rare cases there might be hoarseness due to compression of left laryngeal nerve.(2)

Authors

Dr Alexandros Marinakis
Foundation Year 2
Papworth Hospital NHS Foundation Trust
Papworth Everard, Cambridge CB23 3RE, UK

Dr Patrick Calvert BM, BCh, MA, PhD, MRCP, FACC
Consultant Cardiologist - Lead for Structural Intervention
National Specialty Lead for Atherosclerosis
and Cardiovascular Prevention NIHR CRN
Honorary Senior Visiting Research Fellow University of Cambridge
Papworth Hospital NHS Foundation trust
Papworth Everard, Cambridge CB23 3RE, UK
patrick.calvert1@nhs.net

Corresponding Author

Dr Alexandros Marinakis
alexandros.marinakis@nhs.net

References

1. Luong C, Starovoytov A, Heydari M et al.Clinical presentation of patients with spontaneous coronary artery dissection. Catheter Cardiovasc Interv. 2017; 89(7) :1149-1154

2.Jolly E, Fry A , Chaudhry A. (2016) . Training in Medicine, Oxford Specialty Training, pp 114-115

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

CARDIOGENIC SHOCK DUE TO RIGHT VENTRICULAR INFARCTION

S Norman, M Al-Khafaji

Abstract

Infarction of the right ventricle (RV) is a rare entity, frequently overlooked and often missed in patients presenting with acute coronary syndrome (ACS). A standard 12-lead ECG is insufficient in detecting ischaemic changes originating in the right ventricle, the use of posterior leads and right sided leads is thus essential in confirming the diagnosis. Initial management is essentially identical to other acute coronary syndromes with use of anti-platelet agents and prompt reperfusion.

We describe the case of a 56-year-old female who attended hospital with non-cardiac symptoms (confusion and falls) and was found to have an inferior ST-elevation myocardial infarction, with evidence of posterior involvement.

She became critically unwell with hypotension requiring inotropic support and use of an intra-aortic balloon pump. This clinical case highlighted the subtle features of a right ventricular infarct and the differences in managing cardiogenic shock due to RV infarction.

Learning Points

1. RV infarction typically presents as a typical ACS but has subtle ECG features, posterior (15-lead/RV) ECG leads should be recorded on patients in whom RV infarction is suspected.

2. Initial management of RV infarction is essentially identical to that of other acute coronary syndromes with anti-platelet therapy and timely reperfusion.

3. Signs of Cardiogenic Shock from RV infarction include: hypotension with clear lung fields and raised JVP.

4. Management thereafter involves optimal fluid balance (consider pulmonary artery catheter) and inotropic support.

5. Atrioventricular block is more frequent in RV infarction (1).

6. Even with optimal management, RV infarction carries a poor prognosis (up to 30% in-patient mortality with ST-elevation in lead V4R, compared to 6% without) (1).

Description

A 56-year-old female with a past medical history of type II diabetes mellitus, angina and depression presented to the Emergency Department (ED) with confusion and a head injury due to a fall. The ED doctors arranged a CT scan which showed no acute abnormality.

She did not have an electrocardiogram (ECG) performed within the department, but was noted to be hypertensive (189/102mmHg) and diaphoretic. On arrival at the Acute Medical Unit (AMU) she had a 12-lead ECG performed which revealed significant ST-elevation in the inferolateral leads.

At this point she was given aspirin, clopidogrel and treatment dose low molecular weight heparin. Troponin-T was checked which was elevated at 3.960 µg/L.

Her case was discussed with the local percutaneous coronary intervention (PCI) centre and due to uncertainty over the timing of her presentation and lack of chest pain, she was deemed not for urgent angiography.

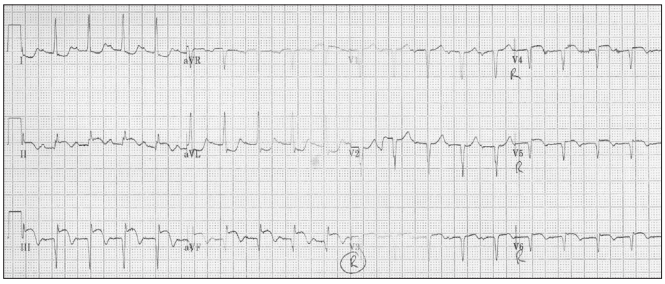


Figure 1: 12-lead ECG showing extensive inferolateral ST-elevation myocardial infarction.

The patient was reviewed the following day by a consultant cardiologist who requested right-sided precordial ECG leads which revealed ST-elevation in leads V4R – V6R. An echocardiogram showed severe right ventricular systolic dysfunction and moderate left ventricular systolic dysfunction.

She was subsequently transferred for emergency PCI. Coronary angiography revealed diffuse mild to moderate disease in her left coronary circulation and a proximal subtotal occlusion of the dominant right coronary artery (RCA). PCI was performed to the proximal RCA with balloon angioplasty and deployment of a bare metal stent.

CARDIOGENIC SHOCK DUE TO RIGHT VENTRICULAR INFARCTION

S Norman, M Al-Khafaji

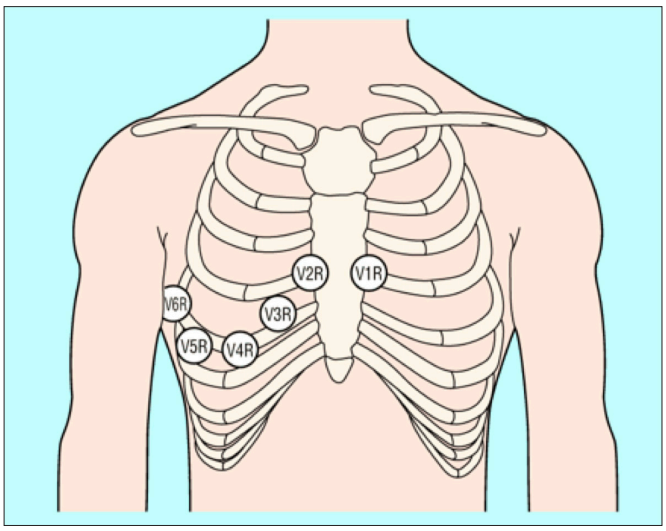


Figure 2: Right Ventricular ECG Leads. Reproduced from Morris and Brady, 2002. www.lifeinthefastlane.com/right-ventricular-infarction.

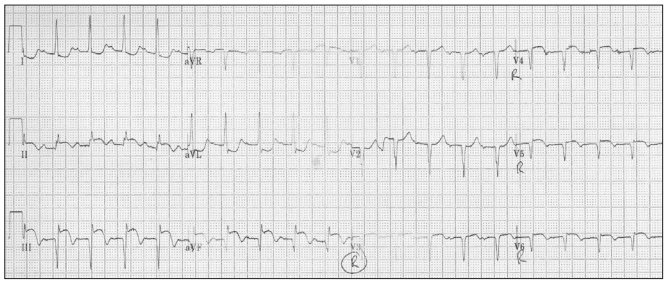


Figure 3: Right ventricular leads showing infarction of the right ventricle.

Over the following 24 hours the patient developed cardiogenic shock with multi-organ failure. Despite intensive treatment including inotropic support and an intra-aortic balloon pump, the patient deteriorated to the point of cardiac arrest. Unfortunately, resuscitation attempts were unsuccessful, and the patient passed away.

Discussion

Right ventricular (RV) infarction is known to occur in around 40% of inferior ST-elevation myocardial infarctions (MI). Isolated RV infarction is extremely rare, and standard electrocardiogram leads are poorly sensitive in detecting this. Infarction of the right ventricle is associated with inferior ischaemic change and ST-elevation in lead V (1).

Use of the right sided chest leads, especially V4R, are sensitive and should be utilised in patients presenting with an inferior MI. Infarction of the RV is usually associated with occlusion of the right coronary artery proximal to the branches which supply it. Less commonly in patients with left dominant coronary circulation, occlusion of the circumflex artery can produce inferolateral and posterior infarction with RV involvement (2).

Studies have shown that patients with ST-elevation in V4R are at higher risk of high grade AV block and other complications along with a significantly higher risk of death (31% compared with 6%, P=<0.001) (1).

Patients who present with myocardial infarction with RV involvement should initially be managed identically to that of any other territorial infarct. If a blocked coronary artery is suspected, reperfusion should be sought, typically with percutaneous coronary intervention. The goal of which is to preserve myocardial muscle and avoid resultant heart failure.

Cardiogenic shock usually manifests from a failing left ventricle and management of this involves reducing preload and augmenting left ventricular contractility with inotropic support. There are several methods of variable invasiveness that can be used to diagnose right ventricular failure. The most sensitive method is cardiac MRI, this is usually not feasible in the context of haemodynamic instability.

Pulmonary artery catheters (PACs) can be used to measure haemodynamic parameters related to RV function. For example, measurements of pulmonary artery pressure (PAP) and RV stroke work index can be obtained3. Echocardiography is of paramount importance, however 2-dimensional methods of assessing RV function do not represent the irregular shape of this chamber. Recent studies have shown that parameters obtained from 3D echocardiography are better predictors of RV failure (4).

Treatment of RV failure involves careful optimization of volume status, RV inotropy enhancement and RV afterload reduction. Cardiogenic shock from RV failure can be described as preload dependent, poor venous return to the right heart will reduce the RV ejection fraction. However, excessive preload can worsen RV dilatation, shift the intraventricular septum worsening LV function and exacerbating systemic hypotension (3).

Dobutamine is the traditional inotrope of choice in cardiogenic shock and acts by increasing myocardial contractility (ß-1 receptors) and reducing afterload via vasodilation (ß-2 receptors). Low-dose dobutamine has been shown to be beneficial in RV failure, with reduction in PAP and increased RV contractility (5).

Dobutamine can however worsen systemic hypotension through systemic ß-2 receptor mediated vasodilation, requiring concomitant use of a vasopressor such as noradrenaline3. Intra-aortic balloon pump devices are frequently used to support the failing heart in cardiogenic shock secondary to MI. However, they do not confer a reduction in mortality (6).

CARDIOGENIC SHOCK DUE TO RIGHT VENTRICULAR INFARCTION

S Norman, M Al-Khafaji

Insufficient oxygenation leads to hypoxic pulmonary vasoconstriction which increases RV afterload, further impairing RV function. Thus, oxygen saturations should be maintained above 92%. It is well understood that mechanical ventilation carries the potential risk of adverse haemodynamic effects upon both the left and right ventricles. High tidal volumes and the use of positive end-expiratory pressure (PEEP) are particularly detrimental due to the increase they incur in PAP which increases RV afterload. Furthermore, PEEP may reduce venous return and thus reduce RV preload (3).

MCQs

Q1: RV infarction has a totally different manifestation from LV infarction.

Q2: Usually due to spasm of circumflex branch of the left coronary artery.

Q3: Most commonly presented with acute pulmonary oedema.

Q4: IV fluid challenge may help in the diagnosis.

Q5: ECG changes of acute inferior&/ or true posterior infarction.

Q6: Myocardial rupture and tamponade is unlikely to happen.

Q7: Titral regurgitate murmur is commonly present.

Q8: Tricuspid murmur is very easily identified.

Q9: Beta blockers, nitrate, ACE inhibitors + stanine should be immediately started.

Q10: Intra aortic balloon is of great help to limit the size of infarction $ symptoms as a bridge to PCI.

Answers

A1: False
A2: False
A3: False
A4: True
A5: True
A6: False
A7: False
A8: False
A9: False
A10: True

Authors

MN Al-Khafaji
Consultant Cardiologist
Cross House University Teaching Hospital
Kilmarnock, KA1 0BE
mohammed.al-khafaji@aapct.scot.nhs.uk

S Norman
Clinical Teaching Fellow
Cross House University Teaching Hospital
Kilmarnock, KA1 0BE

Corresponding Author

S Norman
mohammednaji48@outlook.com

References

1. Zehender M, Kasper W, Kauder E, Schonthaler M, Geibel A, Olschewski M et al. Right Ventricular Infarction as an Independent Predictor of Prognosis after Acute Inferior Myocardial Infarction. NEJM 1993;328:981:988.
2. Morris F. ABC of clinical electrocardiography: Acute myocardial infarction---Part I. BMJ. 2002;324(7341):831-834.
3. Lahm T, McCaslin C, Wozniak T, Ghumman W, Fadl Y, Obeidat O et al. Medical and Surgical Treatment of Acute Right Ventricular Failure. Journal of the American College of Cardiology. 2010;56(18):1435-1446.
4. Vitarelli A, Mangieri E, Terzano C, Gaudio C, Salsano F, Rosato E et al. Three-Dimensional Echocardiography and 2D-3D Speckle-Tracking Imaging in Chronic Pulmonary Hypertension: Diagnostic Accuracy in Detecting Hemodynamic Signs of Right Ventricular (RV) Failure. Journal of the American Heart Association. 2015;4(3):e001584-e001584.
5. 4. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P et al. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure®. Critical Care Medicine. 2004;32(4):1035-1040.
6. Romeo F. Percutaneous assist devices in acute myocardial infarction with cardiogenic shock: Review, meta-analysis. World Journal of Cardiology. 2016;8(1):98.

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

ENTRESTO - NEW HOPE IN SEVERE HEART FAILURE

S Hobson, SD Rosen

Abstract

This article presents a patient with ischaemic cardiomyopathy of sufficient severity to warrant assessment for transplantation. We discuss established and novel heart failure therapies including the striking effect witnessed following the introduction one of the more novel agents; Sacubitril/Valsartan (Entresto).

Case History

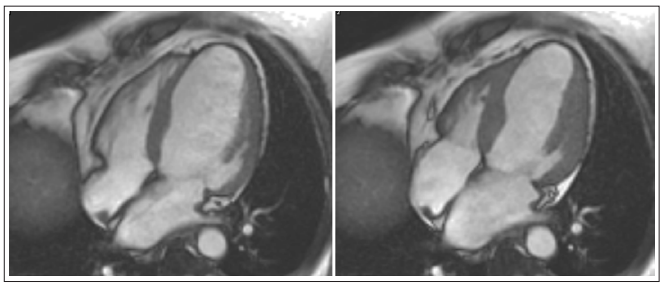
This case based discussion focuses on patient A, a 44 year old male with ischaemic cardiomyopathy.

Past medical history includes ischaemic heart disease, type 2 diabetes mellitus complicated by retinopathy and nephropathy, hypertension, hypercholesterolaemia and peripheral vascular disease.

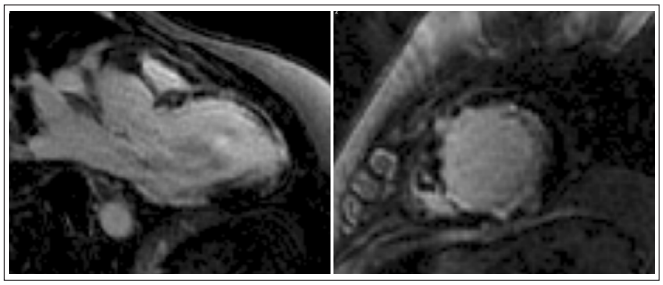
The history of ischaemic heart disease was extensive. He first presented with non ST-elevation myocardial infarction in 2010 requiring two coronary stents. Echocardiography at the time revealed regional wall motion abnormalities, grade 2 diastolic dysfunction and reduced LV systolic function, with an ejection fraction of 42% (i.e. heart failure with reduced ejection fraction, HFREF).

At the time he was appropriately started on first line heart failure therapy. This consisted of ACE inhibitor, beta blocker and diuretic alongside eplerenone and dual antiplatelet therapy given his recent acute coronary syndrome.

Cardiac MRI imaging is an invaluable tool in the assessment of cardiomyopathy. Extremely detailed images can be obtained, generating functional and prognostic information on anatomy, global and regional contractility, fibrosis, infiltration, inflammation and perfusion.



End systolic and end diastolic anatomical views displaying severely impaired systolic function.



Cardiac MRI evidence of significant wall scarring

Persistent angina prompted elective diagnostic coronary angiography in 2012. This revealed significant stenosis of the LAD, circumflex and right coronary arteries. In this case, cardiac MRI revealed limited viability in the corresponding areas. He was discussed at the revascularisation MDT where he was deemed unsuitable for coronary artery bypass grafting given the limited viability and poor graft targets.

Given his on-going symptoms, his medical therapy at the time was optimised in accordance with NICE guidelines;

IHD – aspirin, clopidogrel, atorvastatin

Angina – isosorbide mononitrate, ivabradine, ranolazine, nicorandil, PRN glyeryl trinitrate

Heart failure – ramipril, bisoprolol, bumetanide, eplerenone

Diabetes – metformin; Lantus and Humalog insulin

Other – lansoprazole, senna, movicol

He remained stable until 2015 when he had a number of hospital admissions.

Admission 1 (August 2015)

Admitted with worsening shortness of breath on exertion, orthopnoea, peripheral oedema and chest pain.

There was no suggestion of another ischaemic event. ECG revealed non-dynamic, chronic ischaemic changes with a narrow QRS. Troponin levels were chronically elevated but non-dynamic at 60 and 59.

Repeat echocardiography revealed stable LV ejection fraction of 40% and grade 2 diastolic dysfunction. He was managed with IV furosemide diuresis with a good response.

Prior to discharge his medications were optimised;

- *Bisoprolol dose was increased*
- *Isosorbide mononitrate dose increased*
- *Bumetanide dose increased*

ENTRESTO – NEW HOPE IN SEVERE HEART FAILURE

S Hobson, SD Rosen

Admission 2 (March 2016)

Admitted with shortness of breath, angina and weight gain.

BNP elevated at 3552, chest x-ray revealed pulmonary oedema. Stable LVEF of 40%.

Again managed with IV furosemide diuresis with a good response.

- *Hydralazine was added*

Admission 3 (May 2016)

Admitted with shortness of breath, angina and oedema. Repeat echocardiography revealed a reduction in LVEF to 29%.

On this occasion the patient failed to respond to IV furosemide. His management was complicated by hypotension, low urine output and acute kidney injury. He developed cardio-renal syndrome resistant to IV diuresis, requiring admission to ITU for dobutamine and haemofiltration.

Despite optimal medical therapy the patient's deteriorating cardiac function left him severely symptomatic and largely bedbound. He was dependent on 24hr IV diuretic therapy. It was felt that, given his young age, the best hope for improvement was cardiac transplant. He was formally assessed by the transplant team, but unfortunately was deemed unsuitable given his history of microvascular diabetic disease.

Cardiac MRI imaging is an invaluable tool in the assessment of cardiomyopathy. Extremely detailed images can be obtained, generating functional and prognostic information on anatomy, global and regional contractility, fibrosis, infiltration, inflammation and perfusion.

At this time his prognosis was extremely poor and a palliative approach was under consideration as being in his best interests. However, according to NICE guidelines, the patient also qualified for Sacubitril/Valsartan (Entresto), a novel therapy for heart failure with reduced ejection fraction.

Sacubitril/Valsartan was commenced on the cardiology ward with extremely positive results. His breathlessness and exercise tolerance improved markedly, albeit slowly. Nevertheless, after four weeks he had improved sufficiently to be medically fit for discharge.

He was discharged on Sacubitril/Valsartan and PRN Metolozone with strict instructions on daily weights and fluid restriction. He was closely followed up in the community by the heart failure specialist nurse.

Following the introduction of Sacubitril/Valsartan, the patient has improved substantially. In contrast to multiple admissions in 2015/16, he has since been admitted only once; a short four day hospitalisation in October 2017. Given he is a relatively young patient with a young family, enabling him to remain independent at home is a significant accomplishment. Although not all patients can expect such profound results, outcomes such as this are encouraging.

Discussion

Heart failure is increasingly common and associated with a substantial morbidity and mortality.

All heart failure patients should be offered education about their condition as well as advice on;

- *Exercise*
- *Smoking*
- *Alcohol*
- *Diet*
- *Depression*
- *Vaccination (pneumococcal and annual influenza)*
- *Cardiovascular comorbidities should be managed in line with NICE guidelines*
- *Driving regulations and air travel*

In heart failure, it is important to establish whether the left ventricular ejection fraction is reduced or preserved.

Unfortunately little evidence is available to support pharmacological or device therapy in heart failure with preserved ejection fraction (HFPEF). In such cases, diuretics are used to control symptoms whilst ACE inhibitors and beta blockers are used in an attempt to prevent progression. Further medication can be introduced at the discretion of a heart failure specialist.

In HFREF (LVEF <50%) there is a stepwise approach to management.

1. First Line

All patients with heart failure, irrespective of ejection fraction, should be started on an ACE inhibitor (ACEi) and beta blocker. Angiotensin II receptor antagonists (ARB) can be used in those patients who are intolerant of ACEi therapy.

Providing these are tolerated, they should be titrated every two weeks to the maximum dose. Blood pressure, heart rate and renal function should be closely monitored during this time. Patients intolerant of ACEi & ARB can instead be started on a combination of hydralazine and nitrate following specialist advice.

ENTRESTO – NEW HOPE IN SEVERE HEART FAILURE

S Hobson, SD Rosen

2. Second Line

In patients with LVEF <35% consider adding an aldosterone antagonist (such as eplerenone). In HFPEF, there is no evidence to support the use of aldosterone antagonists (7). An exception is when heart failure is diagnosed within one month of myocardial infarction, as was the case in this patient. Renal function and serum potassium should be closely monitored following initiation of this therapy.

Other second line treatment options include;

- Addition of an ARB if the patient has mild-moderate heart failure (NYHA II-III). Only certain ARBs are licenced for such usage hence should only be started with specialist advice.

- Addition of Hydralazine in combination with nitrate if the patient has moderate-severe heart failure (NYHA III-IV)

3. Third line:

Ivabradine is recommended for patients with HFREF in sinus rhythm >75bpm who remain symptomatic despite four weeks of optimised first and second line therapy.

Digoxin is recommended for patients with worsening HFREF despite first and second line therapy. Digoxin is particularly beneficial in patients with atrial fibrillation in addition to HFREF.

4. Diuretic therapy is solely for symptomatic relief. This should again be titrated according to symptoms ensuring no deterioration in renal function. Bumetanide has been shown to exhibit improved gut absorption compared to furosemide however, this has failed to translate into improved clinical outcomes (1).

5. Although this patient was not currently suitable, the next step in heart failure management is implantable device therapy. Devices are limited to those patients with severe reductions in ejection fraction in combination with a prolonged QRS and/or risk of sudden cardiac death. Discussion of device therapy is beyond the scope of this article (8).

It has been shown to reduce death and hospitalisation in patients compared to ARB therapy alone. ACEi/ARB should not be prescribed in conjunction with Sacubitril/Valsartan. Side effects include hypotension and renal impairment therefore close monitoring is required.

Sacubitril/Valsartan (Entresto)

Following the publication of the PARADIGM-HF trial in September 2014, NICE approved the use of Sacubitril/Valsartan for patients with LVEF <35% and moderate-severe symptoms despite a stable dose of ACEi/ARB. Sacubitril/Valsartan is now included under second line therapies.

Entresto is the brand name for Sacubitril/valsartan, a combination therapy consisting of a neprilysin-inhibitor and ARB. Inhibition of neprilysin prevents the breakdown of BNP and ANP, thereby counteracting the neurohormonal over-activation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling in heart failure (5).

Another significant but often overlooked intervention in heart failure is the impact of a community heart failure specialist nurse. Specialist nurse input can help to encourage lifestyle modifications and compliance with medication. This has been shown to reduce hospital admission rates and length of stay.

Case Evaluation

This case typifies a patient with moderate to severe HFREF. Patients will typically have multiple admissions with a 5 year mortality rate of 50%6. In particular, a poorer prognosis is observed in heart failure secondary to coronary ischaemia and with a greater reduction in ejection fraction.

With the introduction of newer agents such as Sacubitril/Valsartan, hopefully more patients with severe heart failure can continue to live in the community benefitting from an improved quality of life.

Questions

1. What vaccinations should patients with heart failure receive?

a. No regular vaccination regime is recommended
b. Annual influenza
c. Hepatitis B
d. Pneumococcus and annual influenza
e. Meningococcus, pneumococcus, haemophilus

2. Which drugs are recommended for the treatment of HFPEF?

a. None
b. Diuretics
c. ACE inhibitors
d. Beta Blockers
e. All of the above

3. What is the role of neprilysin?

a. Aldosterone antagonist
b. Blocks the effect of ADH in the collecting duct
c. Reduces levels of circulating BNP
d. Increases venous return to the right atrium
e. Reduces afterload therefore reducing the 'work' of the heart

4. Why is bumetanide often preferred ahead of furosemide?

a. Cost-effective
b. Does not cause hypotension
c. Improved intestinal absorption
d. Does not affect electrolytes
e. Once daily dosage

ENTRESTO – NEW HOPE IN SEVERE HEART FAILURE

S Hobson, SD Rosen

5. Which of the below is a contraindication to Ivabradine therapy?

a. Atrial Fibrillation
b. Sinus tachycardia
c. Sacubitril/Valsartan
d. Severely impaired LVEF
e. Long term beta-blockade

Answers

1. (d)
Patients with heart failure should receive a pneumococcal vaccination and an annual influenza vaccine. With regards to the pneumococcal vaccination, adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years.

2. (e)
Although there is no trial data to support any specific pharmacological or device therapy in heart failure with preserved ejection fraction (HFPEF), NICE recommends that ACE inhibitors and beta blockers can be used in an attempt to prevent disease progression. Diuretic therapy can also be used to manage symptoms. Further medication can be introduced at the discretion of a heart failure specialist.

3. (c)
Neprilysin is a neutral endopeptidase which degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin therefore increases the levels of these substances, countering the neurohormonal over activation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling. In the PARADIGM trial, combined inhibition of the renin–angiotensin system and neprilysin had beneficial outcomes that were superior to those of either approach alone in experimental studies.

4. (c)
Studies have shown that, in both CHF and normal subjects, more bumetanide than furosemide was absorbed from the gut into the circulation. However, this has failed to translate into improved clinical outcomes

5. (a)
Ivabradine is a class of anti-anginal drug which works by reducing the heart rate. It acts on the If ('funny') ion current which is highly expressed in the sinoatrial node, reducing cardiac pacemaker activity. Adverse effects include visual effects (particularly luminous phenomena are common), headache and bradycardia. The criteria for Ivabradine stipulates that the patient is already on suitable first and second line therapy, is in sinus rhythm with a heart rate > 75bpm and left ventricular fraction < 35%. Sacubitril/Valsartan is now included in second line therapies for chronic heart failure.

Authors

Dr Stuart D Rosen
Consultant Cardiologist
Ealing Hospital
London NW University Healthcare NHS Trust
stuart.rosen@nhs.net

Dr Simon Hobson
FY2 Doctor
Ealing Hospital
London NW University Healthcare NHS Trust

Corresponding Author

Dr Simon Hobson
simon.hobson@nhs.net

References

(1) Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney Int. 1984 Aug: 26(2): 183-9. https://www.ncbi.nlm.nih.gov/pubmed/6503136
(2) NICE clinical Guideline (CG108). Chronic heart failure in adults :management. Published August 2010. Accessed 14/12/17. https://www.nice.org.uk/guidance/cg108/chapter/1-Guidance#treating-heart-failure
(3) NICE Pathways. Chest pain. Accessed 16/12/17. https://pathways.nice.org.uk/pathways/chest-pain#path=view%3A/pathways/chest-pain/managing-stable-angina.xml&content=view-node%3Anodes-drugs-for-treating-stable-angina
(4) NICE Pathways. Chronic heart failure. Accessed 16/12/17. https://pathways.nice.org.uk/pathways/chronic-heart-failure#path=view%3A/pathways/chronic-heart-failure/treating-chronic-heart-failure-due-to-left-ventricular-systolic-dysfunction.xml&content=view-node%3Anodes-ivabradine
(5) McMurray JJV, et al. Angiotensin-Neprilysin Inhibition versus Enalapirl in Heart Failure: PARADIGM-HF Trial. NEJM. 17/9/2014. http://www.nejm.org/doi/full/10.1056/NEJMoa1409077#t=article
(6) NICE Clinical Knowledge Summaries: Heart failure – chronic. Published 1/3/16. Accessed 18/12/17. https://cks.nice.org.uk/heart-failure-chronic#!backgroundsub:3
(7) Pitt B, et al. The Effect of Spironolactone on Morbidity and Mortality in patients with Severe Heart Failure: RALES trial. NEJM. 2/9/1999. http://www.nejm.org/doi/full/10.1056/NEJM199909023411001#t=article
(8) Device therapies, NICE Pathways. Chronic heart failure. Accessed 18/12/17. https://pathways.nice.org.uk/pathways/chronic-heart-failure#path=view%3A/pathways/chronic-heart-failure/treating-chronic-heart-failure-due-to-left-ventricular-systolic-dysfunction.xml&content=view-node%3Anodes-implantable-devices

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"**(https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

MANAGING RECURRENT POLYMORPHIC VENTRICULAR TACHYCARDIA

J Hooper, S Arya

Abstract

Cardiac arrhythmias are a common medical presentation and in particular ventricular tachycardia (VT) can result in cardiovascular collapse. Torsades de pointes (TdP) is a specific form of polymorphic VT in patients with a long QT interval requiring prompt recognition and specific treatment. Many junior doctors fear being the first clinician on the scene in this type of emergency. This article covers a real clinical case, with some diagnostic difficulties and guides the reader through basic management in a safe and methodical manner.

Case History

A 72-year-old female presented with a painful knee after an unwitnessed collapse with loss of consciousness. Plain X-ray of the knee confirmed a tibial plateau fracture. Whilst returning from the X-ray department she had a further episode of syncope. She was urgently transferred to the emergency room and connected to a heart monitor showing polymorphic VT.

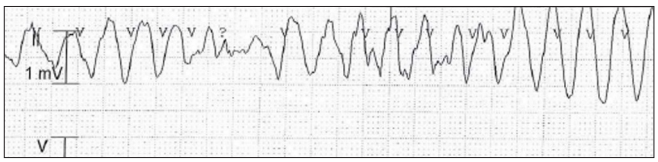


Figure 1: Rhythm strip showing typical Torsades de Pointes.

Rapid assessment revealed the following:

A: patent, oxygen saturation 95% on room air, trachea central

B: respiratory rate 22/min, chest clear

C: BP 100/60 mmHg, HR 260 bpm, capillary refill >4 s, clammy

D: GCS 15, BM 6

E: no evidence of head injury, abdomen soft non-tender, swollen right knee

Initial management involved oxygen, intravenous (IV) fluids and urgent magnesium infusion. As the magnesium was being prepared, the patient's blood pressure (BP) became unrecordable, and the carotid pulse was not palpable.

Cardiac arrest was confirmed, and immediate defibrillation was successful in restoring spontaneous circulation. A post-defibrillation 12-lead electrocardiogram (ECG) showed a broad-complex tachycardia (BCT) with left-bundle branch (LBBB) morphology.

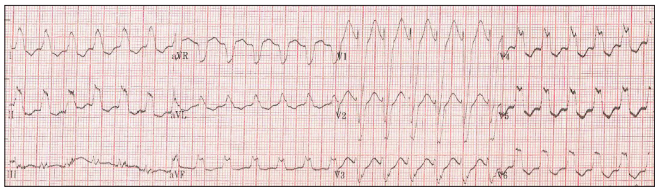


Figure 2: Broad complex tachycardia with LBBB morphology.

Supraventricular tachycardia (SVT) with aberrancy is a differential, but in this clinical context the BCT was considered most likely to be monomorphic VT (additionally, transient fusion and capture beats to support this were seen on the monitor).

Although the BP was stable, the patient was clammy and symptomatic with chest pain, palpitations and shortness of breath. Therefore, urgent electrical cardioversion under sedation was performed. This was successful in restoring sinus rhythm.

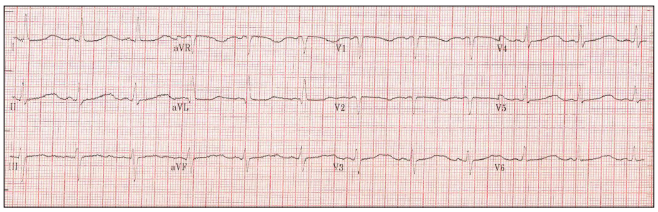


Figure 3: Sinus Rhythm.

Bloods were sent for full blood count, urea and electrolytes, magnesium, calcium, troponin and thyroid function. Chest X-ray was unremarkable. Once the patient was stabilised, further questioning revealed a past medical history of splenectomy, pulmonary sarcoidosis and a 10-month history of recurrent, unexplained syncope for which cardiology referral had been made.

Medications included amitriptyline 10 mg ON, hydroxychloroquine 200 mg OD, prednisolone 10 mg OD. There was no significant family history of note, in particular no sudden cardiac death. The patient was a non-smoker, teetotal, independently mobile and lived with family.

A repeat ECG on admission to the Coronary Care Unit (CCU), showed sinus rhythm with a progressively lengthening QT interval. Given the history of both monomorphic and polymorphic VT, in the context of prolonged QT interval, continuous cardiac monitoring and close monitoring of electrolytes was needed.

MANAGING RECURRENT POLYMORPHIC VENTRICULAR TACHYCARDIA

J Hooper, S Arya

Initial blood tests were as follows: magnesium 0.92 mmol/L, potassium 4.8 mmol/L and adjusted calcium 2.2 mmol/L. Target levels for magnesium and potassium were set at >1 mmol/L and >4 mmol/L respectively.

Several hours later, the QT interval was 770 ms on a repeat and the patient subsequently went back into polymorphic VT, (TdP) requiring 7 shocks to restore sinus rhythm. An isoprenaline infusion was commenced at 2mcg/minute to maintain a target heart rate (HR) of 90-100 bpm. Further episodes of refractory polymorphic VT occurred after the patient underwent surgery for her tibial fracture. This was treated with a combination of defibrillation, IV magnesium and further isoprenaline infusion.

Subsequent cardiac catheterisation revealed normal coronary arteries excluding an ischaemic aetiology. Initial echocardiography also showed normal LV function. Following recovery from orthopaedic surgery, an implantable cardiac defibrillator was inserted, and the patient was later discharged from hospital.

Discussion

This is a case of recurrent unstable VT in the context of a significantly prolonged QT interval. The patient's history of repeated blackouts is a clue that this presentation of VT is not an isolated event, but rather an acute presentation in a patient with a clear tendency to this condition.

The patient has a prolonged QT interval, a known trigger for polymorphic VT. A prolonged QT interval can be caused by drugs, electrolyte imbalance, genetic mutations or diseases affecting the cardiac conduction system.

Our patient was taking two medications known to prolong the QT interval: hydroxychloroquine and amitriptyline, which were stopped during the admission. Additionally, a historical ECG from 10 years prior, predating the prescription of these medications, was obtained demonstrating a prolonged QT interval.

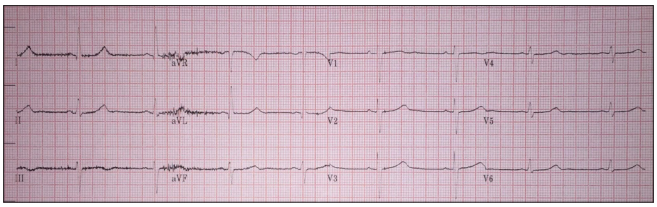


Figure 4: Historical ECG.

Therefore, in this specific case the differential diagnosis includes a congenital long QT syndrome, acquired long QT interval due to medications (hydroxychloroquine and amitriptyline), cardiac sarcoidosis with involvement of the conduction system - or most likely a combination.

How and when to call the registrar

Upon finding any patient with haemodynamically unstable VT (eg. Systolic BP <90 mmHg, chest pain, syncope, heart failure) - this should be treated as a medical emergency and a peri-arrest call for the resuscitation team should be made.1 If the patient is breathing with palpable pulses, then assess using the ABCDE method and obtain a 12-lead ECG. If cardiac arrest is confirmed, commence cardio-pulmonary resuscitation (CPR) whilst awaiting help. (1)

What will my registrar want to know?

In an emergency, keep it simple and be concise. Age, reason for admission, heart rhythm and observations (HR/BP/oxygen saturations) are all that is needed in the first instance.

"I'm Dr Jones from Ward 7, patient X, 72 years old, presented with collapse, has gone into VT 5 minutes ago, BP 60/40, HR 260, airway maintained. I've put out the arrest call but I need you to come urgently"

This is sometimes done in the SBAR format: Situation, Background, Assessment, Recommendation. In a more stable patient, you will have more time to obtain the latest blood results, send a repeat sample for electrolytes (+/- thyroid function/troponin) and find out the patient's recent history, including current medications.

First steps if the registrar is unavailable:

1. Assess the patient from A to E.

2. Connect to cardiac monitor.

3. Stabilise the patient and correct abnormalities: oxygen for hypoxia, IV fluid and leg elevation for hypotension and treat electrolyte abnormality.

4. Perform continuous BP monitoring and repeat ECG.

5. Review the medication chart.

6. Consider performing a chest X-ray.

A shocked patient with VT requires urgent electrical cardioversion under sedation (if not already there, you will need to fast bleep the anaesthetist). (1)

MANAGING RECURRENT POLYMORPHIC VENTRICULAR TACHYCARDIA

J Hooper, S Arya

MCQs

1: Treatment of polymorphic VT in patients with long QT interval (TdP) includes:

a) Beta-blockers

b) Amiodarone

c) Magnesium

d) Isoprenaline

e) Flecainide

2: A patient on CCU complains of central chest pain, day 2 post NSTEMI. The cardiac monitor shows sustained monomorphic VT. Observations are HR 300 bpm, BP 60/40 mmHg. What is the next most appropriate step:

a) IV fluids

b) Morphine

c) Amiodarone

d) Electrical cardioversion

e) CPR and defibrillation

Answers

1. Answer C

The management of polymorphic VT primarily involves an IV bolus of 2g Magnesium. As with any unstable arrhythmia, if the BP is persistently less than 90 mmHg, urgent electrical cardioversion is required. In refractory cases, lidocaine or isoprenaline infusions may be required – and if these do not work then overdrive pacing with a temporary pacing wire usually at a rate of 100 bpm to prevent any pauses will almost always work (transcutaneous pacing is fine for temporary relief as a bridge to transvenous pacing).

Importantly, amiodarone is possibly harmful by prolonging the QT interval. Similarly, beta-blockers should be avoided unless the patient carries a diagnosis of congenital long QT syndrome or if catecholaminergic polymorphic VT (which has a normal QT interval) is suspected e.g. in the setting of onset during physical activity, acute emotional stress or pyrexia.

2. Answer: D

Management of haemodynamically stable monomorphic VT with a pulse is typically IV amiodarone. However, management of haemodynamically unstable VT is urgent electrical DC cardioversion. Pulseless VT should be treated as per the advanced life support (ALS) algorithm, with good quality CPR and early defibrillation. (1)

Authors

J Hooper

Corresponding Author

S Arya

References

1. Nolan J, Soar J, Hampshire S eds. Advanced Life Support, 7th edition. London: Resuscitation Council (UK) 2016.

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

TO PACE OR NOT TO PACE… PAUSES IN NEURALLY-MEDIATED SYNCOPE

D Ahlert, A Mitchell

Abstract

Neurally-mediated syncope (NMS) is common and comprises a group of conditions including reflex syncope, vasovagal syncope, situational syncope, carotid sinus syncope and atypical forms of syncope where the trigger is not apparent. We describe a case of NMS in a 25-year-old female patient with significant cardioinhibitory response demonstrated on electrocardiogram monitoring. We discuss the diagnostic and management challenges including the role of medication and permanent pacemaker implantation.

Keywords: S*yncope, neurally-mediated syncope, asystole, pacemaker.*

T-LOC

Transient loss of consciousness (T-LOC) is a common acute medical presentation with many possible causes. Syncope is a type of T-LOC characterised by global cerebral hypoperfusion (1). Neurally-mediated syncope (NMS) is common and comprises a group of conditions including reflex syncope, vasovagal syncope, situational syncope, carotid sinus syncope and "atypical" forms of syncope where the trigger is not apparent (2).

Patient

A 25-year-old female presented to the emergency department after three collapses at home over a period of 12 hours. One of these episodes resulted in a head injury. Each collapse was preceded by symptoms of nausea and sweating and one with an episode of vomiting.

A witness explained that she collapsed with little warning, would lye still and had her eyes open. Recovery was quick and full. On presentation to hospital, her observations and clinical examination were normal, the electrocardiogram (ECG) showed normal sinus rhythm with no bradycardia and baseline blood tests including thyroid hormone levels were normal.

She was treated with intravenous fluids and a computed tomography head scan was performed which was normal. The patient was discharged home with advice to stay hydrated and referred to the specialist nurse led T-LOC clinic. Over the following two weeks she had several episodes of T-LOC, mostly occurring at rest when lying down and sitting, and usually associated with nausea.

Clinic

The patient was reviewed in the specialist nurse-led T-LOC clinic. The patient did not have any significant past medical history and there was no history of epilepsy or loss of consciousness prior to the above events. She did not take any medications, consumed minimal alcohol and was a never smoker and denied the use of illicit substances.

She was able to exercise to exhaustion without any undue symptoms. There was no family history of cardiac events or deaths. The only potentially significant detail was that she had been made unexpectedly redundant two days prior to the onset of the events. The clinical examination and ECG were normal.

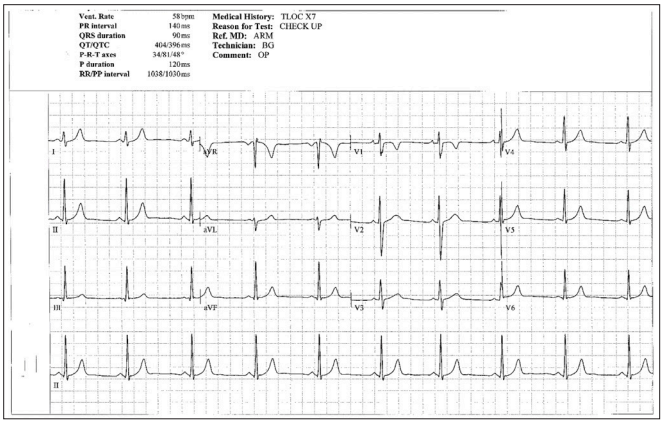


Figure 1: Resting 12 lead ECG.

ECG monitoring

Urgent prolonged heart rhythm monitoring was recommended and the patient was sent home with a seven-day ECG monitor. Over the following days the patient had two episodes of syncope that were associated with sinus pauses (23.4 seconds and 29.5 seconds).

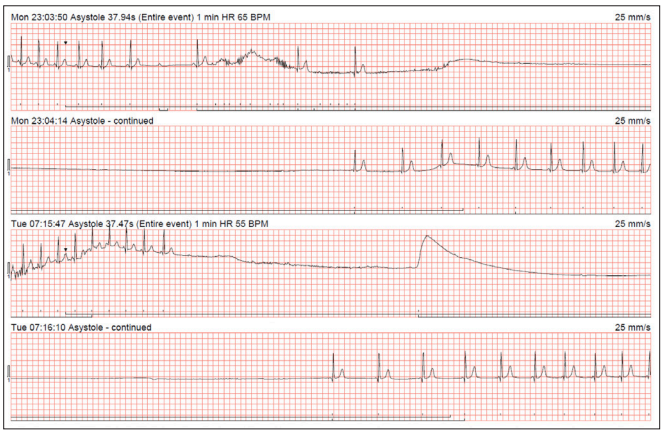


Figure 2: Holter ECG monitoring during events of loss of consciousness.

TO PACE OR NOT TO PACE... PAUSES IN NEURALLY-MEDIATED SYNCOPE

D Ahlert, A Mitchell

One episode occurred at 11pm during the night and the other at 7am. The first event was preceded by significant nausea and T-LOC with no injuries. During the second event the patient experienced significant confusion and sweating upon waking in the morning. Inspection of the ECG showed periods of sinus rate acceleration before bradycardia.

The patient was contacted and reviewed on the ward. Echocardiography revealed no structural heart disease. The patient was diagnosed with neurally mediated syncope with a marked cardioinhibitory response. A trial of Fludrocortisone 100 micrograms per day was recommended. Advice was given to avoid driving, to reduce the risk of hypotension with adequate and regular hydration and to recognise warning signs.

Follow-up

The patient was closely followed up in the T-LOC clinic and pharmacological therapies were discussed. A tilt table test was conducted off medication looking for evidence of a vasopressor response but this was negative after 45 minutes of head-up tilt.

The patient had a further cluster of episodes of syncope and given the significant impact of these on the patient's quality of life, a pacemaker was offered. The patient declined this and since then has remained free of syncope on no medical therapy and with a good quality of life.

Discussion

Syncope is defined as a transient loss of consciousness caused by inadequate cerebral blood flow (1), and has to be differentiated from other causes of T-LOC, including epileptic seizures, hypoglycaemia, metabolic disorders, intoxication and concussion due to trauma. Most of these can quickly be ruled in or out during assessment with a good history, examination and baseline investigations. A thorough patient and witness history including events before, during and after the episode (2-4) is essential.

Syncope can be further separated into NMS and cardiac syncope. Autonomic features such as nausea, sweating, pallor and fatigue post syncope suggest NMS, which is thought to be a benign cause with peak incidence in young adults (4). Cardiac syncope is a major risk factor for sudden death and bears a worse prognosis than NMS (5).

Echocardiography and ECG are recommended to exclude structural heart disease including valvular disease, systolic dysfunction and cardiomyopathy (2). Deep T-wave inversion in the pre-cordial leads (cardiomyopathy), a Brugada pattern ECG, QT interval changes and the presence of a delta wave should all prompt cardiology review (6, 7). Advanced second and third degree heart block qualify for permanent pacemaker implantation (4).

The seven-day ECG monitoring in our patient showed two significant sinus pauses associated with syncopal events. Sinus node dysfunction in more common in older patients due to fibrosis of the sinus node (sick sinus syndrome), however in younger patients, with no evidence of structural or congenital heart disease it is most likely due to increased vagal tone (neurally mediated).

Syncope through increased vagal parasympathetic signals can be mediated by orthostatic or psychological stress (vasovagal), coughing, sneezing and post exercise (situational) and vasodilation and bradycardia mediated by the carotid sinuses (carotid sinus syncope) (2, 4). The negative tilt table test supports that orthostatic stress was not the prime mechanism for the patient's syncope.

The main form of treatment of NMS is patient education and reassurance and advice to avoid known triggers such as dehydration. It is important as a discharging doctor to ensure that the correct advice on driving is given as per Driver and Vehicle Licensing Agency (8).

The mineralocorticoid fludrocortisone works by increasing water retention, and has been shown to be effective in small trials for patients with autonomic orthostatic hypotension (9, 10). Beta blockers reduce the ventricular contraction and the mechanoreceptor stimulation which are believed to be involved in the mechanism of NMS (10). SSRIs have been proposed in NMS as they may be blunting a serotonin surge observed prior to syncope (11).

Current evidence base however suggests little or no benefit of using SSRIs or beta blockers versus placebo (12). Midodrine is an alpha-1-agonist, licensed in the UK for the treatment of severe orthostatic hypotension and works similarly to fludrocortisone by increasing blood pressure (13). Overall, a Cochrane review concluded in 2011 that there is insufficient evidence to recommend any specific pharmacological therapy for neurally mediated syncope (14).

A pacemaker is often thought to be the obvious choice of treatment for significant bradycardia or pauses yet this depends on the nature of the arrhythmia (15). Whilst atrioventricular block or sinus node dysfunction is likely to progress, NMS has been demonstrated to be a benign condition that is usually self-limiting, especially in young patients. Assuming this this condition is self-terminating, a permanent pacemaker may not be the ideal treatment for NMS.

TO PACE OR NOT TO PACE... PAUSES IN NEURALLY-MEDIATED SYNCOPE

D Ahlert, A Mitchell

Short term complications of pacemaker implantation are mostly related to vascular access (pneumothorax), the generator (pocket haematoma or infection), and leads (displacement, infection, thrombosis) with a complication rate of 4.2-7.5% (16-18).

Large studies of long term complications of pacemaker implantation in young patients have been conducted in populations with congenital heart disease. In a 12 year follow up of adults with congenital heart disease and implantation at a relatively young age, long term complications requiring intervention were reported in over one-third (19).

The same authors found that an independent predictor of late-pacemaker related complications was a young age at insertion. A similar lead related complication rate (27%) has been shown in a further study which followed up patients for 11 years (20). Furthermore, pacemaker batteries are expected to last up to 10 years, so a patient in their mid-twenties who receives a pacemaker, might potentially expect five or more repeat operations in their lifetime to change the generator, each with associated complication risks.

Due to the multifactorial aetiology of NMS, a further risk of pacemaker therapy is that symptoms will not resolve and syncope will continue despite pacing. This is often due to the profound vasopressor hypotensive response that can occur with NMS. So even though the pacemaker is providing a heart rhythm, there is little blood pressure to maintain cerebral circulation. A long term follow up study in a Danish population of over 1400 patients showed an incidence of syncope of 21.1%, eight years post pacing (21).

In a group of patients with neurally mediated syncope and documented sinus pauses, a randomized study of pacing vs no pacing (ISSUE-3) found a two year syncope recurrence rate of 25% despite pacing (22). Pacemaker implantation however in this group can prolong prodrome symptoms so that patients get a longer warning to sit or lie down and avoid injury.

Conclusions

T-LOC is common and a thorough clinical assessment of the patient is essential as is a good collateral history from witnesses. NMS should be a diagnosis of exclusion, is often benign but can have a significant impact on a patient's life. Management can be complex and often unsatisfactory with ongoing symptoms in spite of medical therapy. Pacemaker implantation in young patients should not be first line therapy as the long-term implications of device implantation are substantial.

Multiple choice questions

1) Which of these presentations most fits neurally mediated syncope (NMS)?

A) Collapse of a 70-year-old heavy smoker, preceded by central chest pain and nausea.

B) Collapse of a 29-year-old male in the street at 2am following a physical altercation with another person.

C) First collapse of a 55-year-old female with a new mass on CT brain imaging.

D) Collapse of a 21-year-old female nurse in the morning at work. She missed breakfast and co-workers noticed seconds of 'limb shaking'.

E) Collapse of a 21-year-old male during exercising. He reports his brother died suddenly of an unknown cause a few years ago.

2) Which of the answers below are treatments for NMS?

A) Midodrine

B) Permanent Pacemaker

C) Beta Blocker

D) Reassurance

E) All of the above

3) Which of these ECG findings are not an indication for permanent pacemaker insertion?

A) Second degree heart block with associated syncope.

B) Third degree heart block without syncope

C) Bifascicular block with associated syncope

D) Sinus bradycardia rate 29, with frequent syncope and pre-syncopal symptoms, no reversible factors.

E) Sinus pause of 2 seconds with syncope

TO PACE OR NOT TO PACE... PAUSES IN NEURALLY-MEDIATED SYNCOPE

D Ahlert, A Mitchell

4) A 51 year old patient presents for review in the T-LOC clinic. For the last 4 months, he loses consciousness on average once a month with little warning from standing, one episode was associated with a head injury. He recovers quickly from those episodes.

He no longer drives. Resting ECG, echocardiogram and 24h Holter ECG monitoring were all normal. Lying and standing blood pressure was normal. He has no significant past medical history and does not take any medications. As episodes are ongoing, which is the optimal choice of management?

A) Trial of fludrocortisone 100 micrograms OD.

B) Implantable loop recorder

C) Seven day Holter monitoring

D) Re-assurance

E) Permanent pacemaker

5) How frequently on average does a pacemaker generator need to be replaced?

A) Every year

B) Every one to five years

C) Every five to ten years

D) Every 10 to 20 years

E) Over 20 years

Answers

1. Answer: D

NMS is most common in young patients and in most cases is mediated by orthostatic stress. In this case dehydration and standing for extended periods of time may be a factor. Whilst movement of limbs may be a feature of a clonic seizure, a brief period is also common in syncope.

Answer A is suspicious of an ischaemic event with associated arrhythmia, in answer B alcohol and a head injury needs to be ruled out. In answer C a seizure is likely cause for the collapse due to the brain mass and in answer E the family history of sudden death is suspicious of an inherited cardiac cause of syncope. Collapse during exertion may be linked to a sinister cause, as with NMS the loss of consciousness is likely to occur at rest post exercise.

2. Answer: E

Midodrine is an alpha-1-agonist, used to increase blood pressure in syncope caused by orthostatic hypotension. A pacemaker can be used to treat the severe cases of NMS with a significant cardioinhibitory pathology (most often carotid sinus hypersensitivity).

Beta blockers have been used to treat vasovagal syncope and varying efficacy is described in the literature. Re-assurance and explanation are often sufficient, especially if the patient understands to avoid activities that cause symptoms and recognise warning signs.

3. Answer: E

In an older patient with no reversible cause this may be due to intrinsic sinus node disease. Whilst not physiologically "normal", pauses of 2 seconds may occur in neurally mediated syncope which can be seen as extrinsic sinus node dysfunction. All the other answers will likely lead to pacing.

4. Answer: B

In this example, the aetiology of loss of consciousness is not known and investigations were normal. An arrhythmia cannot be excluded and episodes occur so rarely that even seven day Holter ECG monitoring would not be likely to capture an episode. This is likely to have a significant impact on the patient's quality of life so an implantable loop recorder is reasonable.

This is a small device implanted under the patient's skin that constantly monitors the rhythm for approximately three years until the battery runs out. Fludrocortisone is unlikely to be beneficial as no blood pressure deficit has been documented and episodes are rare. Re-assurance cannot be safely given as serious causes (i.e. an arrhythmia) have not been ruled out. There is not enough evidence that warrants permanent pacemaker implantation.

5. Answer: D

The battery of a permanent pacemaker generator has a limited lifespan that differs depending on how much the patient relies on pacing to maintain a minimum heart rate. On average pacemaker batteries last five to 10 years, at which point the patient will be invited for a "box change" which is a surgical procedure where the old generator is exchanged with a new one.

TO PACE OR NOT TO PACE... PAUSES IN NEURALLY-MEDIATED SYNCOPE

D Ahlert, A Mitchell

Authors

Dr Daniel Ahlert
Clinical Fellow Cardiology
Jersey General Hospital
The Parade
St Helier
Jersey
JE1 3QS

Dr Andrew Mitchell
Consultant Cardiologist
Jersey General Hospital
The Parade
St Helier
Jersey
JE1 3QS
an.mitchell@health.gov.je

Corresponding Author

Dr Daniel Ahlert
d.ahlert@gmail.com

References

1. Benditt D. Syncope in adults: Clinical manifestations and diagnostic evaluation 2017 [updated August 2017. Available from: https://www.uptodate.com/contents/syncope-in-adults-clinical-manifestations-and-diagnostic-evaluation?source=search_result&search=syncope&selectedTitle=1~150.]

2. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). European Heart Journal. 2009;30(21):2631-71.

3. National Institute for Health and Care Excellence. Transient loss of consciousness ('blackouts') in over 16s [CG109] 2010 [updated August 2010. Available from: https://www.nice.org.uk/guidance/cg109.]

4. Shen W-K, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. Circulation. 2017.

5. Iacovino JR. Mortality outcomes of various causes of syncope. Journal of insurance medicine (New York, NY). 2004;36(1):4-9.

6. Arnar DO. Syncope in patients with structural heart disease. Journal of internal medicine. 2013;273(4):336-44.

7. Maisel WH, Stevenson WG. Syncope — getting to the heart of the matter. New England Journal of Medicine. 2002;347(12):931-3.

8. Driver and Vehicle Licensing Agency. Assessing fitness to drive: guide for medical professionals. 2016 11 March 2016.

9. National Institute for Health and Care Excellence. Postural hypotension in adults: fludrocortisone Evidence summary [ESUOM20] 2013 [Available from: https://www.nice.org.uk/advice/esuom20/chapter/Key-points-from-the-evidence.]

10. Kaufmann H, Freeman R. Pharmacological treatment of reflex syncope. Clinical autonomic research: official journal of the Clinical Autonomic Research Society. 2004;14 Suppl 1:71-5.

11. Samoil D, Grubb BP. Neurally mediated syncope and serotonin reuptake inhibitors. Clinical Autonomic Research. 1995;5(5):251-5.

12. Theodorakis GN, Leftheriotis D, Livanis EG, Flevari P, Karabela G, Aggelopoulou N, et al. Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2006;8(3):193-8.

13. Anwar AS, Saeed Y, Zaki A, Petkar S, Collitt S, Rice N, et al. Midodrine is safe and effective in the treatment of reflex syncope. British Journal of Cardiology. 2016;23(2):73-7.

14. Romme JJCM, Reitsma JB, Black CN, Colman N, Scholten RJPM, Wieling W, et al. Drugs and pacemakers for vasovagal, carotid sinus and situational syncope. Cochrane Database of Systematic Reviews. 2011(10).

15. Cunningham D, Cunningham M, Donkor A, Linker N, Murgatroyd F. National Audit of Cardiac Rhythm Management Devices University College. National audit of cardiac rhythm management devices. National Institute of Cardiovascular Outcomes Research, University College London. 2016; [Available from: https://www.ucl.ac.uk/nicor/audits/cardiacrhythm/documents/annual-reports/crm-devices-national-audit-report-2015-16.]

16. Link MS, Estes NAM, Griffin JJ, Wang PJ, Maloney JD, Kirchhoffer JB, et al. Complications of dual chamber pacemaker implantation in the elderly. Journal of Interventional Cardiac Electrophysiology. 1998;2(2):175-9.

17. Tobin K, Stewart J, Westveer D, Frumin H. Acute complications of permanent pacemaker implantation: their financial implication and relation to volume and operator experience. American Journal of Cardiology.85(6):774-6.

18. Bond R, Augustine D, Dayer M. Pacemaker complications in a district general hospital. The British Journal of Cardiology. 2012;19:90-4. 90-4 p.

19. Opic P, van Kranenburg M, Yap S-C, Van Dijk A, Budts W, W Vliegen H, et al. Complications of pacemaker therapy in adults with congenital heart disease: A multicenter study. 2013;168(4):3212-6.

20. Walker F, Siu SC, Woods S, Cameron DA, Webb GD, Harris L. Long-Term outcomes of cardiac pacing in adults with congenital heart disease. Journal of the American College of Cardiology. 2004;43(10):1894-901.

21. Ng Kam Chuen MJ, Kirkfeldt RE, Andersen HR, Nielsen JC. Syncope in paced patients with sick sinus syndrome from the DANPACE trial: incidence, predictors and prognostic implication. Heart. 2014;100(11):842-7.

22. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. Third International Study on Syncope of Uncertain Etiology (ISSUE-3): A Randomized Trial. Circulation. 2012;125(21):2566-71.

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"**(https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

A CASE OF MUSCLE-INVASIVE BLADDER CANCER TREATED WITH CHEMORADIOTHERAPY WITH CURATIVE INTENT

T Young, S Hughes, D Enting

Abstract

A 79 year old male was diagnosed with non-metastatic muscle-invasive bladder cancer, after presenting with haematuria. He was treated with neoadjuvant chemotherapy, before undergoing definitive treatment with chemoradiotherapy.

He currently has no evidence of disease recurrence 11 months after treatment completion. In this article we discuss the importance of the specialist multidisciplinary team in appropriately investigating, staging, and managing this patient's disease. We also explore the rationale for bladder-preservation in this particular patient as well as specific issues presented by his treatment.

Case History

A 79 year old male initially presented to his General Practitioner with worsening frank haematuria. Examination was unremarkable. He was referred to his local hospital's one-stop haematuria clinic under the 'two week wait' rule. His past medical history consisted of previous colorectal cancer in 2010 (treated with a left hemicolectomy and 8 cycles of adjuvant capecitabine), as well as hypothyroidism, benign prostatic hyperplasia and glaucoma.

At the one-stop haematuria clinic he underwent clinical assessment and further investigation: flexible cystoscopy showed a suspicious bladder lesion; Computurised Tomography (CT) demonstrated a 15mm bladder tumour but no evidence of metastatic disease or cancer in the upper urinary tracts; a subsequent Transurethral Resection of Bladder Tumour (TURBT) revealed the a diagnosis of muscle-invasive bladder cancer, histologically graded/staged as Grade 3 pT2 (at least) urothelial carcinoma with adjacent carcinoma-in-situ (CIS).

Following these initial investigations, the patient was referred to the regional tertiary bladder cancer multidisciplinary meeting (MDM), where a recommendation was made for repeat TURBT to maximise resection and investigate for other areas of CIS, and repeat staging due to 2 month delay between initial CT scan and referral to specialist MDM. Repeat TURBT confirmed persistent Grade 3 pT2 disease but no distant CIS.

Repeat CT scan now showed a T3 tumour (Figure 1) with borderline bilateral lymphadenopathy at the level of the common iliac vessels. To elicit whether these lymph nodes were malignant the patient underwent an FDG Positron Emission Tomography (PET) scan, which revealed no evidence of metastatic disease or lymph node involvement (final staging of T3 N0 M0 disease).

Re-discussion at the bladder cancer MDM led to a recommendation to discuss radical treatment options (neoadjuvant chemotherapy then radical cystoprostatectomy or chemoradiotherapy) with the patient.

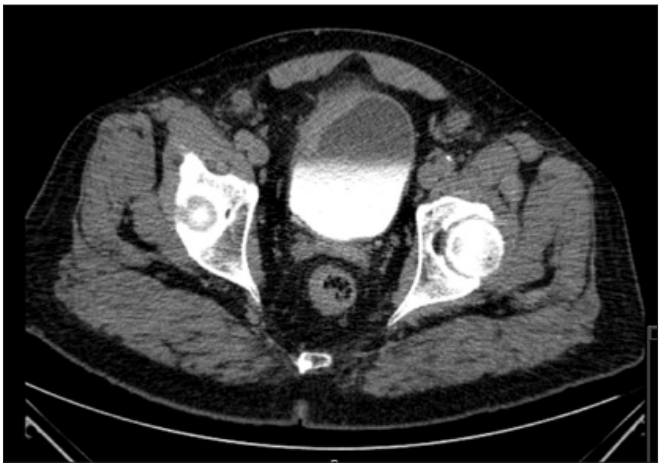


Figure 1: CT axial image of the pelvis showing an anterior / right-sided bladder tumour.

The patient had a Performance Status of 1. He commenced treatment with neoadjuvant gemcitabine and cisplatin chemotherapy at a 25% dose reduction with granulocyte colony stimulating factor (G-CSF) support.

He tolerated chemotherapy well aside from grade 1 diarrhoea and fatigue. He had a planned CT scan after 2 cycles which showed a good response to treatment (and no progression of disease), and therefore he went on to complete his third and final cycle of neoadjuvant chemotherapy.

Upon completion of chemotherapy he consented for radical radiotherapy (64 Gray in 32 Fractions) as definitive treatment for his tumour. Image-guided intensity-modulated radiotherapy (IMRT) was used, with daily cone-beam CT scans on treatment to ensure the internal anatomy matched that of the radiotherapy planning CT scan.

Concomitant with the radiotherapy he received chemotherapy as a radiosensitiser (mitomycin and 5-Fluorouracil). He again tolerated treatment relatively well, apart from grade 1 side effects of dysuria, nocturia and occasional diarrhoea.

A CASE OF MUSCLE-INVASIVE BLADDER CANCER TREATED WITH CHEMORADIOTHERAPY WITH CURATIVE INTENT

T Young, S Hughes, D Enting

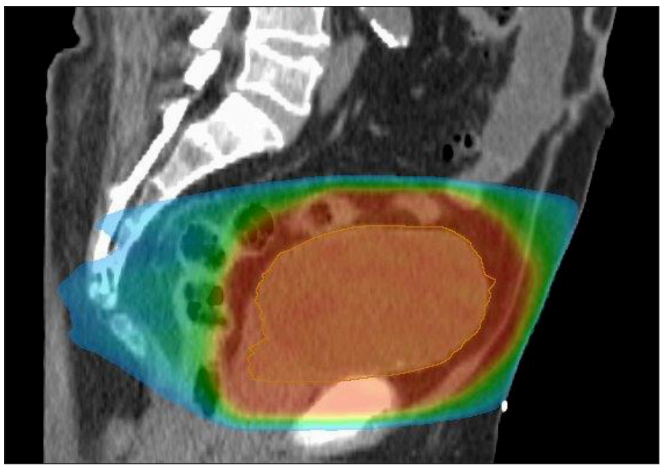


Figure 2: Sagittal midline image of the radiotherapy plan for this patient's bladder cancer. Yellow line denotes clinical target volume (bladder), red area indicates volume receiving planned treatment dose of radiotherapy, green and blue areas indicate areas receiving lower level radiation doses (due to beam entry and exit).

The patient had a CT scan at 12 weeks after treatment completion to assess disease response, which showed no evidence of metastases, but some residual thickening of the bladder wall.

A flexible cystoscopy showed a small sloughy region at the dome and right lateral wall of the bladder, so a TURBT was performed.

Histology from resection of these areas showed radiation changes only, with no evidence of residual malignancy. On review at 6 months after completing treatment, he remained well apart from a degree of residual nocturia.

A further surveillance CT scan at 9 months post-treatment showed no evidence of recurrence, and further flexible cystoscopy again showed no tumour. He is currently 17 months post-diagnosis and remains disease free.

Discussion

The diagnostic work-up of this patient after presentation exemplifies the need for prompt investigation of haematuria in men and women (1). Referral to a one-stop haematuria clinic for further assessment and investigation facilitated rapid access for this patient to key investigations used in both diagnosis and staging of bladder cancer.

As in this case, after clinical assessment patients will typically undergo blood tests, urinalysis, flexible cystoscopy and imaging (most commonly ultrasound) in one visit (2).

Patients aged 45 and over with:

- *Unexplained visible haematuria without urinary tract infection*
- *Visible haematuria persisting after treatment of urinary tract infection*

Patients aged 60 and over with:

- *Unexplained non-visible haematuria and either dysuria or raised white cell count*

Box 1: When to refer patients with haematuria (3)

The role of the tertiary centre bladder cancer MDM was crucial in the staging and management of this patient. The bladder cancer multidisciplinary team consists of urologists, medical oncologists, clinical oncologists, histopathologists, radiologists and specialist nurses all with a specific expertise in bladder cancer, facilitating recommendations tailored to this patient's disease and needs (4).

Here the management options were discussed including whether the patient should have neoadjuvant chemotherapy, and whether cystectomy or radiotherapy would be more appropriate. Repeat TURBT prior to starting chemotherapy was used to debulk the tumour, improving likelihood of local control with radiotherapy and thus allowing preservation of the bladder. Excluding widespread CIS with this repeat TURBT was also important as widespread or distant CIS would have indicated surgery as a preferable treatment option due to high risk of disease recurrence elsewhere in the bladder.

A criticism of this patient's management was the 2 month delay in referral to the bladder cancer MDM. Such delays between different centres are unfortunately not uncommon and can lead to the need for repeat up to date investigations, as in this patient's case where repeat re-staging imaging was required.

A CASE OF MUSCLE-INVASIVE BLADDER CANCER TREATED WITH CHEMORADIOTHERAPY WITH CURATIVE INTENT

T Young, S Hughes, D Enting

Although the cancer treatment target of 62 days (from initial GP '2 week wait' referral under to treatment) is achieved when the patient undergoes TURBT (5), evidence has shown delays of more than 90 days between initial diagnosis and definitive treatment of bladder cancer can be detrimental to survival (6).

PET scanning was used to exclude metastatic or nodal disease, which if found would have significantly altered this patient's management. PET scanning does not have a routine role in determining the management of muscle-invasive bladder cancer but is a useful tool in selected cases such as this where there is uncertainty regarding the staging on conventional imaging (CT / MRI – magnetic resonance imaging), for example questions over possible lymph node involvement (7).

This case demonstrates the importance of careful selection of patients for neoadjuvant chemotherapy and its potential benefits to treat micrometastatic disease. This patient had a good Performance Status (important in selecting patients for neoadjuvant chemotherapy), but it was felt that he required chemotherapy to be given with a dose reduction to improve tolerance (with G-CSF to reduce neutropenic sepsis risk) given his co-morbidities.

Whilst 60-70% patients respond to neoadjuvant chemotherapy, it only increases 5 year survival rates by around 5% for T2-4 disease (8). Currently there are no accepted and validated test that can be performed to predict whether a patient will benefit from neoadjuvant platinum-based chemotherapy or not (9).

Definitive treatment with radiotherapy was favoured as the patient had small volume muscle invasive disease and a preference for bladder-preserving treatment. The patient was also very keen to avoid further surgery given his prior surgical history. Additionally, given the patient's co-morbidities (including multiple previous abdominal operations) radical radiotherapy also reduced the risk of iatrogenic adverse events compared to those potentially posed by surgical morbidity and mortality (10).

The patient received concomitant radiosensitising chemotherapy as per national guidelines (11), which has been demonstrated to provide a survival benefit and improved local control (12). He did experience grade 1 self-limiting urinary and bowel side effects, commonly seen with radical radiotherapy to the bladder (13). An IMRT technique was used to maximize the conformality of the high dose region to the target, whilst minimizing the dose to surrounding normal tissue.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting activities

Grade 3: Severe but not immediately life-threatening; hospitalisation indicated; disabling

Grade 4: Life-threatening consequences requiring urgent intervention

Grade 5: Death

Box 2: When to call the registrar? Grading of radiotherapy and chemotherapy side effects (14)

Despite successful treatment of the patient's bladder cancer, his disease has a high risk of recurrence (particularly within the first 2 years). The overall survival rate at 5 years is approximately 50% (12). He therefore requires careful surveillance. For the first 2 years he will undergo cystoscopy every 3 months and CT scans every 6 months to assess for evidence of local recurrence or metastatic disease, before the intensity of follow-up is reduced.

If this patient were found to have recurrent disease, early detection allows intervention at a time when he is likely to be fit enough to consider further treatment options. Local recurrence within the bladder could be managed with potentially curative salvage cystectomy.

Metastatic disease would be amenable to further treatment with chemotherapy. Recent developments in the oncological management of urothelial carcinoma are paving the way for additional options such as immunotherapy in the second-line setting (15).

- **Frank haematuria in men and women over 45 years old requires prompt referral and investigation via the '2 week wait' pathway.**
- **Timely referral to specialist MDM prevents unnecessary delays in care, which can affect patient outcomes.**
- **Radical radiotherapy is an alternative to surgical resection of bladder cancer as a definitive treatment.**

Box 3: Key learning points

A CASE OF MUSCLE-INVASIVE BLADDER CANCER TREATED WITH CHEMORADIOTHERAPY WITH CURATIVE INTENT

T Young, S Hughes, D Enting

Test Yourself

1) Neoadjuvant chemotherapy is chemotherapy given:

a) Before radiotherapy or surgery

b) During surgery

c) During radiotherapy

d) After surgery

e) After radiotherapy

2) What is the 5 year survival benefit of neoadjuvant platinum-based chemotherapy prior to definitive management of Grade 3 muscle-invasive non-metastatic bladder cancer?

a) No clear evidence

b) 2-3%

c) 5-7%

d) 10-12%

e) 20-22%

3) What percentage of bladder cancer patients present with muscle-invasive disease?

a) 5%

b) 15%

c) 25%

d) 40%

e) 50%

4) Which of the following is not a common site for metastases from muscle-invasive bladder cancer?

a) Brain

b) Lung

c) Liver

d) Bone

e) Pelvis

5) If this patient were found to have new widespread disseminated pulmonary metastases on a future CT scan more than 12 months after initial treatment, what would be the first-line treatment?

a) Re-challenge with platinum-based chemotherapy

b) Vascular Endothelial Growth Factor Inhibitor

c) Surgery

d) Radiotherapy

e) Immunotherapy

Answer

1. Answer: A

Neoadjuvant chemotherapy is chemotherapy given prior to definitive management (16)

2. Answer: C

Clinical trials have shown neoadjuvant platinum-based chemotherapy to have a 5 year survival benefit of around 5% (8)

A CASE OF MUSCLE-INVASIVE BLADDER CANCER TREATED WITH CHEMORADIOTHERAPY WITH CURATIVE INTENT

T Young, S Hughes, D Enting

3. Answer: C

25% of bladder cancer patients present with muscle-invasive disease (16).

4. Answer: A

Although bladder cancer can metastasise to the brain (4-7%), it is a much less common site of disease spread in comparison to the lungs, liver, bone or within the pelvis (16).

5. Answer: A

If the patient was to relapse more than 12 months after previously receiving neoadjuvant gemcitabine and cisplatin chemotherapy, currently re-challenge treatment with platinum-based chemotherapy would be the best first-line option once again (15), particularly in this patient who had a good response in the neoadjuvant setting.

Relapse earlier than 12 months after completing neoadjuvant chemotherapy would suggest disease would be less likely to respond to platinum-based chemotherapy regimens, and therefore second-line options would include taxane-based chemotherapy combinations. Patients should however be offered enrollment in clinical trials where possible to further evaluate new therapies.

Authors

Tom Young
Medical Oncology Clinical Fellow
Guy's Hospital, Great Maze Pond, London, SE1 9RT
thomas.young@gstt.nhs.uk

Simon Hughes
Consultant Clinical Oncologist
Guy's Hospital, Great Maze Pond, London, SE1 9RT
simon.hughes@gstt.nhs.uk

Deborah Enting
Consultant Medical Oncologist
Guy's Hospital, Great Maze Pond, London, SE1 9RT
deborah.enting@gstt.nhs.uk

References

1. Marzouk S, Lamb BW, Harris A, et al. A retrospective cohort study of patients diagnosed with bladder cancer referred with visible haematuria: the impact of source of referral on prognostic indicators. Journal of Clinical Urology 2014;7(6): 384-388.
2. Guy's and St Thomas' NHS Foundation Trust. Urology One-Stop Clinic. Available from: https://www.guysandstthomas.nhs.uk/resources/patient-information/urology/clinics/urology-one-stop-clinic2014(FINAL).pdf [Accessed 1st January 2018].
3. British Association of Urological Surgeons. NICE Guideline Suspected Cancer: Recognition & Referral June 2015 Haematuria guidelines. Available from: https://www.baus.org.uk/_userfiles/pages/files/Publications/BAUS%20Cancer%20Guidelines%20Summary.pdf [Accessed 1st January 2018].
4. Lamb BW, Jolil RT, Sevdalis D, et al. Strategies to improve the efficiency and utility of multidisciplinary team meetings in urology cancer care: a survey study. BMC Health Services Research 2014;14: 377.
5. Department of Health National Cancer Waits Project. Cancer Waiting Targets – A Guide (Version 4). Available from: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4116413.pdf [Accessed 1st January 2018].
6. Mahmud SM, Fong B, Fahmy N, Tanguay S, Aprikian AG. Effect of preoperative delay on survival in patients with bladder cancer undergoing cystectomy in Quebec: a population based study. J Urol 2006;175: 78–83.
7. Goodfellow H, Viney Z, Hughes P et al. Role of fluorodeoxyglucose positron emission tomography (FDG PET)-computed tomography (CT) in the staging of bladder cancer. BJU Int 2014;114: 389-395.
8. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48(2): 202-5.
9. Seiler R. Predicting response to neoadjuvant chemotherapy in bladder cancer: controversies remain with genomic DNA sequencing. Transl Androl Urol 2016;5(2): 271-273.
10. Gore JL, Yu H, Setodji C, et al. Urinary Diversion and Morbidity After Radical Cystectomy for Bladder Cancer. Cancer 2010;116(2): 331-339.
11. National Insititue for Health and Care Excellence. Bladder cancer: diagnosis and management. Available from: https://www.nice.org.uk/guidance/ng2/resources/bladder-cancer-diagnosis-and-management-of-bladder-cancer-51036766405 [Accessed 1st January 2018].
12. James ND, Hussain SA, Hall E et al. Radiotherapy with or without chemotherapy in muscle invasive bladder cancer. N Engl J Med 2012;366(16): 1477–1488.
13. Cancer Research UK. Bladder cancer radiotherapy side effects. Available from: http://www.cancerresearchuk.org/about-cancer/bladder-cancer/treatment/invasive/radiotherapy/side-effects [Accessed 1st January 2018].
14. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [Accessed 1st January 2018].
15. Waldron N, Young T, Enting D. Current management of advanced bladder cancer. Trends in Urology & Men's Health 2017;8(6): 8-12.
16. Cassidy J (ed.), Bissett D (ed.), Spence RAJ (ed.). Oxford Handbook of Oncology. 4th edition. London: OUP Oxford; 2015.

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

A RARE PRESENTATION OF METACHRONOUS ISOLATED PAROTID METASTASIS FROM PREVIOUS BREAST CARCINOMA

K Krishna Pai, D Gahir, A Jegannathen, T Malins, S Narayanan, C Howitt

Abstract

Late parotid gland oligo-metastasis from breast cancer is extremely rare and also associated with good prognosis although it is palliative. We reported a case of Invasive lobular carcinoma of breast which spread to the parotid gland with literature review. Metachronous parotid metastasis with a long disease free period has a good prognosis, parotid surgery does not improve life expectancy, and management of parotid metastasis is palliative with 5 year survival rate beiong only 10 % for generic parotid metastasis irrespective of site of origin.

We concluded that not all parotid lumps are primary tumours. Before considering radical approach careful history taking and tru-cut biopsy of the parotid mass is most essential. As in our case although the background history of breast cancer was thirteen years ago, the patient had no other history of malignancy elsewhere and we established the diagnosis by comparing the histology of the parotid metastasis with the primary breast cancer slides and further confirmed it with immuno-histochemistry. We thus avoided major surgery/radiotherapy. Hormone treatment is equally effective in the metastatic set up.

Introduction

In general among head and neck cancers, salivary gland tumours and in them metastatic tumours are rare. The literature shows a total of 14 cases reported between 1982 to2010. (1) We report a case of Invasive lobular carcinoma of breast which spread to the parotid gland with literature review.

Case Report

A 71 year old Caucasian female was referred to us from the ENT department with a left sided parotid enlargement and discomfort since May 2016. Examination also revealed a 2 x 2 cm left parotid lump, firm in front of left ear. No facial nerve involvement nor cervical lymphadenopathy noted.

A detailed history revealed left breast invasive cancer in 1990 for which she had an excision biopsy which was not fully staged with no nodal sampling along with loco-regional radiotherapy .She had a relapse of the left breast cancer in 1996 followed by mastectomy and axillary lymph node clearance and then chemotherapy with 6 courses of CMF (Cyclophosphamide, Methotrexate 5-Flurouracil).She was on tamoxifen since 1994 which she stopped in 2002. She was discharged to community care in 2003.

The patient was disease-free for the following thirteen years until a growing left cheek mass led her to seek medical advice to the ENT department in early 2016.

For her parotid lump she went on to have FNAC (Fine needle aspiration cytology) of the parotid gland which was reported as Malignant Epithelial tumour most likely Metastatic breast carcinoma.

A tru-cut biopsy was done which was reported as adenocarcinoma of mixed ductular/lobular pattern after discussion with breast pathologist it was confirmed to be consistent with a metastasis from a previous breast cancer primary. Immunohistochemistry revealed ER+, PR+, Her-2 borderline + and strong positivity for Cam 5.2.

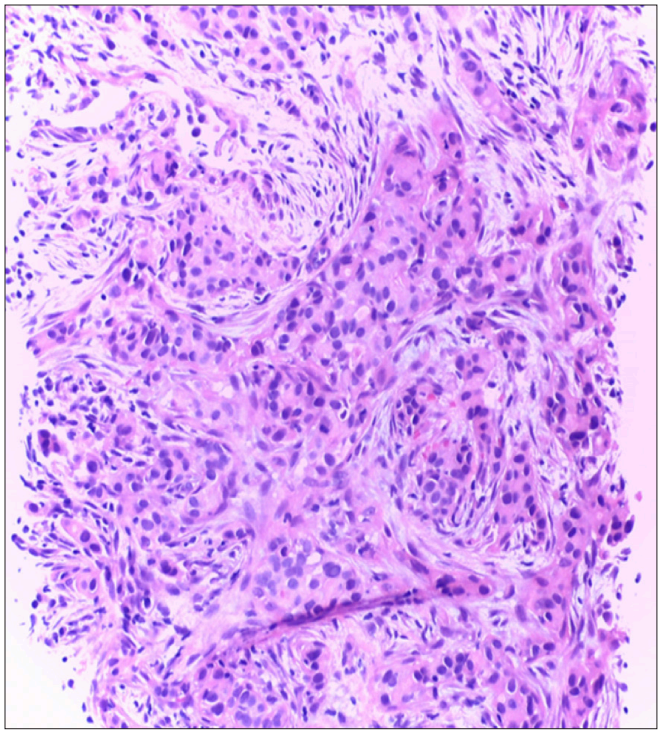


Figure 1: Histopathology-Core of parotid, H&E. x 20 magnification- The cores of parotid gland tissue have been infiltrated by carcinoma formed of cells showing a mixed ductal and lobular pattern.

Fluorescence in situ hybridization (FISH) came back as negative for Her-2.

A CT scan of thorax/abdomen/pelvis done showed right lung parenchymal changes with stability or minor interval improvement .Appearances were more likely to be inflammatory or infective rather than metastatic.

A RARE PRESENTATION OF METACHRONOUS ISOLATED PAROTID METASTASIS FROM PREVIOUS BREAST CARCINOMA

K Krishna Pai, D Gahir, A Jegannathen, T Malins, S Narayanan, C Howitt

PET scan revealed an avid parotid lesion consistent with known metastasis. Right lung changes not convincing for primary but required further assessment. Breast cancer primary remained a possibility although no evidence of active disease or metastasis elsewhere was noted.

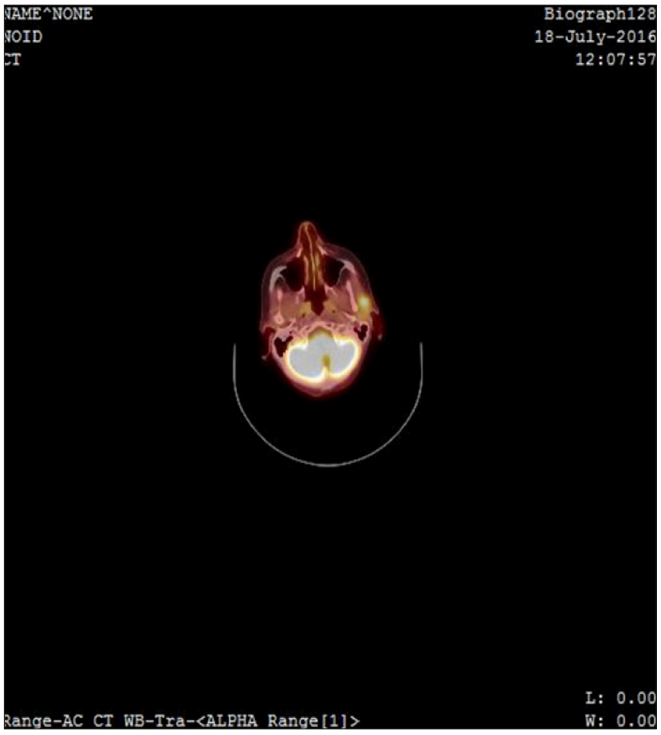


Figure 2: PET-FDG scan-Marked focus of FDG uptake seen in the left parotid which should be consistent with known possible metastasis.

She did not have a MRI scan of the head and neck. She was put on Arimidex 1 mg daily dose and plan for her is to continue on that with regular follow ups. She was also not taken up for any major surgery or radiotherapy.

But currently she is responding both clinically and biochemically with decreasing CA 15.3.

Discussion

Metastasis to the parotids from primary breast cancer is a very rare event, with few case described in literature. Parotid metastasis amounts to 9-14 % of all parotid tumours. (2) Synchronous parotid involvement from primary tumours at initial presentation and metachronous spread years after primary diagnosis have been reported. (3) In our case metachronous spread occurred after being disease free for thirteen years.

Most commonly, parotid metastasis from breast origin commonly reported in literature is of Invasive ductal carcinoma. (4) Invasive lobular carcinoma and phyllodes spread to parotids have also been reported but rare. We reported spread of an Invasive lobular cancer.

Contralateral parotid involvement are equally reported to ipsilateral thus implying hematogenous spread rather than direct lymphatic spread. (5) In our case we reported ipsilateral involvement of parotid.

Most patients clinically present with a painless swelling of the parotid gland and if there is facial nerve involvement it usually suggest malignant tumour. (6) Radiological work up with CT and MRI is used to confirm the clinical assessment however primary tumour and metastasis cannot be distinguished based on imaging alone. (7) In our case there was slow growing parotid mass with discomfort but no facial nerve involvement.

Fine needle aspiration cytology (FNAC) has 85% accuracy in distinguishing benign from malignant lesions and also primary from metastatic spread. (8) In our case the FNAC definitely pointed the mass to be a Malignant Epithelial tumour most likely Metastatic breast carcinoma.

It becomes very essential to communicate the history accurately to the reporting pathologist regarding history about breast cancer since primary parotid tumours are common in elderly men and association with primary breast cancer is a rare event. (8) Once parotid FNA confirms metastasis, FDG PET CT scan is done to look for local and distant spread.

In our case PET scan revealed a parotid lesion consistent with known metastasis with breast cancer being a possibility.

In our case a tru-cut biopsy was also done which was reported as adenocarcinoma of mixed ductular/lobular pattern and after discussion with breast pathologist it was confirmed to be consistent with a metastasis from a previous breast cancer primary.

On immunohistochemistry, the absence of oestrogenic receptors points more towards primary parotid tumours. (9) In our case Immunohistochemistry revealed ER+, PR+, Her-2 borderline + Fluorescent in situ hybridization (FISH) for Her 2 was negative and strong positivity for Cam 5.2 again favouring metastasis from breast cancer. Although primary parotid tumours can also express ER positivity, in our case radiology and histology ruled out a primary parotid lesion and confirmed that the lesion in the parotid was a metastatic deposit from her previous lobular breast carcinoma.

With regards to treatment, Superficial parotidectomy was successful in providing local control in most cases. (2) Metachronous parotid metastasis with a long disease free period has good prognosis (6), parotid surgery does not improve life expectancy (9), and management of parotid metastasis is palliative with 5 year survival rate being on 10%. (3)

A RARE PRESENTATION OF METACHRONOUS ISOLATED PAROTID METASTASIS FROM PREVIOUS BREAST CARCINOMA

K Krishna Pai, D Gahir, A Jegannathen, T Malins, S Narayanan, C Howitt

Hence in our case, as stated from previous studies of late presenting metachronous tumours we did not resort to surgery and with a palliative intent started her on aromatase inhibitors as the tumour was oestrogen positive. The plan was to follow her up regularly. The aim for her was to have a better quality of life.

Conclusion

Not all parotid lumps are primary tumours. Before considering radical approach careful history taking and tru-cut biopsy of the parotid mass is most essential. As in this case although the background history of breast cancer was thirteen years ago, we established the diagnosis by comparing the histology of the parotid metastasis with the primary breast cancer slides and further confirmed it with immuno-histochemistry. We thus avoided major surgery/ radiotherapy. Hormone treatment is equally effective in the metastatic set up.

Authors

Kavitha Krishna Pai
ST1 trainee Histopathology
Royal Stoke University Hospital
Stoke on Trent
ST4 7NR

Daljit Gahir
Consultant Oncology
Royal Stoke University Hospital
Stoke on Trent
ST4 7NR
daljit.gahir@uhnm.nhs.uk

Apurna Jegannathen
Consultant Oncology
Royal Stoke University Hospital
Stoke on Trent
ST4 7NR
apurna.jegannathen@uhnm.nhs.uk

Timothy Malins
Consultant Oral and Maxillofacial Surgery
Royal Stoke University Hospital
Stoke on Trent
ST4 7NR
timothy.malins@uhns.nhs.uk

Sankaran Narayanan
Consultant Oncoplastic Breast Surgeon
Royal Stoke University Hospital
Stoke on Trent
ST4 7NR
sankaran.narayanan@uhns.nhs.uk

Cordelia Howitt
Consultant Histopathology
Royal Stoke University Hospital
Stoke on Trent
ST4 7NR
cordelia.howitt@uhnm.nhs.uk

Corresponding Author

Kavitha Krishna Pai
kavitha.pai@uhnm.nhs.uk

References

1) Andoa K, Masumotoa N, Sakamotoa M, et al. Parotid Gland Metastasis of Breast Cancer: Case Report and Review of the Literature. Breast Care 2011;6:471–473
2) Sellinger M, Neubauer K, William M, et al. Contralateral metastasis of parotid gland in advanced breast cancer with peripheral facial paralysis," Archives of Gynecology and Obstetrics 2011; 284(6):1557–60
3) Dangore-Khasbage SB, Degwekar SS, Bhowate RR, et al. "Metastatic involvement of parotid from carcinoma of the breast—a case report," Oral and Maxillofacial Surgery 2009; 13(1):49–53
4) Ando K, Masumoto M, Sakamoto M et al., "Parotid gland metastasis of breast cancer: case report and review of the literature," Breast Care 2011;6(6):471–473
5) Kmeid M, Kamar FG, Nasser S, et al. Metachronous, Single Metastasis to the Parotid, from Primary Breast Cancer: A Case Report and Review of the Literature. Case Reports in Oncological Medicine 2016;1-5
6) Spreafico R, Nicoletti G, Ferrario F, R, et al. "Parotid metastasis from renal cell carcinoma: a case report and review of the literature," Acta Otorhinolaryngologica Italica 2008 ;28(5):266–268
7) Alath P, Kapila K, Hussein S, et al., "Parotid gland metastasis of breast cancer diagnosed on fine needle aspiration cytology: case report and review of literature," Cytopathology 2014;25(5): 346–348
8) Erra S, Costamagna D, "Breast cancer metastatic to the submandibular gland. Case report," Il Giornale di chirurgia 2011;32(4):194–198
9) Shimoyama T, Horie N, Yamada T, et al. "Parotid lymph node metastasis from adenocarcinoma of the urachus,"Dentomaxillofacial Radiology 2000;29(3):185–188

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

CASE BASED DISCUSSION: ACUTE PORTAL VEIN THROMBOSIS IN ADVANCED CHOLANGIOCARCINOMA

K Csenki, R Conroy

Abstract

We present a case of acute portal vein thrombosis (PVT) in a patient receiving palliative chemotherapy for an advanced cholangiocarcinoma. Although rare in the general population, PVT is an important differential in the patient presenting with acute abdominal pain, especially in patients with cirrhosis or hepatobiliary carcinomas where it becomes much more prevalent. The Foundation Doctor is expected to be able to recognise and manage acutely unwell patients regardless of the underlying cause.

In this case liaising with Radiology colleagues and early involvement of Critical Care enabled prompt diagnosis of a pre-terminal event and allowed appropriate escalation plans to be enacted, leading to good end of life care. Good communication skills were paramount, and in patients with advanced malignancy having difficult discussions regarding prognosis early on can be of benefit to both patient and family and can be facilitated and aided by the Foundation Doctor. All Hospitals in England have access to an Acute Oncology Service where unwell cancer patients can be discussed and reviewed by specialist teams if necessary.

Case history

A 59 year old man was admitted overnight to a tertiary cancer centre with a one day history of worsening epigastric pain, constipation and fever. His oncological diagnosis was a locally advanced intrahepatic cholangiocarcinoma (CCA) with liver metastases and a suspicion of an omental metastasis. He had recently completed cycle 2 of a planned 6 cycles of palliative Cisplatin/ Gemcitabine chemotherapy. His only previous medical history was cirrhosis, and he was a non-smoker with an alcohol intake of 18 units/week. His only regular medication was spironolactone.

Initial observations on admission to the Medical Assessment Unit were as follows: HR 90, BP 142/78, T 36.2, RR 28, SpO2 98% RA. IV access was secured and bloods taken including lactate and blood cultures. Given the clinical suspicion of sepsis, broad spectrum antibiotics and fluids were given, urine output was monitored and a senior doctor was asked to review the patient immediately.

On examination he was alert and orientated but felt generally fatigued and complained of severe umbilical and epigastric pain. Peripheral stigmata of liver disease including gynaecomastia and jaundiced sclera were evident. Abdominal examination revealed a distended but soft abdomen without significant focal tenderness. Bowel sounds were reduced, no organomegaly was evident and shifting dullness was found indicating ascites.

An intra-abdominal pathology was suspected and abdominal and erect chest radiographs were arranged to look for perforation or bowel obstruction. They did not reveal any significant pathology although incidentally the abdominal radiograph did show a linear area of gas in the right side of the abdomen consistent with air in the appendix. This finding in isolation is normal. A CT abdomen with contrast was requested to further investigate.

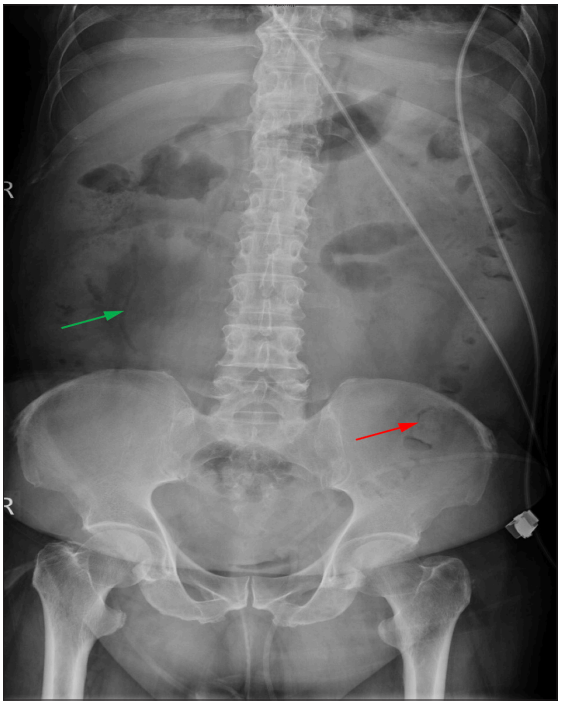


Figure 1: AXR: bowel gas pattern unremarkable. Note faeces in the descending colon (red arrow) and air within the appendix.

His initial lactate reading came back as 11mmol/L prompting urgent critical care review, and arterial blood gas analysis (figure 2) taken shortly afterward initial resuscitation revealed a compensated metabolic acidosis, most commonly seen in sepsis or renal failure.

pH	7.40		7.35 - 7.45	Normal
PC02	3.35	kPa	4.66 - 5.99	▼ Low
P02	16.51	kPa	9.98 - 13.30	▲ High
S02%	99.2	%	95.0 - 98.0	▲ High
HC03-	15.8	mmol/L	21.0 - 28.0	▼ Low
Lactate	8.9	mmol/L	0.5 - 2.0	▲ High

Figure 2: ABG: Compensated metabolic (lactic) acidosis.

CASE BASED DISCUSSION: ACUTE PORTAL VEIN THROMBOSIS IN ADVANCED CHOLANGIOCARCINOMA

K Csenki, R Conroy

Critical care reviewed the patient given the high lactate and he was regularly reviewed throughout the night whilst continuing treatment with a differential diagnosis of severe sepsis, potentially of a biliary source. Full blood count revealed he was not neutropenic and U+Es showed a mild dehydration whilst LFTs were as follows: AST 73, Alk Phos 297, γGT 834, Bil 51, PT 12.8, Alb 35.

Lactate improved with fluid resuscitation to 7.6 and blood pressure and urine output were monitored hourly, remaining just within acceptable parameters. Given his advanced malignancy the Specialty Trainee felt he would not be a good candidate for resuscitation, and asked the Consultant to review this patient first thing on arrival to the ward in the morning.

Given the history of upper GI malignancy and the presentation of abdominal pain; persistently raised lactate and raised liver enzymes, the Consultant queried portal venous thrombosis. The abdominal CT was expedited after discussions between the junior doctor and the Radiologist and was performed in both an arterial and a delayed-venous phase to opacify the portal vein and look for other causes of ischaemic bowel.

This revealed the diagnosis to be a large portal venous thrombosis, extending into the superior mesenteric vein causing venous congestion, leading to bowel oedema and ischaemia. (Figure 3a/b) Low molecular weight heparin was administered alongside the existing treatments, however the patient continued to gradually deteriorate haemodynamically.

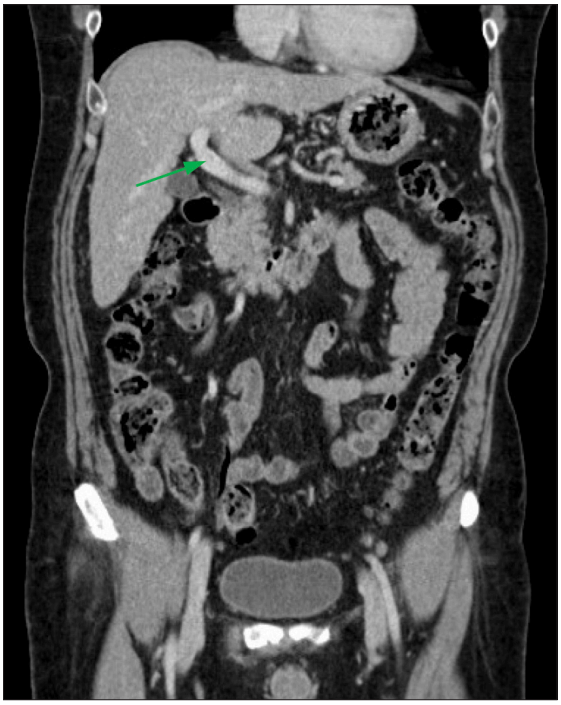


Figure 3A: CT abdomen + contrast, coronal reformat, demonstrating uniform filling of the hepatic portal vein (green arrow) Same patient 3 months earlier.

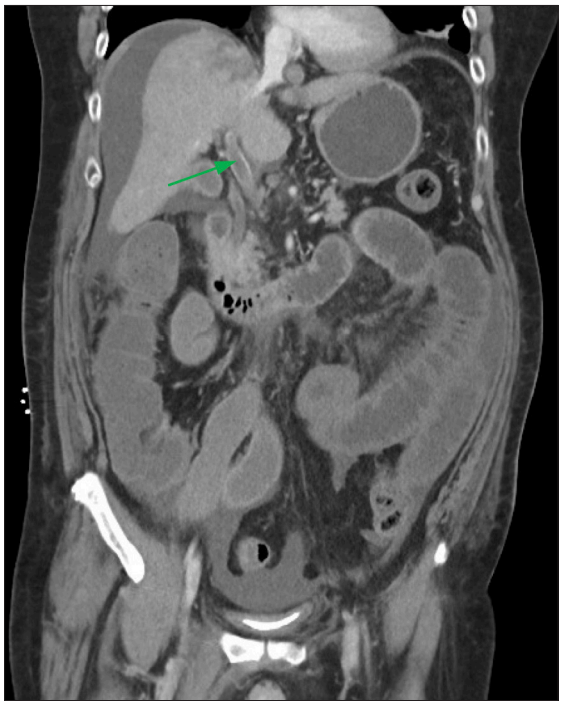


Figure 3B: CT abdomen + contrast, coronal reformat, demonstrating a large thrombus within the hepatic portal vein, bowel oedema + ileus and ascites.

Given he was on maximal appropriate medical therapy for PVT and bearing in mind his underlying malignancy and its palliative nature it was felt he would not benefit from admission to ICU. After further discussions with the patient and his family a ward level ceiling of care was put in place and an a Do Not Attempt Resuscitation (DNAR) form completed.

The patient continued to deteriorate over the course of the day and that night the Foundation doctor noticed a change in his breathing and called his family in. They arrived in time to be with him as he died peacefully.

CASE BASED DISCUSSION: ACUTE PORTAL VEIN THROMBOSIS IN ADVANCED CHOLANGIOCARCINOMA

K Csenki, R Conroy

Discussion

This is an interesting case of an uncommon acute pathology (portal vein thrombosis) in a patient with a relatively rare cancer (Cholangiocarcinoma). We will discuss various important aspects of the case paying attention to the importance of prompt recognition and treatment of acutely unwell oncology patients and the need to make early decisions with senior colleagues regarding potential ceilings of care.

Acute Oncology Service (AOS)

Not all patients with cancer will present to a tertiary cancer centre acutely. In the general hospital setting it is essential to involve the Acute Oncology Team at the earliest opportunity.

The National Chemotherapy Action Group (NCAG), guided partly by reports from NCEPOD and NPSA and from previous cancer peer review results, has recommended that a more systematic approach should be taken to dealing with cancer-related emergencies. These recommendations have been embodied in the concept of the Acute Oncology Service . All hospitals in England now have access to an AOS.

Often there will be systems in place that will flag any patients with a known cancer diagnosis to the team so that they can review the reason for admission and determine if AO input is required also they will accept referrals from other hospital teams if specialist oncology input is felt to be beneficial.

Often one of the specialist acute oncology nurses will be the first to come and assess the situation and provide immediate advice; where needed they can then involve a local acute oncology consultant to also advise. The AOS can also help liaise with the tertiary centre for further specialist advice as required. Early involvement of the team is essential in complex cases such as this.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is rare cancer arising from the bile duct epithelium and accounts for around 3% of gastrointestinal malignancies. It is classically associated with primary sclerosing cholangitis, where the prevalence rises to 13%. It can occur at any point along the biliary tree in either an intrahepatic, extraheptic or perihilar region. Cancers arising from the gallbladder and ampulla of Vater are considered separate entities and are more common.

CCA carries a poor prognosis measured in months, in part because it tends to present late after local spread to the liver has occurred. Whilst surgical resection might be attempted for localised CCA recurrence is common and locally advanced cholangiocarcinoma is non-resectable surgically.

Treatment goals must be focussed on palliating the patient from symptoms such as pain or pruritis. Treatment options include palliative chemotherapy, which may be combined with external beam radiotherapy. Interventional procedures to the biliary tree may be required to relieve obstruction.

Our patient had opted for chemotherapy with Gemcitabine and Cisplatin. Gemcitabine is generally well tolerated but may cause flu-like symptoms, lethargy and nausea/vomiting. As with many cytotoxic chemotherapy agents the main serious side effect to be aware of is myelosuppression which could result in dangerously low blood counts, predisposing to serious infection or bleeding. Cisplatin is a platinum based chemotherapy that as well as the above listed side effects can cause renal failure and is classically associated with hypomagnesemia.

End of Life Discussions

It is important for patients and their families to be made fully aware of the goals of their cancer treatment whether that be curative or palliative. A study of over 1000 end-stage cancer patients in the New England Journal of Medicine revealed that up to 80% of them did not understand that their palliative chemotherapy was not at all likely to cure their cancer.

Patients with incurable malignancies should be gently encouraged to approach issues such as end of life care early on as this can in some way prepare them for the difficult decisions and situations that may lie ahead. Although the Foundation doctor will not ordinarily be the right person to have such discussions, it can be very beneficial to take opportunities to explore patients' understanding of their illness, and to facilitate appropriate conversations with more senior colleagues.

Our patient and his family had been fully informed of the poor prognosis associated with his condition and the palliative nature of his treatment at his first clinic appointment and even though nothing could fully prepare a family for such an acute deterioration, having such conversations early on meant that end of life discussions were somewhat easier to approach.

CASE BASED DISCUSSION: ACUTE PORTAL VEIN THROMBOSIS IN ADVANCED CHOLANGIOCARCINOMA

K Csenki, R Conroy

Sepsis

In September 2017 NICE updated its guidance on managing adults with suspected sepsis. Whilst the traditional SIRS criteria are still important in recognising and diagnosing the condition, they advocate using certain criterion to stratify risk of severe illness and death from sepsis.

On admission our patient only had 1 of the SIRS criteria, a raised respiratory rate (RR) of 28, however together with suspicion of sepsis this would place him in the 'high risk' category (RR>25) mandating immediate review by a 'senior decision maker'.

His recent history of chemotherapy should also prompt careful clinical evaluation given the high mortality associated with neutropenic sepsis and for this reason antibiotics were administered immediately rather than waiting for blood results. Although he was not pyrexial on admission he had been monitoring his temperature at home and thus gave a reliable history of pyrexia. Good patient education regarding risks of chemotherapy treatment and signs to look out for can improve outcomes.

Early senior input and early critical care review following the lactate reading allowed appropriate and timely decisions to be made regarding escalation and resuscitation. He was managed appropriately at ward-level until the Foundation Doctor correctly recognised he was entering a terminal phase at which point he was kept comfortable and the family were informed. Earlier conversations had warned the family this was a possibility and so they had made themselves contactable overnight and stayed locally.

A high lactate that is not rapidly improved with fluid should prompt thorough and early investigation and escalation as it is a poor prognosticator in sepsis. Alternative diagnoses should also be considered, especially in the context of severe abdominal pain where ischaemic bowel must be ruled out, a rare cause of this being portal vein thrombosis.

Portal Venous Thrombosis

Portal Vein Thrombosis (PVT) is an important differential in the patient presenting with acute abdominal pain. Although uncommon in the general population (1%) , its prevalence rises sharply in those with cirrhosis (>10%) and malignancy (up to 40% in patients with Hepatocellular carcinoma). It is usually classified into its acute and chronic subtypes.

Chronic portal vein thrombosis is more strongly associated with cirrhosis and may present more subtlety with the sequalae of portal venous hypertension such as splenomegaly, ascites and/or oesophageal varices. The presence of ascites in our patient was not a specific sign given his history of cirrhosis and intraabdominal malignancy.

Acute portal vein thrombosis is more strongly associated with malignancy and tends to present acutely in an ischaemic bowel type picture. Abdominal pain, nausea and ileus are features often with a very high lactate. It has a very poor prognosis given surgical resection of all the affected bowel is not possible. Like the more commonly encountered deep vein thrombosis (DVT), risk factors for PVT can be understood through Virchow's triad of hypercoagulability, stasis of blood flow and endothelial injury.

Diagnosis can be made with ultrasound abdomen where colour doppler may show absent flow in the portal vein however CT with contrast is usually the most effective and appropriate imaging technique to evaluate these patients and reveal any associated pathology that may be present. A brief discussion with a Radiologist can not only help expedite an urgent scan but will also ensure the correct imaging techniques are used to answer the clinical question: In this case a delayed venous phase scan was added on by the Radiologist ensuring adequate opacification of the portal vein.

Summary

Although this patient had a rare cancer and an uncommon underlying cause for his acute deterioration, Foundation Doctors need to be equipped to deal with a range of emergency presentations. The underlying principles of this case can be applied to a wide range of scenarios. Early recognition and initiation of sepsis management is key, especially in the immunocompromised chemotherapy population.

If patients do not respond well to initial resuscitation, the Foundation Doctor must consider alternative diagnoses and involve seniors early on. Acutely unwell cancer patients should be discussed with the Acute Oncology Service for specialist advice. Discussing and clarifying escalation and resuscitation decisions early on with the patient and the family, can improve patient care and the Foundation Doctor has an important role in recognising the dying patient.

CASE BASED DISCUSSION: ACUTE PORTAL VEIN THROMBOSIS IN ADVANCED CHOLANGIOCARCINOMA

K Csenki, R Conroy

Questions

1. Which of the following could be causes for the gynacomastia seen in this patient?

a. Spironolactone

b. Liver cirrhosis

c. Alcohol use

d. Malnutrition

e. All of the above

2. Liver metastases are most likely to occur in which primary malignancy?

a. Prostate

b. Rectal

c. H+N

d. Ovarian

e. Brain

Authors

Dr Konrad Csenki BSc, MBChB
Junior Oncology Fellow
The Christie NHS Foundation Trusts
Manchester., M20 4BX
kcsenki@gmail.com

Dr Ruth Conroy MBBS, MRCP, FRCR
Consultant Clinical Oncologist
The Christie NHS Foundation Trusts
Manchester., M20 4BX
ruth.conroy@christie.nhs.uk

References

1. National Cancer Peer Review Programme Manual for Cancer Services: Acute Oncology - Including Metatastic Spinal Cord Compression Measures https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216121/dh_125889.pdf

2. Farhat MH, Shamseddine AI, Tawil AN, et al. Prognostic factors in patients with advanced cholangiocarcinoma: role of surgery, chemotherapy and body mass index. World J Gastroenterol. 2008, 14(20):3224–30.

3. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol 2002, 36:321–7.

4. Lajer H, Daugaard G. Cisplatin and hypomagnesemia: Cancer Treat Rev. 1999, 25(1):45-58.

5. Weeks JC, Catalano PJ, Cronin A et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012, 367(17):1616-25.

6. NICE guideline [NG51] Sepsis: recognition, diagnosis and early management https://www.nice.org.uk/guidance/ng51

7. Ponziani FR, Zocco MA, Campanale C, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol. 2010, 16(2):143–55.

8. Cohen J, Edelman RR, Chopra S. Portal vein thrombosis: a review. Am J Med. 1992, 92:173-82.

9. Tsochatzis EA1, Senzolo M, Germani G, et al. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther. 2010, 31(3):366-74.

10. Quirk M, Kim YH, Saab S, et al. Management of hepatocellular carcinoma with portal vein thrombosis. World J Gastroenterol. 2015, 21(12):3462–71.

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"(**https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

Abstract

Adnexal masses are common gynaecological findings in women and therefore, it is important that doctors know how to manage these cases as well as when to refer for further management. A focused history taking and thorough clinical examination are essential in reaching a diagnosis in most gynaecological conditions while investigations will aid in the confirmation of a working diagnosis.

It is also important for doctors to recognise the management of different aetiologies of adnexal masses so that these women can have appropriate care and in a timely manner. This article focuses on the clinical assessment of adnexal masses in non-pregnant women, providing detailed information in helping doctors and manage these patients.

Introduction

An adnexal mass is a lump located in the tissue of the adnexae of the uterus, which are the structures closely related functionally and structurally to the uterus such as the ovaries, the fallopian tubes, or any of the adjacent connective tissues. They are known to be a common finding in gynaecology. Since adnexal masses may be benign or malignant, they need to be treated with a high index of suspicion thus requiring a comprehensive history taking, physical examination, and investigations which will enable the appropriate management of these patients.

This article focuses on the clinical assessment of adnexal masses in non-pregnant women, providing detailed information in helping doctors assessment these masses.

History

A thorough medical history is important in the diagnosis of a suspected adnexal mass as patients present with varying symptoms (Table 1). An important thing to note is that ectopic pregnancy should be excluded in all women of reproductive age (10-60 years old) before arriving at other differential diagnosis.

A problem-focused approach should be used while taking history of patients with abdominal pain. Pain should be described by its site, onset, duration, character, periodicity, radiation, severity, aggravating and or relieving factors as well as other associated factors.

Pain related to an adnexal mass is usually secondary to ovarian distension or compression of surrounding structures (1). This may be felt in the iliac fossa and radiates down the front of the thigh up to the knee (2). The presence of other associated pain for example dyspareunia, whether it is deep or superficial may suggests endometriosis, ovarian cyst, or pelvic inflammatory disease (3).

Post-coital pain may suggest ruptured follicular or corpus luteal cyst (1). Furthermore, sudden onset of severe, intermittent, and unilateral pain associated with nausea and vomiting classically suggest ovarian torsion (1). Acute extreme abdominal pain may suggest peritonism and may be due to bleeding or rupture of a mass/cyst.

Red flag symptoms of ovarian malignancy include persistent abdominal distension, change in appetite, alteration of bowel habits, increased satiety, bloating, increased urinary urgency and/or frequency and weight loss. Although these symptoms can be present in patients with benign ovarian masses (4), up to 93% of patients with ovarian cancer experienced them too (5).

Menstrual history is the next important component in the history taking. It is essential to find out about the date of last menstrual period (LMP; first day of bleeding) or menopause, menstrual cycle (number of days bleeding, length of cycle), regularity, amount/character of bleeding (flooding, clots), and menstrual pain (2).

The presence of any intermenstrual bleeding (IMB), post-coital bleeding (PCB) or post-menopausal bleeding (PMB) should also be explored (6). Vaginal bleeding or discharge should be established further in terms of amount, colour, onset, nature (thick or copious), or presence of any smell or itch (2). Severe dysmenorrhea and menorrhagia may signify endometriosis or fibroids (1,2). Solid ovarian mass associated with post-menopausal bleeding increases the possibility of ovarian malignancy to 45% compared to 13% in pre-menopausal women (7).

Other gynaecological history including previous gynaecological surgeries especially tubal surgery, sexual history, contraception, subfertility/infertility, sexually transmitted infections, cervical smears, and previous gynaecological treatment should also be explored (2).

Obstetric history should also be recorded and this comprises of the number of pregnancies and children, miscarriages, terminations, or ectopic pregnancies. For each pregnancy, it is important to find out about pre-conceptional and antenatal care, gestation at delivery, mode of delivery, birth weight, postnatal problems and current health of the child(ren) (6).

A past medical history and a family history of ovarian, breast, endometrial, or colon cancer should be taken to deduce the likelihood of ovarian malignancy.

Every year, 7 300 women are diagnosed with ovarian cancer in the UK (8). The risk of developing ovarian cancer for the general population of women is approximately 2% (8). Therefore, risk factors for ovarian malignancy should be identified while taking the patient's history.

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

These include women above the age of 50 years old, early menarche, late menopause, nulliparity, delayed child-bearing, infertility, obesity, unopposed oestrogen exposure, past medical history of breast or bowel cancer, those with known or suggested presence of BRCA or other hereditary cancer syndromes (9), and family history of breast, bowel, endometrial or ovarian cancer (10).

Diagnosis	Possible symptoms	Examination findings
Ovarian cancer - 6% of ovarian tumours	Abdominal distension (often described as bloating, but persistent), increased abdominal girth, change in bowel habit, urinary symptoms (pressure effect), abnormal vaginal bleeding, loss of appetite, fatigue, lethargy, pelvic or abdominal pain, weight loss	Pelvic or abdominal mass, ascites, omental mass (common site for metastasis), pleural effusion, supraclavicular lymphadenopathy
Benign ovarian cyst - 94% of ovarian tumours	May be asymptomatic or may present with chronic dull ache, urinary frequency (pressure effect), bowel disturbance, dyspareunia, cyclical pain, abnormal uterine bleeding; or acute pain when bleeding (into the cyst or intra-abdominal), rupture or torsion occurs. Ovarian torsion presents with sudden onset of severe, intermittent, and unilateral pain associated with nausea and vomiting	Abdominal: Pelvic mass, tenderness, signs of peritonism, upper abdominal masses suggest cyst likely to be benign Pelvic: PV discharge/bleeding, cervical excitation, adnexal mass or tenderness
Endometrioma	Menorrhagia, irregular/dysfunctional uterine bleeding, deep dyspareunia, dysmenorrhoea, may be constant pain if adhesions present, secondary dysmenorrhoea	Fixed retroverted uterus or uterosacral ligament nodules and general tenderness, adnexal mass
Acute salpingitis (often associated with endometritis, peritonitis, abscess, and chronic or recurrent infection)	Being unwell, fever, spasms of lower abdominal muscles, abdominal or pelvic pain, nausea, vomiting, profuse, purulent, or bloody vaginal discharge. Symptoms vague in subacute infection.	Abdominal tenderness or tenderness in the fornices bilaterally, worse on one side; cervical excitation, fever, vaginal discharge
Chronic salpingitis (unresolved, unrecognised, or inadequately treated acute salpingitis) leading to fibrosis and adhesions, tubo-ovarian abscess, pyosalpinx, or hydrosalpinx	Lower abdominal or pelvic pain, menorrhagia, secondary dysmenorrhoea, vaginal discharge, deep dyspareunia, depression	Palpable tubal masses, abdominal or adnexal tenderness
Polycystic ovaries	Oligomenorrhoea, amenorrhoea, or menorrhagia, central obesity, hirsutism, head hair thinning, acne, infertility.	Unilateral or bilateral adnexal fullness or enlarged ovary or ovaries

Table 1: Differential diagnoses of adnexal masses and their possible symptoms and examination findings

The symptoms presented can commonly be quite vague, thus it is worth to consider other origin of symptoms for example gastrointestinal, urinary or metastatic sources (primary breast and bowel carcinoma).

Clinical Examination

The patient should have her height and weight measured to calculate her body mass index and these should be documented in her clinical records at the clinic visit. An increased body mass index (BMI) may indicate an increased risk of ovarian malignancy and polycystic ovaries.

At general examination, it is important to assess the patient's well-being, performance status and to exclude signs of anaemia or thyroid disease (6). The performance status of the patient can be assessed using the World Health Organisation (WHO) performance status score (Table 2), this may have a bearing on the options of treatment that may be offered to the patient.

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 2: WHO performance status

Examination of the abdomen is mandatory to assess any visible abdominal or pelvic masses, ascites, distention or scars from previous surgeries which the patient might have forgotten to mention while taking her history. The clinician should note areas of tenderness, guarding, or rigidity on palpation.

Gynaecological examination has a sensitivity of 45% and specificity of 90% (12) for the detection of pathology. Pelvic examination is an intimate examination as such a chaperone is required as recommended by the Royal Colleges and General Medical Council (GMC). The patient should be positioned dorsally, examination should start with inspection for any swelling, inflammation, skin changes, or ulceration around the vulval area (6).

Speculum examination should be carried out using a Cusco's bivalve speculum to visualise the vaginal walls, vaginal fornices and cervix fully (13). If required, obtain a high vaginal swab (HVS) to test for the presence of vaginal pathogens and flora. Endocervical swabs may be obtained to test for chlamydia and gonorrhoea infection. A Cervical smear may also be obtained if required.

Following Cusco's speculum examination, a bimanual vaginal examination is essential to have a feel of the vaginal walls, cervix, uterus, and adnexa with special attention to any tenderness and masses. Normal premenopausal ovaries are not always palpable while postmenopausal fallopian tubes should not be palpable (13).

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

For any adnexal mass felt, note the size, shape, consistency, mobility, and whether it is fixed to the uterus or not (13). Uterine masses usually move with cervix while ovarian masses do not (6). A cervical excitation tenderness can be assessed by gently tipping the cervix from side to side, this may be positive in cases with adnexal distention and pelvic inflammatory disease.

The possible examination findings are listed in Table 1.

The clinician should be able to formulate a list of differential diagnoses following a detailed history and examination. Bowel or urinary related pathologies should also be considered depending on the clinical presentation of the woman.

Investigations

These should include urine or serum pregnancy (Ð-hCG) test, urinalysis, full blood count and a group and save. Additional blood tests may be required depending on the clinical presentation. A low haemoglobin levels may indicate blood loss e.g. menorrhagia, PMB, or PCB and raised inflammatory markers may indicate signs of infection/inflammation e.g. pelvic inflammatory disease or tuba-ovarian abscess.

Serum cancer antigen 125 (CA-125) should be measured in women with suspected ovarian malignancy. It has a pooled sensitivity and specificity of 78% for differentiating benign from malignant adnexal masses, with higher values in postmenopausal women (14).

CA-125 is increased in 80% of epithelial cancer (which is the most common form of ovarian cancer) although it can be raised in other conditions such as fibroids, PID, endometriosis, liver disease, adenomyosis, pregnancy, acute events in benign cysts e.g. torsion or haemorrhage, or in several other malignant conditions e.g. breast, colon, lung and pancreatic cancers (15,16). Other tumours such as alpha-fetoprotein (Ð-FP) may be raised in germ cell tumours, lactate dehydrogenase (LDH) and beta-human chorionic gonadotrophin (Ð-hCG) may be raised in dysgerminomas (10).

Human epididymis protein 4 (HE4) is a relatively newer tumour marker expressed by epididymal epithelium and may be raised in ovarian cancer (17). It is not raised in endometriosis, as such has fewer false positive results compared to CA-125 (17). However, HE4 assays are currently not readily available in the UK.

A transvaginal pelvic ultrasound (TVS) is recommended as the first-line imaging in assessing adnexal pathology (10). With a sensitivity of 89% and a specificity of 73% when using with a morphology index, TVS is helpful in characterising benign and malignant cysts (18). Nonetheless, transabdominal ultrasound (TAS) is recommended when an ovarian cyst is large or beyond the field of view of TVS (19). Older women may also find TVS examination uncomfortable.

Computer tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are not recommended for the initial assessment of ovarian pathology as they do not improve the sensitivity or specificity obtained by TVS (10).

CT scan of the abdomen and pelvis should only be arranged when malignant disease is suspected based on the clinical picture, tumour serum markers, and ultrasonographic findings (10). It is useful for the staging of a suspected primary ovarian cancer or to identify the primary intra-abdominal cancer (e.g. colon, gastric, pancreatic) (20,21). On the other hand, MRI is recommended when ultrasound is inconclusive or limited due to body habitus (10) or to further characterise certain pelvic masses such as dermoid cysts.

Management

The National Institute for Health and Care Excellence (NICE) guideline recommends the use of risk malignancy index (RMI) in assessing women with suspected ovarian malignancy. RMI is useful in identifying women with high risk of cancer. It uses an algorithm based on the product of serum CA-125 (CA-125); menopausal status (M); and ultrasound score (U) (6) (refer to Table 3).

RMI Criteria	Scoring
Ultrasound scan score (U)	1 point for each of the following characteristics: • multilocular cysts • evidence of solid areas • evidence of metastases • ascites • bilateral lesions U = 0 (if no feature) U = 1 (if one feature) U = 3 (if two or more features)
Menopausal Status (M)	Premenopausal, M= 1 Post-menopausal, M= 3
Serum CA-125	Serum cancer antigen 125 level (U/L)
RMI = U x M x CA-125	

Table 3: RMI criteria and scoring

Patients with a high RMI have a high probability of diagnosis of ovarian cancer (Table 4). These cases are reviewed by the gynaecological cancer multidisciplinary team who agree on a treatment plan for individual cases. The treatment offered is a typically a combination of surgery and or chemotherapy.

Surgery may be offered as interval (surgery after 3-4 cycles of chemotherapy) or primary debulking operation. Surgery involves a staging laparotomy (which may consist of laparotomy, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymph node sampling, peritoneal biopsies, and pelvic washings/ascitic sampling) with the aim of removing as much tumour as possible (6). Discussion on the prognosis will depend on the stage of the disease, volume of residual disease following surgery, the sensitivity of the cancer to chemotherapy and the fitness of the patient.

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

Risk	RMI score	Risk of Cancer
Low	<25	<3%
Moderate	25 - 250	20%
High	> 250	75%

Table 4: RMI score and ovarian cancer risk

In the case of benign ovarian cyst, management varies depending on the size and presentation of the cyst. According to guidelines published by the Royal College of Obstetricians and Gynaecologists (RCOG), pre-menopausal women with simple ovarian cysts of less than 50 mm in diameter generally do not require follow-up as these cysts are very likely to be physiological and almost always resolve within 3 menstrual cycles (10).

On the other hand, women with simple ovarian cysts of 50–70 mm in diameter should have yearly ultrasound follow-up (10). Those with larger simple cysts should be considered for either further imaging (MRI) or surgical intervention (10). Additionally, ovarian cysts that persist or increase in size are unlikely to be functional and may warrant surgical management (10).

In terms of presentation, patients presenting with acute lower abdominal pain without signs of systemic upset/peritonism can be treated conservatively with analgesia (6). However, if there are signs of systemic upset/peritonism with the lower abdominal pain (where the possible diagnoses may be ovarian torsion, rupture, haemorrhage of a cyst), surgical intervention is appropriate. The route of surgery can be by laparoscopy or laparotomy depending on the experience or expertise of the clinician. The operative procedure may include a cystectomy, oophorectomy, oophropexy, salpingo-oophorectomy or salpingectomy depending on the findings at operation.

The treatment of pain and subfertility are the main management principles for endometrioma or endometriosis. The medical treatment options for pain from endometriosis include the combined oral contraceptive pills (COCP), medroxyprogesterone acetate or other progestogens, levonorgestrel-releasing intrauterine device, and GnRH analogues (6).

Surgical treatment is indicated when medical treatment has failed and these include laparoscopic coagulation, excision, or ablation with the last option being oophorectomy with or without hysterectomy (6). In treating subfertility, surgical removal of endometriotic lesions or endometriomas may be considered (6).

The management of confirmed pelvic inflammatory disease (PID) should involve referral of women and their sexual partner(s) to sexual health clinic for infection screening and contact tracing (22). The woman should also be screened for other sexually transmitted infections (STI) before treating with antibiotics.

Nevertheless, treatment should not be delayed as the condition may get worse and have serious complications e.g. ectopic pregnancy, subfertility, or chronic pelvic pain (22). Empirical antibiotics should be commenced as soon as a possible diagnosis of PID is made. Further information on the antibiotic treatment for PID can be found on NICE guidelines or the British Association for Sexual Health and HIV (BASHH).

For polycystic ovarian syndrome, the management focuses on the main concern of the women such as being overweight, hirsutism and subfertility/infertility. Management includes lifestyle modification, improving menstrual regularity, controlling symptoms of hyperandrogenism, managing subfertility, screening for cardiovascular risk factors, impaired glucose tolerance, type 2 diabetes, and gestational diabetes (6,23).

Conclusion

A good history and a thorough pelvic examination may be adequate for diagnosis in most gynaecological conditions. Investigations will help in the confirmation of a working diagnosis and to rule out other differentials. It is important that clinicians are attentive and thorough with their history taking and clinical examination. This will enable appropriate triage and management of these patients.

MCQ

1. A 63-year old woman is urgently referred to the gynaecology clinic by her general practitioner (GP). She had been complaining of lower abdominal pain. CA125 comes back as 27 U/ml (normal 0-35 U/ml) and pelvic ultrasound scan arranged by the GP shows a 3.5 cm simple right ovarian cyst. What is the most appropriate management?

A. Laparoscopic ovarian cystectomy

B. Laparotomy and oophorectomy

C. Conservative management

D. Total laparoscopic hysterectomy and bilateral salpingo-oophorectomy

E. Referral to a specialist cancer unit

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

2. A 26-year old woman presented in accident and emergency with a two-week history of increasing abdominal pain and minimal greenish yellow vaginal discharge. She has been feeling feverish and generally unwell for the past few days.

She feels nauseous but has no vomiting. She has no urinary symptoms and bowels have been opening normally. She has a history of PID which was treated. She is on treatment (cyclical norethisterone) recently for heavy and prolonged periods, commenced on a recent hospital visit by her gynaecologist.

Her temperature is 38.1°C, pulse 105/min, and blood pressure 122/72 mm/Hg. Pregnancy test is negative. On examination, the abdomen appears slightly distended. There is tenderness in the left iliac fossa and a mass can be felt in the left iliac fossa. On vaginal examination, the cervix appears normal but she is found to have offensive discharge and adnexal tenderness. Blood results are as follows:

Haemoglobin	10.2 g/dL	11.7 – 15.7 g/dL
Mean cell volume	89 fL	80 – 99 fL
White cell count	14.5 x 10^9/L	3.5 – 11 x 10^9/L
Neutrophils	9.1 x 10^9/L	2 – 7.5 x 10^9/L
Platelets	523 x 10^9/L	150 – 440 x 10^9/L
C-reactive protein	164 mg/L	<5 mg/L
Transvaginal ultrasound scan report: ultrasound scan shows a uterus with multiple fibroids. The right ovary appears normal. The left ovary cannot be identified separately from a complex adnexal mass, measuring 8 x 7 x 4 cm.		

What is the most likely diagnosis?

A. Diverticular abscess

B. Tubo-ovarian mass

C. Appendix abscess

D. Ovarian malignancy

E. Endometrioma

3. A 23-year old woman presented with constant right-sided abdominal pain for 2 days. The pain started suddenly while she was sleeping which woke her up. The pain was severe and she was not able to get out of bed for hours.

She feels nauseous and was not able to eat much. She reported no vaginal discharge or bleeding. She has no urinary or bowel symptoms. The pain is still present but has improved today. She reported to have had similar episodes twice previously but were not as severe.

She has a history of ectopic pregnancy and is currently on the 'mini-pill' for contraception. She has no history of sexually-transmitted infections and has been with the same partner for 3 years. Her temperature is 37.3°C, pulse 78/min and blood pressure is 115/68 mm/Hg.

On examination, there is tenderness in the suprapubic and right iliac fossa on palpation with minimal rebound tenderness but no guarding. Speculum examination is normal and she is tender in the left adnexa on bimanual examination but no cervical excitation.

Blood results are unremarkable with inflammatory markers within the normal values. Urinalysis is negative and pregnancy test is also negative. Transvaginal ultrasound scan report is as follows:

Transvaginal Ultrasound Scan

The uterus is anteverted and normal in size. The endometrium measures 3.2 mm. Both ovaries appear normal. There is a moderate amount of anechoic free fluid in the pouch of Douglas, measuring 32 x 25 x16 mm.

What is the most likely diagnosis?

A. Ovarian torsion

B. Ruptured ovarian cyst

C. Ectopic pregnancy

D. Appendicitis

E. PID

4. A 27-year-old woman came to your clinic with a 3-year history of lower abdominal pain. The pain occurs at any time but worse during her period. She has been with the same partner for 4 years and has pain with almost every sexual intercourse. She is not on any contraception as they are keen to start a family. However, she has never been pregnant and they have been trying for 2 years.

On examination, there is generalized tenderness in the lower abdomen particularly in the suprapubic area, but no masses palpable. Normal white vaginal discharge is seen on speculum examination and swabs are taken.

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

On bimanual palpation, the uterus is axial and fixed with cervical excitation. The Pouch of Douglas is very tender and a mass can be felt. the adnexae are both tender but no adnexal masses are palpable. Investigations are shown below:

A diagnosis of endometrioma is deduced. What is the most appropriate management?

A. Analgesia

Urinalysis: *protein negative, blood negative, leucocytes negative, nitrites negative*

Endocervical swab: *negative*

Chlamydial swab: *negative*

High vaginal swab: *negative*

Transvaginal ultrasound scan report: *the uterus is normal size and axial. The endometrium measures 12mm. Both ovaries appear enlarged at and in close proximity to each other. The left ovary measures 5 x 4.5 x 4 cm while the right ovary measures 6 x 7 x 5.5 cm.*

Laparoscopy findings: *brown spots on the peritoneum, adhesions, and bilateral endometriomas.*

B. Combined oral contraceptive (COC)

C. Oral progestogen

D. Excision or ablation of endometrial deposits

E. Total abdominal hysterectomy with bilateral salpingo-oophorectomy

5. A 58-year-old woman attends her GP clinic with a 1-year history of bloating, early satiety, and occasional crampy pelvic pain. She also has been having been passing urine more frequently and her bowel habit varies. She is known to have irritable bowel syndrome (IBS), which was diagnosed 2 years ago.

On examination, the abdomen is soft and non-tender and a mass is palpable in her left iliac fossa. Her serum CA 124 came back as 85 IU/mL (normal range < 36IU/mL). What is the most appropriate management?

A. Trial of mebeverine and lifestyle modification

B. Pelvic examination and pipelle biopsy

C. Computed tomography of the abdomen and pelvis

D. Ultrasound scan of the abdomen and pelvis

E. Urgent referral to the gynaecology clinic for urgent suspected cancer

Bibliography

1. Bottomley C and Rymer J. 100 Cases in Obstetrics and Gynaecology. London: CRC Press; 2015.

2. Dubb SS, Bailey A, Rodrigues C, Rhoads M, Ahmed J, and Maclaren E. 450 Single Best Answers in the Clinical Specialties. London: Hodder Arnold; 2012.

3. Cartledge P, Bach F, Cairns R, Jayaram M, and Watson M. Get Ahead! Specialties 100 EMQs for Finals. 2nd ed. London: CRC; 2016.

Answers

1. (C)

The risk of malignancy index (RMI) must first be establish to determine the risk of ovarian malignancy thus guiding its management. It can be calculated by using the product of serum CA-125 (CA-125), menopausal status (M), and ultrasound score (U) (see Table 3). The RMI for this lady would be 0 and therefore the most appropriate management would be conservative management (C) with 4-monthly scans and CA 125 levels for 1 year.

Immediate referral to a specialist (E) is not required and surgical management to remove an ovary (B) or both ovaries and the uterus (D) are unnecessary in this case. Laparoscopic cystectomy (A) (the removal of cyst, normally by aspirating the cyst contents and excising the cyst capsule to prevent recurrence) would be a potential management option if all other therapies have failed and the patient is sufficiently symptomatic. Nonetheless, a cyst this small is unlikely to cause any significant symptoms.

2. (B)

The woman is systemically unwell with pyrexia, tachycardia, raised inflammatory markers, neutrophilia and reactive thrombocythaemia which suggests an underlying infective process. Transvaginal ultrasound scan (TVS) showed a mass in the left iliac fossa which might be the cause thus leading to the most likely diagnosis to be tubo-ovarian mass (B), possibly an abscess. Blood cultures and vaginal and endocervical swabs should be taken although it is common for no organism to be cultured in women with PID.

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

Nonetheless, the diagnosis of diverticular abscess (A) could potentially be the cause although it is more common in the elderly. If the mass is found to be on the right side, consider the diagnosis of appendix abscess (C). Ovarian malignancy (D) would be unlikely to present with this acute inflammatory episode. Endometriosis/endometrioma classically presents with pelvic pain, cyclical dysmesnorrhoea, dyspareunia, infertility, and on TVS ('kissing cysts') and laparoscopy images show bilateral endometriomas ('chocolate cysts'), a complication of this disease.

Anaemia in this woman could be due to chronic menorrhagia or anaemia of chronic disease. Ferritin and folate levels would be useful to see whether there is a degree of iron deficiency too. This woman needs to be admitted for IV antibiotics. Please refer to your local antimicrobial guidelines for the management of PID. If there is no improvement within 24 - 48 hours with antibiotics, or the diagnosis is unclear, then laparoscopy or laparotomy should be performed to confirm the diagnosis and surgically drain the abscess.

With the diagnosis of PID, it can be due to sexually transmitted infection (STI) either acutely or in the past. Her partner also needs to be screened and treated for STI and contact tracing should be carried out to prevent reinfection and further spread of STI. The couple should avoid intercourse or use condoms until treatment has completed.

3. (B)

The sudden onset of left iliac pain in a non-pregnant woman suggests rupture, haemorrhage, or torsion of an ovarian cyst. In ovarian torsion (A), patient may present with being acutely systemically unwell, but in this case, the woman's condition has improved. Furthermore, there would also be an adnexal mass visible on the TVS. In the case of rupture of ovarian cyst (B) it is common for the ovary to appear normal on TVS, and the finding of free fluid in the pouch of Douglas suggests this pathology.

Since the patient is already clinically improving, the free fluid which is causing the peritoneal irritation and the rebound tenderness is expected to resolve spontaneously and she only requires expectant management with analgesia. In the longer term, the woman should be advised to use a different contraceptive as progesterone-only pill (POP/'mini pill') is known to be associated with an increased incidence of ovarian cysts and it seems from the history that this is the third episode for this woman.

Ectopic pregnancy (C) is unlikely as the woman is not pregnant. PID (E) and appendicitis (D), are unlikely as the woman seems to be clinically improving with no signs of infection i.e. apyrexial, normal heart rate, inflammatory markers within normal range, and TVS suggesting other pathology.

4. (D)

Endometriosis classically presents with pelvic pain, dysmenorrhoea, dyspareunia, and infertility. It is a painful inflammatory condition where active endometrial glands and stroma are found outside the endometrial cavity. The endometrial glands and tissue respond to cyclical hormonal changes and will bleed during menstruation causing pelvic and abdominal scarring. Endometriomas develop as ectopic endometriosis on the ovary produces blood which builds up into an encapsulated cyst with each consecutive menstrual cycle.

The management plan will depend on the woman's symptoms, priorities, and preferences particularly on their fertility wishes. Medical management includes analgesia (A), combined oral contraceptive pill (COCP) (B), progestogens (C), and gonadotrophin-releasing hormone (GnRH) analogues are useful for symptomatic relief however will not improve fertility.

Surgical treatment involving ablation or excision of endometriomas laparoscopically (D) has shown to increase the chance of pregnancy in some cases in addition to symptomatic relief. This woman has been trying for years to have children thus making option (D) the most preferable management. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (E) is reserved for women who have completed their families when other treatments have failed.

5. (E)

This woman presents with progressive bloating, early satiety, and abdominal/pelvic pain which raise the suspicion of ovarian malignancy, particularly in woman of this age. Although she has been diagnosed with irritable bowel syndrome (IBS), which might have been the cause of her symptoms, a new diagnosis of IBS at this age is rare and treating her symptoms (A) without any further investigation is inadvisable.

Her CA 125 is high and this case, the next appropriate step would be organizing an urgent ultrasound scan of the abdomen and pelvis (D). The risk of malignancy index (RMI) can then be calculated from the CA 125 value, ultrasound scan findings, and her menopausal status to determine the potential diagnosis. CT of abdomen and pelvis (C) is more appropriately used when ovarian cancer is suspected in a specialist setting where there is a need for staging the disease. Pipelle biopsy (B) is used when there is a suspicion of endometrial abnormality and not ovarian malignancy.

CLINICAL ASSESSMENT OF ADNEXAL MASSES IN NON-PREGNANT WOMEN

AO Alalade, NBM Sum

References

1. Drake J. Diagnosis and Management of Adnexal Masses. Am Fam Physician. 1998; 57(10): 2471-2476. Available from: http://www.aafp.org/afp/1998/0515/p2471.html [Accessed: 24 Aug 2017].

2. Coller J, Longmore M, Amarakone K. Oxford Handbook of Clinical Specialties. 9th ed. Oxford: Oxford University Press; 2013.

3. 3.Llewelyn H, Ang HA, Lewis K, Al-Abdullah A. Oxford Handbook of Clinical Diagnosis. 3rd ed. Oxford: Oxford University Press; 2014.

4. Givens V, Mitchell G, Harraway-Smith C, Reddy A, Maness DL. Diagnosis and Management of Adnexal Masses. Am Fam Physician. 2009; 80(8): 815-820. Available from: http://www.aafp.org/afp/2009/1015/p815.html [Accessed: 24 Aug 2017].

5. Olson SH, Mignonoe L, Nakraseive C, Caputo TA, Barakat RR, Harlap S. Symptoms of ovarian cancer. Obstet Gynecol. 2001:98(2):212–217. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11506835 [Accessed: 18 Sept 2017].

6. Collins S, Arulkumaran S, Hayes K, Jackson S, Impey L. Oxford Handbook of Obstetrics and Gynaecology. 3rd ed. Oxford: Oxford University Press; 2013.

7. Koonings PP, Campbell K, Mishell DR Jr, Grimes DA. Relative frequency of primary ovarian neoplasms: a 10-year review. Obstet Gynecol. 1989; 74: 921-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2685680 [Accessed: 18 Sept 2017].

8. Target Ovarian Cancer. Risk and Protection Factors of Ovarian Cancer. Available from: http://www.targetovariancancer.org.uk/information-and-support/what-ovarian-cancer/risk-and-protection-factors-ovarian-cancer [Accessed 24 Aug 2017].

9. Biggs WS, Marks ST. Diagnosis and Management of Adnexal Masses. Am Fam Physician. 2016; 93(8): 676-681. Available from: http://www.aafp.org/afp/2016/0415/p676.html [Accessed: 25 Aug 2017].

10. Royal College of Obstetrics and Gynaecologists (RCOG). Management of Suspected Ovarian Masses in Premenopausal Women. RCOG Guideline [Green-top Guideline No. 62] 2011. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_62.pdf [Accessed 24 Aug 2017].

11. National Institute for Health and Care Excellence (NICE). Appendix C. WHO performance status classification. Available from: https://www.nice.org.uk/guidance/ta121/chapter/appendix-c-who-performance-status-classification [Accessed: 4 Nov 2017]

12. Schutter EM, Kenemans P, Sohn C, Kristen P, Crombach G, Westermann R, et al. Diagnostic value of pelvic examination, ultrasound, and serum CA 125 in postmenopausal women with a pelvic mass. An international multicenter study. Cancer. 1994;74(4):1398–406. Available from: http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19940815)74:4%3C1398::AID-CNCR2820740433%3E3.0.CO;2-J/abstract [Accessed: 18 Sept 2017]. -11

13. Onwere C, Vakharia HN. Obstetrics and Gynaecology. 3rd ed. London: Elsevier; 2014. 12

14. Myers ER, Bastian LA, Havrilesky LJ, Kulasingam SL, Terplan MS, Cline KE, et al. Management of adnexal mass. Evid Rep Technol Assess (Full Rep) 2006;(130):1–145. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17854238 [Accessed: 20 Sept 2017]. 13

15. Zorn KK, Tian C, McGuire WP, Hoskins WJ, Markman M, Muggia FM, et al.The prognostic value of pretreatment CA 125 in patients with advanced ovarian carcinoma: a Gynecologic Oncology Group study. Cancer 2009;115:1028–35. Available from: https://jhu.pure.elsevier.com/en/publications/the-prognostic-value-of-pretreatment-ca-125-in-patients-with-adva-4 [Accessed: 20 Sept 2017].

16. Lu D, Kuhn E, Bristow RE, Giuntoli RL II, Kjær SK, Shih Ie-M, et al. Comparison of candidate serologic markers for type I and type II ovarian cancer. Gynecol Oncol 2011;122:560–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3152615/ [Accessed: 21 Sept 2017].

17. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of

18. multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients

19. with a pelvic mass. Gynecol Oncol 2008;108:402–8.

20. DePriest PD,Varner E, Powell J, Fried A, Puls L, Higgins R, et al. The efficacy of a sonographic morphology index in identifying ovarian cancer: a multi-institutional investigation. Gynecol Oncol 1994;55:174–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7959280 [Accessed: 21 Sept 2017].

21. American College of Obstetricians and Gynecologists. Management of adnexal masses.ACOG Practice Bulletin No. 83. Obstet Gynecol 2007;110:201–14. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17601923 [Accessed: 22 Sept 2017].

22. Togashi K. Ovarian cancer: the clinical role of US, CT, and MRI. Eur Radiol 2003;13 Suppl 5:L87–104. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15018172 [Accessed: 22 Sept 2017].

23. Solnik MJ,Alexander C. Ovarian incidentaloma. Best Pract Res Clin Endocrinol Metab 2012;26:105–16. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22305456 [Accessed: 23 Sept 2017].

24. National Institute for Health and Care Excellence (NICE) CKS, Pelvic Inflammatory Disease: NICE Guideline. 2015. Available from: https://cks.nice.org.uk/pelvic-inflammatory-disease#!scenario [Accessed: 4 Nov 2017].

25. National Institute for Health and Care Excellence (NICE) CKS, Polycsytic Ovary Syndrome: NICE Guideline. 2013. Available from: https://cks.nice.org.uk/polycystic-ovary-syndrome#!scenario [Accessed: 4 Nov 2017].

Authors

Mr Aderemi Olaoluwa Alalade
Wrexham Maelor Hospital
Croesnewydd Road
Wrexham
LL13 7TD
laolu@doctors.org.uk

Dr Norain Binti Muhammad Sum
Wrexham Maelor Hospital
Croesnewydd Road
Wrexham
LL13 7TD

Disclaimers

Conflict of interest: The authors of this article have no conflicts of interest
The Foundation Years Journal requires that authors disclose any potential conflict of interest that they may have. This is clearly stated in the Journal's published "Guidelines for Authors"**(https://www.123library.org/misc/FYJ_Guidelines_For_Authors.pdf).** The Journal follows the Guidelines against Conflict of Interest published in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals **(http://www.icmje.org/urm_full.pdf).**

Financial statement
The authors of this article have not been paid. The Foundation Years Journal is financed by subscriptions and advertising. The Journal does not receive money from any other sources. The decision to accept or refuse this article for publication was free from financial considerations and was solely the responsibility of the Editorial Panel and Editor-in-Chief.

Patient consent statement
All pictures and investigations shown in this article are shown with the patients' consent. We require Authors to maintain patients' anonymity and to obtain consent to report investigations and pictures involving human subjects when anonymity may be compromised. The Journal follows the Guidelines of the Uniform Requirements for Manuscripts **(http://www.icmje.org/urm_full.pdf).** The Foundation Years Journal requires in its Guidelines for Authors a statement from Authors that "the subject gave informed consent".

Animal & human rights
When reporting experiments on human subjects, the Foundation Years Journal requires authors to indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the HelsinkiDeclaration of 1975, as revised in 2008.

123Library

www.123Library.org

Sharing **more** knowledge



Contact us on
0207 253 4363
or email
sales@123library.org
for a
FREE TRIAL

What is 123Library?

123Library is a fast growing and innovative eBook and **digital content provider for libraries** in the field of healthcare.

What are the benefits for your library?

1. FULL FLEXIBILITY ✔
2. KNOWLEDGE ✔
3. CUSTOMER CARE ✔
4. NO HASSLES ✔
5. FULL SECURITY ✔
6. GET FEEDBACK ✔
7. SUPPORT ✔
8. EASE OF USE ✔
9. SAVING MONEY ✔

Benefit today, visit **www.123Library.org**

123Library

Subscribe to the Foundation Years Journal, **visit www.123library.org**
For more info call **0203 0313 866** or email **sales@123library.org**

Volume 12, Issue 2: **Cardiology & Oncology**

2018 Past Issues

Volume 12, Issue 1: Accident & Emergencies + Vascular Disease

2017 Past Issues

Volume 11, Issue 10: Dermatology, Diabetes & Endocrinology + Palliative Care & Gastroenterology
Volume 11, Issue 9: General Medicine & Mental Health
Volume 11, Issue 8: General Surgery
Volume 11, Issue 7: Haematology, Palliative Care & Geriatrics
Volume 11, Issue 6: Immunology, Infectious Disease, Nephrology & Rheumatology
Volume 11, Issue 5: Anesthesia
Volume 11, Issue 4: Urology
Volume 11, Issue 3: Obstetrics & Gynaecology
Volume 11, Issue 2: Radiology & Rheumatology
Volume 11, Issue 1: Ophthalmology & Pediatrics

2016 Past Issues

Volume 10, Issue 10: Diabetes & Endocrinology + Gastroenterology
Volume 10, Issue 9: Orthopaedics
Volume 10, Issue 8: Cardiology & Maxilofacial
Volume 10, Issue 7: Respiratory
Volume 10, Issue 6: Oncology
Volume 10, Issue 5: Palliative Care & ENT
Volume 10, Issue 4: Accident & Emergency & Dermatology
Volume 10, Issue 3: Vascular Disease
Volume 10, Issue 2: Neurology
Volume 10, Issue 1: Psychiatry

2015 Past Issues

Volume 9, Issue 10: Rheumatology
Volume 9, Issue 9: Anaesthesia (Part 2)
Volume 9, Issue 8: Anaesthesia (Part 1)
Volume 9, Issue 7: General Surgery
Volume 9, Issue 6: Ophthalmology
Volume 9, Issue 5: Infectious Diseases & Nephrology
Volume 9, Issue 4: Respiratory
Volume 9, Issue 3: Haematology
Volume 9, Issue 2: Gastroenterology
Volume 9, Issue 1: Urology - Part 2

2014 Past Issues

Volume 8, Issue 10: Urology - Part 1
Volume 8, Issue 9: Obstetrics & Gynaecology - Part 2
Volume 8, Issue 8: Paediatrics - Part 2
Volume 8, Issue 7: Obstetrics & Gynaecology - Part 1
Volume 8, Issue 6: Paediatrics - Part 1
Volume 8, Issue 5: Diabetes & Endocinology
Volume 8, Issue 4: Immunology & Nephrology
Volume 8, Issue 3: Neurology - Part 2
Volume 8, Issue 2: Cardiology - Part 2
Volume 8, Issue 1: Radiology - Part 2

2013 Past Issues

Volume 7, Issue 10: Vascular Disease - Part 2
Volume 7, Issue 9: Radiology Issue - Part 1
Volume 7, Issue 8: Environmental Medicine
Volume 7, Issue 7: Neurology - Part 1
Volume 7, Issue 6: Cardiology - Part 1
Volume 7, Issue 5: Vascular Disease - Part 1
Volume 7, Issue 4: ENT - Part 2
Volume 7, Issue 3: Ophthalmology - Part 2
Volume 7, Issue 2: Accident & Emergency
Volume 7, Issue 1: ENT

2012 Past Issues

Volume 6, Issue 10: Ophthalmology
Volume 6, Issue 9: Oncology
Volume 6, Issue 8: Anaesthesia Part 2
Volume 6, Issue 7: General Surgery Part 2
Volume 6, Issue 6: Psychiatry Part 2
Volume 6, Issue 5: Anaesthesia
Volume 6, Issue 4: General Surgery
Volume 6, Issue 3: Orthopaedics, Oral & Maxillofacial
Volume 6, Issue 2: Rheumatology
Volume 6, Issue 1: Geriatrics

How We Can Help You Succeed?

To find out how 123Doc can help you dramatically increase your medical knowledge, register your interest on our website.

123Doc Education
72 Harley Street
London
W1G 7HG

Tel: +44 (0)203 0313 866
Web: www.123library.org
Email: sales@123library.org

ISSN

1753-6995