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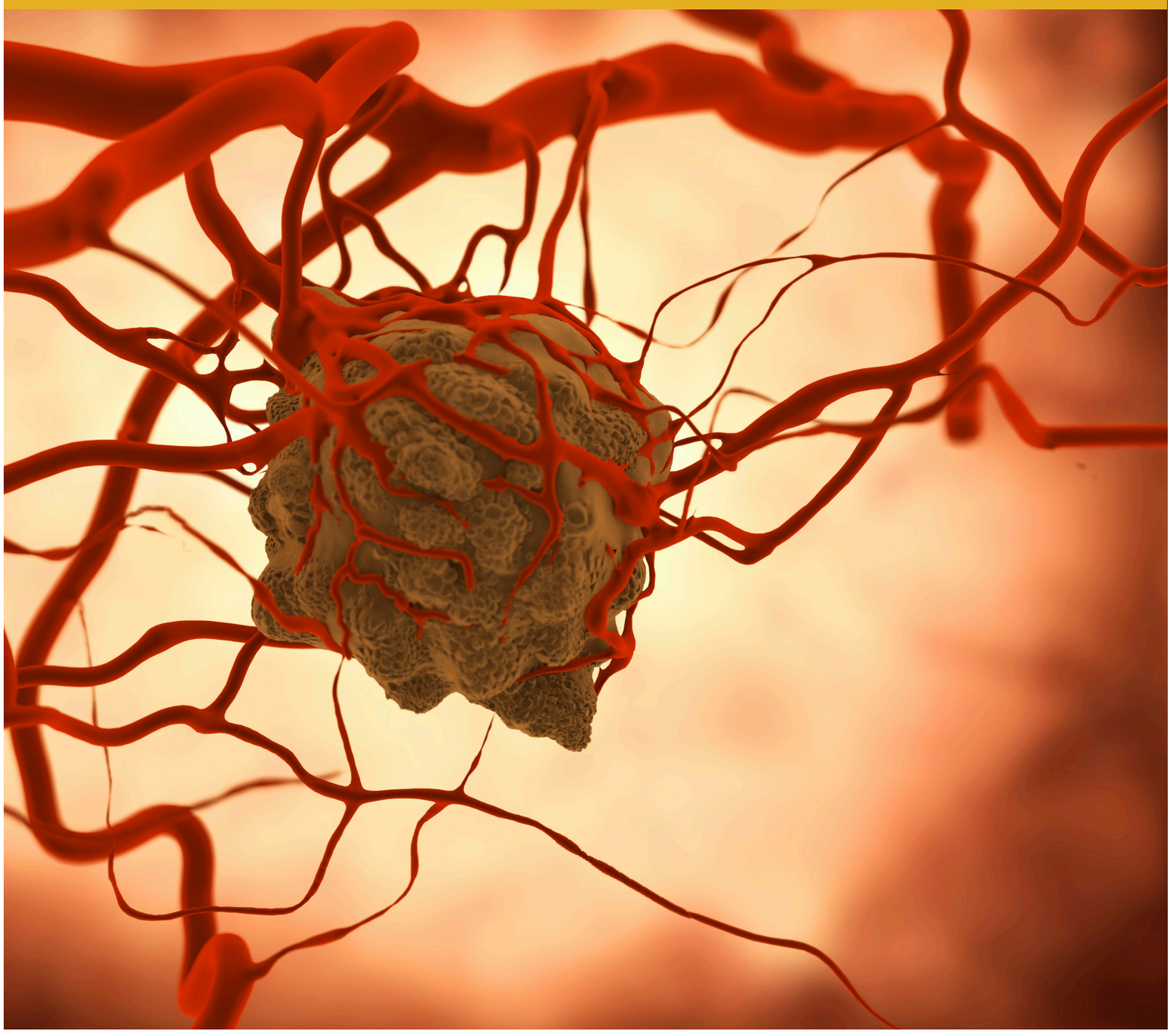

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Foundation Years Journal

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.

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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:

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Editorial

Many people like to hold a book or journal in the hand. The ability to browse by turning pages, for those to annotate, who are prepared to deface paper copies to read without needing to find electronic apparatus to enable viewing (whether by computer, by Kindle device or otherwise), all are powerful stimuli to keep to conventional hard copy, paper publications. The feel of a book, the smell of the paper (maybe the binding), the colourful printing, and the variations in font and style all contribute to this sensual experience. However, paper copies become dated and cannot easily be amended except in loose-leaf form where they lose much of their aesthetic appeal. They are more expensive to produce at the point of the user. They decay with use, whether aided by fingers, thumbs or by mice, and they are bulky for publishers and readers to transport.

Hence, this trends towards electronic publishing. Electronic journals have many advantages and can be accessed from computers worldwide. This journal offers all of these advantages and on this occasion brings to readers aspects of important topics relevant to Foundation Years practitioners.

Christopher Gardner-Thorpe
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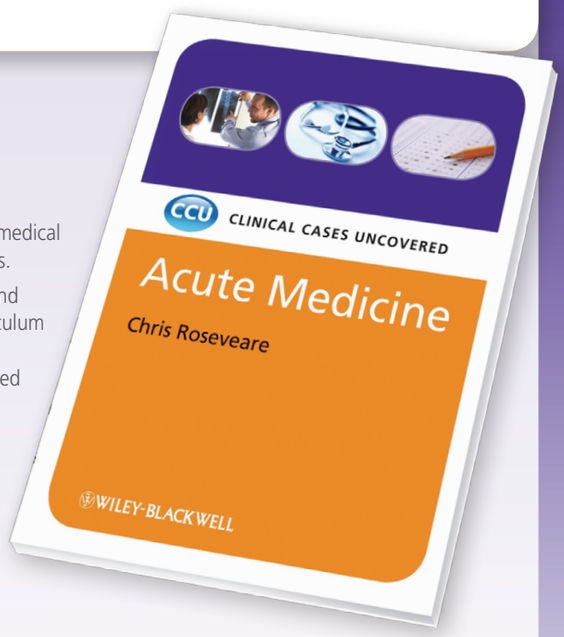
Notice

Acute Medicine

CLINICAL CASES UNCOVERED

Chris Roseveare,
Southampton General Hospital



Acute Medicine is the central part of foundation and specialist general medical training and is one of the most rapidly expanding UK hospital specialties.

Acute Medicine: Clinical Cases Uncovered combines patient cases and outcomes, drawn from real-life experiences, with reference to the curriculum for Training in General (Acute) Medicine. It provides self-assessment MCQs, EMQs and SAQs to give Foundation Programme doctors and allied healthcare professionals the perfect preparation for life on the wards.

"Easy to read, excellent level of information and suitable to take on the wards for quick reference."
FINAL YEAR STUDENT, UNIVERSITY OF LIVERPOOL MEDICAL SCHOOL

"This is an excellent book! It illustrates key concepts in acute medicine through clearly laid out case studies that clinical students will commonly see while "on take" as part of their medical training... I would definitely use this book to study for my medical finals!"
4TH YEAR STUDENT, BRIGHTON AND SUSSEX UNIVERSITY

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WILEY-BLACKWELL

ONCOLOGICAL EMERGENCIES FOR FOUNDATION DOCTORS

R Walshaw, D Warriner, H Innes

Oncological emergencies for foundation doctors
Good Clinical Care

Abstract

Cancer and its complications are becoming increasingly common. All junior doctors should have a basic understanding of the key oncological emergencies, such as febrile neutropenia, hypercalcaemia, metastatic spinal cord compression, superior vena cava obstruction, and upper airways obstruction. We aim to outline the presentation, investigation and management of patients with these conditions, focusing on what would be expected of a junior at completion of the Foundation Training programme. Such patients often present to the acute take, and while not all junior doctors will get the chance to rotate through an oncology job, we hope that this article will serve as a guide and assist all juniors. Finally, the above conditions may be disparate, but the take home message is the same for all; prompt recognition is paramount, protocols are available locally to help the inexperienced, and if in doubt, seek help early.

Introduction

The combination of an ageing population and improvements in detection, treatment, and survival have led to cancer and its complications becoming increasingly common (National Office of Statistics; Yates et al 2009).

Recognition and management of the acutely ill patient are now a key competency in the latest Foundation Programme (Foundation Programme Curriculum). However, Cave et al 2007 showed "foundation year doctors lack knowledge about cancer care and symptom control". With this in mind, all junior doctors must have a basic understanding of the key oncological emergencies. This article aims to discuss the six most common oncological emergencies namely febrile neutropenia, malignant hypercalcaemia, metastatic spinal cord compression, raised intracranial pressure, superior vena cava obstruction, and stridor / upper airways obstruction. Other emergencies, such as thrombosis, haemorrhage, and hyponatraemia, are beyond the scope of this article.

Key phrases

Foundation Doctor, Febrile Neutropenia, Malignant Hypercalcaemia, Cord Compression, Raised Intracranial Pressure, Oncological Emergencies, Superior Vena Caval Obstruction, Upper Airways Obstruction.

Febrile Neutropenia (FN)

FN is a complication of any chemotherapy regimen, some more commonly than others. Chemotherapy can cause bone marrow suppression leading to pancytopenia, i.e. low neutrophils, platelets, and haemoglobin. Patients receiving chemotherapy are advised not to self-medicate fevers at home, but to seek urgent medical attention.

FN comprises two components:

- Fever (a single reading of ≥38.3 °C or >38 °C for one hour)
- Neutrophil count of <0.5x109L

The term 'neutropenic sepsis' (NS) is reserved for patients who have other signs of a systemic inflammatory response syndrome (SIRS), such as tachypnoea or tachycardia.

A review by NCEPOD (2008) on deaths within 30 days of chemotherapy suggested that there is significant room for improvement in the management of FN. An NCAG report (2009) in response to this has set the standard that antibiotics should be delivered within one hour of presentation.

Learning point 1

In practice, any chemotherapy patient presenting with a sustained fever (>37.5ºC) in the presence of a low neutrophil count should be treated as potentially septic.

Dehydrated, elderly, and patients on steroids or anti-pyretics may not develop a fever.

Fever may be part of the disease itself, e.g. lymphoma

History and Examination

- It is imperative that both are undertaken thoroughly, looking for any source of potential infection, including rarer causes such as a perianal abscess.
- A systematic enquiry should be undertaken, particularly about symptoms of infection e.g. cough, dysuria, diarrhoea.
- Examination should be in response to the history, but may include mouth, ears, nose, eyes, chest, abdomen, and indwelling devices/catheters

ONCOLOGICAL EMERGENCIES FOR FOUNDATION DOCTORS

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Investigations

- Septic Screen (see Tables 1 and 2)

Blood Tests
Full Blood Count (FBC)
Urea and Electrolytes (U+Es)
Liver Function Tests (LFTs)
Inflammatory markers e.g. CRP

Table 1

Other Tests
Blood Cultures (2 sets) & line cultures
Urine & Stool Culture
(if symptomatic)
Throat Swab
Chest X-ray

Table 2

When culturing from central lines, each lumen of the line should be cultured, as well as taking peripheral cultures. Portacaths (devices implanted under the skin to provide an access site for IV treatment) often require special needles to obtain a blood sample from them.

Indwelling devices, including all central line ports should be cultured and swabbed.

Chemotherapy inhibits the body's ability to mount an immune response, and in patients with a LRTI this may result in a lower accumulation of alveolar cellular exudate (consolidation). Consequently, patients with a severe lower respiratory tract infection may have a relatively normal CXR.

Management

All acute hospitals should have a specific protocol for the management of FN.

1. Resuscitation

An ABCDE approach should be taken in patients with septic shock

2. Antibiotics

- Broad spectrum intravenous (IV) antibiotics should be given immediately.
- Antibiotic regimen will vary according to local protocol, based on prevalence and resistance patterns of organisms.

Increasingly, gram-positive organisms account for the majority of microbiologically documented infections in FN. However, initial therapy should consist of broad-spectrum intravenous antibiotics to cover both gram-positive and gram-negative organisms.

In majority of the cases, the organisms responsible are not found. It is believed that many infections are endogenously derived.

There is no recommended antibiotic regimen.
Acceptable options include (Taylor et al 2002):

- Monotherapy, e.g. Meropenem 1 g TDS
- Duotherapy, e.g. Piperacillin/Tazobactam 4.5g TDS-QDS with Gentamicin 3-5 mg/kg OD

The addition of vancomycin/teicoplanin may also be appropriate for line infections/MRSA – (check local protocol).

The duration of antibiotics is typically 5-7 days, but will be influenced by:

- Patient's condition
- Improvement in neutrophil count and temperature
- Identification of the culprit organism

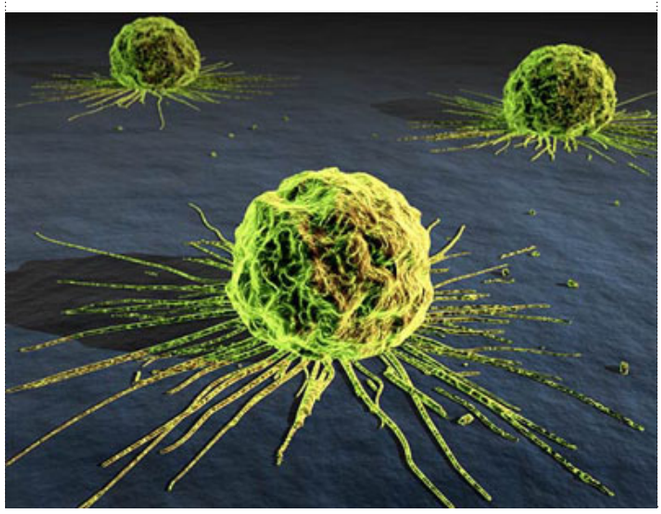
All FN patients will require regular (at least daily) medical assessment depending on their condition, and ideally should have vital signs observations done 1-2 hourly at first until they become more stable. Deterioration in vital signs must prompt urgent medical review. In the first 24-48 hours, antibiotic modification should be guided by clinical well-being, culture results and neutrophil recovery.

Some chemotherapy agents/regimens are known to cause more prolonged neutropenia than others. For patients who are expected to have prolonged neutropenia (more than several days) the addition of antifungal/antiviral agents may be appropriate. This will require discussion with a senior clinician and/or microbiologist.

Learning point 2
If high temperatures continue despite antibiotics, re-culture after 24 hours.

3. Granulocyte

Colony-Stimulating Factor (G-CSF) can be used to boost neutrophil counts during FN (Stanworth et al 2005). See local protocol and seek advice from seniors.



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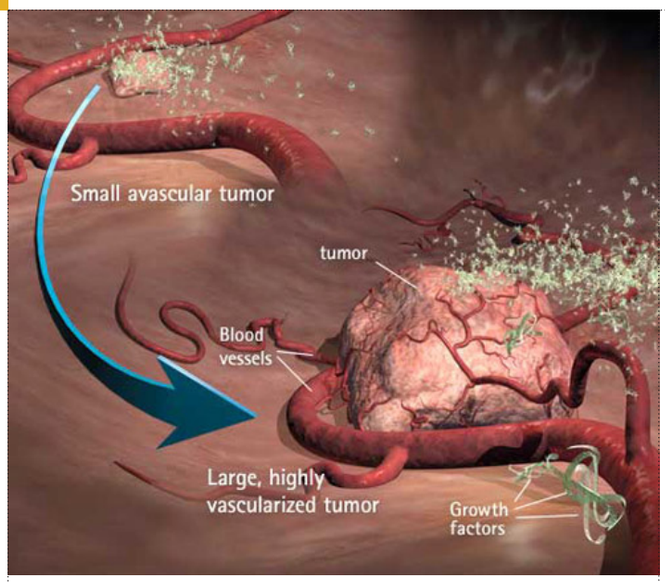


Malignant Hypercalcaemia (MHC)

Definitions of MHC vary, but it should be considered in the presence of a corrected serum calcium > 2.6 mmol/l. Incidence varies widely by cancer type, occurring most commonly in breast, lung and renal cancers, as well as in multiple myeloma.

The rates of survival vary; MHC is a usually a feature of advanced disease with a poor prognosis (Vassilopoulou-Sellin et al 1993).

Hypercalcaemia is mediated by soluble factors secreted by tumour cells and the immune system, including PTHrP. These factors stimulate excess bone resorption and release of calcium from the bone matrix.

Learning point 3

MHC can occur in the absence of bone metastases.

The severity of symptoms is related to the rate of change of calcium, rather than its absolute value.

Presentation (See tables 5 and 6)

Symptoms
- Dehydration
- Pruritus
- Polyuria
- Weakness
- Nausea
- Constipation

Table 5

Signs
- Confusion
- Seizures
- Coma
- Bowel obstruction
- Hyporeflexia

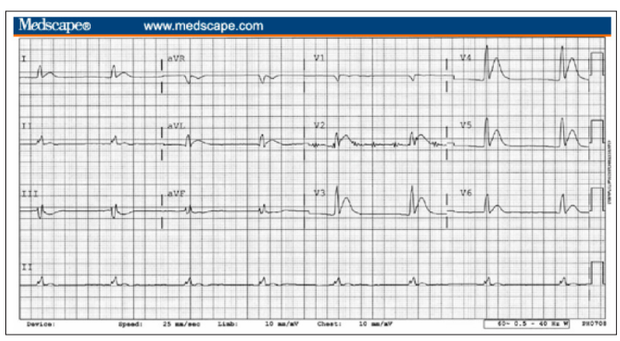
Table 6

Patients with asymptomatic or mildly symptomatic hypercalcaemia with corrected calcium levels <3 mmol/L do not usually require treatment. Symptoms occur typically at corrected calcium >3 mmol/l. Whilst some of the above symptoms may be due to the underlying malignancy, it is important to investigate for MHC if a patient experiences new, a change in, or vague and non-specific symptoms (see Table 7).

A useful mnemonic for the effects of hypercalcaemia
- *Bones*: bone pains
- *Stones*: kidney stones
- *Groans*: constipati=on
- *Psychic moans*: depression

Table 7

Investigations
- Bloods: FBC, U+Es, LFTs including phosphate and calcium
- Measure fluid balance
- Lying/standing blood pressure (a drop will indicate intravascular depletion)
- Confirm corrected Calcium = measured Ca2+ + [(40 - albumin) x 0.02]
- ECG changes may include short QT, widened T, bradycardia and arrhythmias.
- Bone Scan/skeletal imaging of painful areas - if no previous bone involvement, may show lytic lesions



Picture 1: ECG typical of hypercalcaemia (short QT interval, widened T wave)

ONCOLOGICAL EMERGENCIES FOR FOUNDATION DOCTORS

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Management

1. IV rehydration
- 3-4L per day for 2-3 days maintaining urine output 100mL/hr

2. Intravenous bisphosphonates
- inhibit osteoclast activity, therefore reducing serum Ca2+
- Ca2+ levels will take several days to fall

Regimens vary between hospitals. Major et al (2001) have shown Zoledronate to be superior to Pamidronate in MHC.

- IV Zoledronate 4 mg (in 250 mL 0.9% Saline) over 15 minutes, or
- IV Pamidronate 90 mg (in 250 mL 0.9% Saline) over one hour.

Doses and infusion rates of the above can vary in renal impairment.

3. Calcitonin
- It inhibits osteoclast activity and calcium absorption in the gut.
- Generally used in bisphosphonate-resistant hypercalcaemia with advice from clinical biochemist.
- IM/SC Calcitonin 4-8 unit/kg 6 hourly for two days

4. Furosemide
- It maintains diuresis and inhibits calcium resorption in the distal tubule.
- It should only be given following senior advice.

Metastatic Spinal Cord Compression (MSCC)

NICE (2008) defined MSCC as "spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability." Early diagnosis and treatment are imperative to reduce the risk of neurological sequelae, which arise due to direct pressure on the cord by metastasis or indirectly due to instability and collapse of the vertebral body.

Assessment (see tables 8 and 9)

Red flags suggesting Spinal Metastases
- Localised tenderness in the spine
- Spinal pain worse on straining
- Nocturnal or worsening lumbar pain
- Thoracic or cervical spine pain

Contact Cancer Centre < 24 hours

Table 8

Red flags suggesting Acute Compression
- Limb weakness
- Difficulty walking/standing
- Perianal/saddle anaesthesia
- Bladder/bowel dysfunction

Contact Cancer Centre Immediately

Table 9

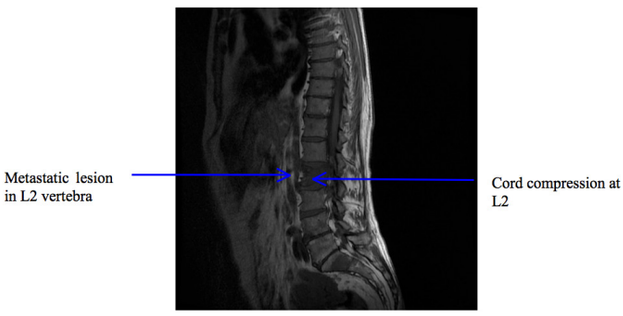
A full neurological examination should include,
- Spasticity, and loss of proprioception,

pinprick and temperature sensation occur early.
- Deep tendon reflexes and Babinski's sign may be absent at first.
- Clear weakness, sensory loss, and bilateral Babinski's sign develop later.
- Lax anal tone is a late sign.

The level of compression of the spinal cord or cauda equina will determine the level of signs and symptoms, as per a dermatomal/myotomal distribution.

Imaging

MRI of the whole spine should be performed <24 hours of the onset of symptoms.



Picture 1: T1-weighted MRI

Referral

Once MRI confirms cord compression, referral should be made to the regional cancer centre as soon as possible. Hospitals should have a specific MSCC management pathway – check individual hospital protocols.

Learning point 4

Percussion tenderness over the spine is not a sensitive sign.

MSCC may, despite all of the above, be painless.

ONCOLOGICAL EMERGENCIES FOR FOUNDATION DOCTORS

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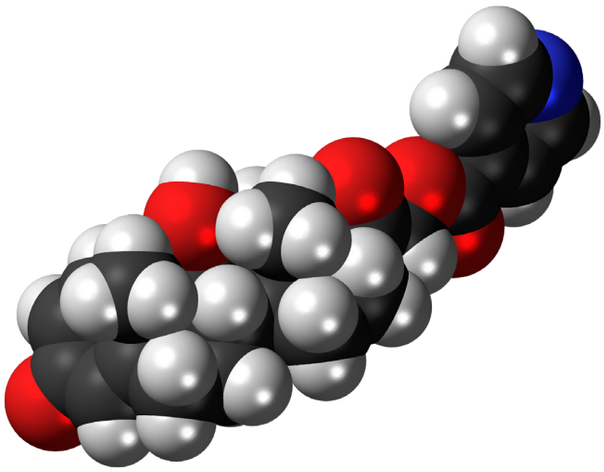

Oncological emergencies for foundation doctors
Good Clinical Care

Symptoms and signs include:

- Headache (classically worse on bending forward)
- Nausea and vomiting
- Visual disturbance and ocular palsies
- Papilloedema
- Altered conscious /coma

Initial treatment is corticosteroids (Dexamethasone 8 mg BD), and consider gastric protection with a proton pump inhibitor. Neurosurgical intervention and IV mannitol (osmotic diuretic) may occasionally be considered in some patients. Seek senior advice.

Management

Dexamethasone 16 mg loading dose, then 8mg BD, until definitive treatment.

- It is reduced and stopped over 5-7 days after definitive treatment is started (NICE, 2008)
- Monitor blood glucose levels and consider gastric protection, such as a proton pump inhibitor (PPI).

Corticosteroids inhibit prostaglandin and interleukin release, reducing vasogenic oedema around the lesion, thus reducing pressure on the cord.

- Analgeisa – opiates are likely to be required
- Keep patient starved until referral to a cancer centre (the patient may be appropriate for urgent neurosurgical intervention requiring a general anaesthetic)
- Early discussion with neurosurgery should be sought if deemed appropriate.
- Definitive treatments to decompress the spinal cord include
  - Radiotherapy
  - Surgery

Complications and supportive care

- Venous thromboembolism: consider compression stockings and/or prophylactic anticoagulant as per local protocols.
- Bed rest, laid flat for 24 hours and gradually sit up over the following days after definitive treatment is begun. Appropriate nursing care should be initiated to avoid pressure sores.
- Long-term urinary or suprapubic catheter may be appropriate, and aperients may be required for constipation.

Raised Intracranial Pressure (ICP)

Cerebral metastases can occur as a presenting symptom of malignancy or during the course of cancer and can cause raised intracranial pressure. Other causes of raised intracranial pressure include primary cerebral tumours, and haemorrhage.

Superior Vena Caval Obstruction

Intrathoracic malignancy can lead to obstruction of the SVC by invasion or external compression of the vessel, with the majority being a result of lung cancer or Non-Hodgkins lymphoma.

Symptoms and signs of SVCO relate to the growth of tumour not allowing adequate blood flow back to the right atrium.

Symptoms	Signs
• Dyspnoea • Head fullness • Cough • Arm swelling • Dysphagia • Headaches	• Facial oedema • Neck/chest wall venous distension • Arm oedema • Cyanosis • Facial plethora • Stridor

Learning point 5

Rapidly worsening upper airway compromise in patients with SVCO is a medical emergency.

See section below "Upper airways obstruction".

ONCOLOGICAL EMERGENCIES FOR FOUNDATION DOCTORS

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Investigation

- FBC, U+E, Group and Save, Clotting
- CXR. Abnormal in the vast majority of patients with SVCO

(Parish et al 1981 e.g. widened mediastinum, pleural effusion)

Further Imaging

- Contrast-enhanced chest CT defines site and extent of blockage and often identifies the underlying cause, e.g. compression or thrombosis.

Treatment

Initial

1. If concerns persist regarding airway, speak to the anaesthetic team early.
2. Raise the head – reduces hydrostatic pressure and oedema.
3. Supplemental oxygen
4. Avoid IM/SC injections in the arms (delayed absorption of drugs due to the slow venous return)

Corticosteroids

- Reduce swelling associated with laryngeal or cerebral oedema
- Can be effective in steroid-sensitive malignancies (e.g. lymphoma)
- A typical regimen may include Dexamethasone 8mg BD for 5-7 days.

Endovascular stents

- Provide rapid relief in patients with severe symptoms
- Used while histological diagnosis is still unknown.

Radiotherapy

- Many tumours causing SVCO are radiation sensitive.
- Radiation causes shrinkage of the tumour.
- Improvement is usually noted within 72 hours

- **Stridor due to airway obstruction or laryngeal oedema**
- **Coma due to cerebral oedema**

Table 12: Indications of emergency stent insertion and radiotherapy

Chemotherapy

Maybe the treatment of choice for patients with very chemosensitive malignancies, e.g. small cell lung cancer (SCLC) and Non Hodgkin's Lymphoma (NHL).

Stridor / Upper airways obstruction

Any advanced malignant disease of the tongue, pharynx, larynx and trachea, as well as extrinsic compression on the upper airways from surrounding masses has the potential to cause obstruction of the airways. This can be fatal if untreated.

Presentation

Upper airways obstruction (UAO) in a patient is often obvious, but if it develops gradually can be relatively asymptomatic at rest. As airway resistance varies inversely with the radius to the power four, only small changes in pathology at the point of obstruction can cause dramatic clinical deterioration. Indeed, sudden worsening of airway patency can be unpredictable.

Signs and symptoms of severe UAO include:

- Stridor (this indicates severe airway obstruction)
- Dyspnoea, tachypnoea
- Cyanosis
- Altered consciousness and agitation
- Reduced air entry on auscultation

Investigations

Imaging modalities such as X-ray, CT and bronchoscopy all have a role in the diagnosis of upper airway obstruction. However, due to the immediacy of the problem, establishing a secure and patent airway, is first and foremost the key challenge.

Management

In a patient with stridor suggestive of upper airways obstruction, a quick history and examination should be undertaken to establish where they lie on the spectrum of severity. Many patients may have a gradual onset of mild symptoms, and can be investigated and managed not as an emergency (out of the scope of this article). Others may have impending respiratory failure and require emergency care.

Learning point 6

Being able to judge where a patient lies on this spectrum requires experience above anything else.

Junior medical staff should have a very low threshold for obtaining urgent senior reviews from ENT/anaesthetics.

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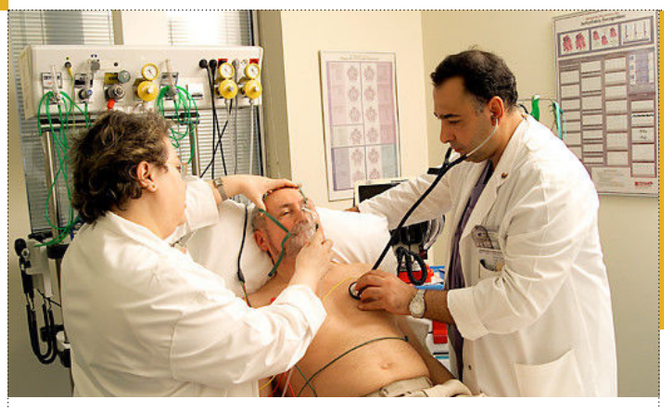

Severe Upper Airways Obstruction

A patient with any new signs of severe UAO should be treated as an emergency. Administer maximum oxygen available and ask for experienced senior help quickly. This may necessitate emergency bleep systems for ENT +/- anaesthetics if available.

In patients with impending respiratory failure, a practitioner trained in airway management should establish a patient airway urgently:

- Endotracheal intubation (direct of fibreoptic) – effective in the vast majority of cases.

- Surgical intervention in the form of crycothyroidotomy or tracheotomy is very rare at this point in UOA caused by malignancy.

Heliox is a helium-oxygen gas mixture with a lower density than air, causing it to generate less airways resistance than air. This reduces the work the patient has to do to ventilate. It has a beneficial role in malignant upper airways obstruction but ,should be considered to buy time, but is by no means a cure.

Further management (see tables 13 and 14)

Once a secure airway is established, there are potentially further treatment options available. These may be with palliative or curative intent, and the decision on which one(s) to offer is undertaken by a multidisciplinary team, taking into account a number of factors:

- Type and location of tumour(s)
- Disease prognosis
- The patient's performance status and co-morbidities
- Patient choice

Oncological emergencies for foundation doctors
Good Clinical Care

Surgical/bronchoscopic
• Tracheostomy
• Laser debulking therapy
• Electrocautery
• Argon-Plasma Coagulation
• Balloon dilatation
• Airways stenting
• Surgical resection

Table 13

Non-surgical
• Corticosteroids
• Radiotherapy
• Brachytherapy
• Chemotherapy

Table 14

Summary

Prompt recognition of oncological emergencies is of paramount importance. Hospitals have protocols on the management of these conditions to help the inexperienced junior doctors. If in doubt, advice from senior colleagues should be sought with urgency.

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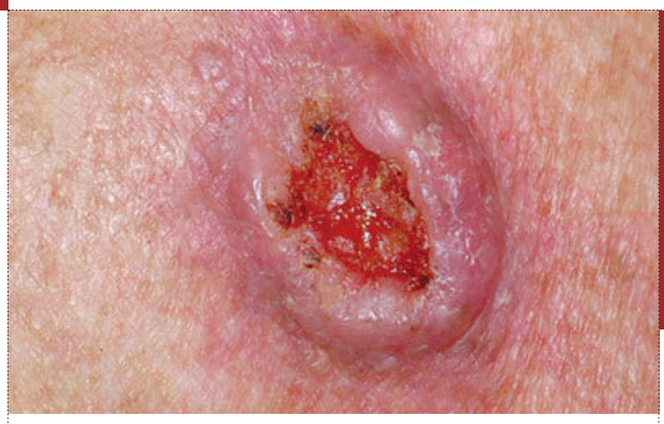
CASE BASED DISCUSSION: MANAGING A PATIENT WITH CARCINOMA OF UNKNOWN PRIMARY

P J Gomes, C Chinyama



Abstract

A 67 year old man presented with fatigue, mild dyspnoea and an aching lower back and rib cage. He was found to have diffusely abnormal bones on imaging and further investigation demonstrated adenocarcinoma of unknown primary site. (1) This case-based discussion describes the process of investigation and management of this patient, some unusual features of his case and potential complications of treatment. He remains well more than two years after diagnosis.

Case history

A 67 year old man gave a three month history of progressive malaise and lethargy associated with aching discomfort in his lower back, neck and rib cage. He had a past history of hypertension for which he was taking amlodipine, indapamide and losartan. He was an ex-smoker having stopped 25 years previously. Further systematic enquiry revealed no evidence of gastro-intestinal or urological symptoms, no respiratory symptoms and no headaches. A thorough physical examination revealed a slim and reasonably fit man who was moderately pale. There was no finger clubbing, no lymphadenopathy and both chest and abdominal examinations, including rectal examination, were normal. There was no bony tenderness. Subsequent examination of the proximal aero-digestive tract was normal.

Laboratory investigations demonstrated a raised alkaline phosphatase (1085, NR 32-122 IU/l), mildly elevated gamma-glutamyl transferase (102, NR 9-96 IU/l), anaemia (haemoglobin 8.4 g/dl) and high ESR (106 mm/hr). Prostate specific antigen (PSA) was normal at 1.7 and a myeloma screen was negative. Initial radiological investigations included X-rays of the chest, lumbar spine and pelvis. These demonstrated widespread bony abnormality with both lytic and sclerotic lesions in ribs, spine and pelvis (figure 1). These changes were confirmed on computed tomography (CT) imaging of the chest, abdomen and pelvis. CT scan of the neck was also carried out in view of the neck pain and demonstrated widespread bony abnormality particularly of the proximal cervical vertebrae. The CT scan failed to demonstrate evidence of soft tissue metastases or a primary tumour. Faecal occult blood tests were negative. The patient consented to undergo bone marrow aspirate and trephine biopsy from the right posterior superior iliac spine – this was within an area of abnormality on imaging. This was carried out under local anaesthesia without sedation.

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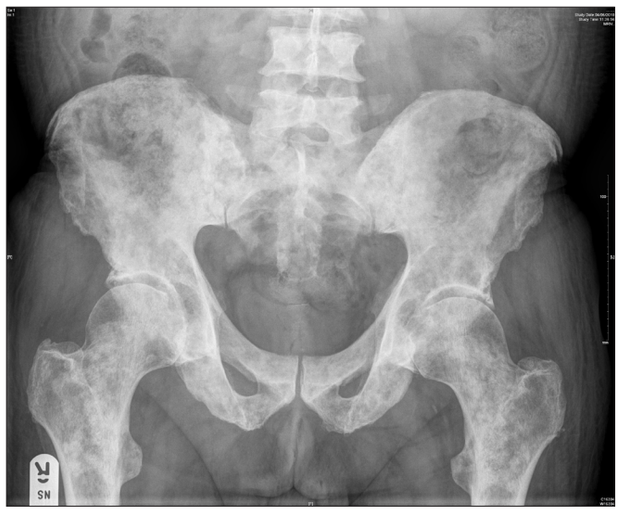

Figure 1

Histology demonstrated complete marrow replacement by fibrosis infiltrated with high grade cancer cells. These were pleomorphic with large hyperchromatic nuclei and some demonstrated signet-ring differentiation (figure 2). Immunocytochemistry demonstrated strong positive Pan K, indicating epithelial origin. In addition BerEP4, another epithelial marker, was mildly positive. The cells were strongly positive for CK72 commonly expressed in lung cancer and cancer of the genito-urinary tract (figure 3). The cells were negative for thyroglobulin, TTF1, PSA and CK20, making cancers of the thyroid, lung, prostate and GI tract less likely. However, up to 10% of lung cancers fail to express TTF1, occasional prostate cancers fail to express PSA and upper gastrointestinal cancers can be particularly difficult to confirm. The mucin stain DPAS was inconclusive. Gene-expression profiling was not pursued as this is not currently recommended in the investigation of carcinoma of unknown primary. The conclusion was that this was a metastatic poorly differentiated carcinoma with features of urothelial or pulmonary origin. A diagnosis of metastatic carcinoma of unknown primary was made and after discussion at both the urological and lung multi-disciplinary team meetings, systemic therapy was recommended.

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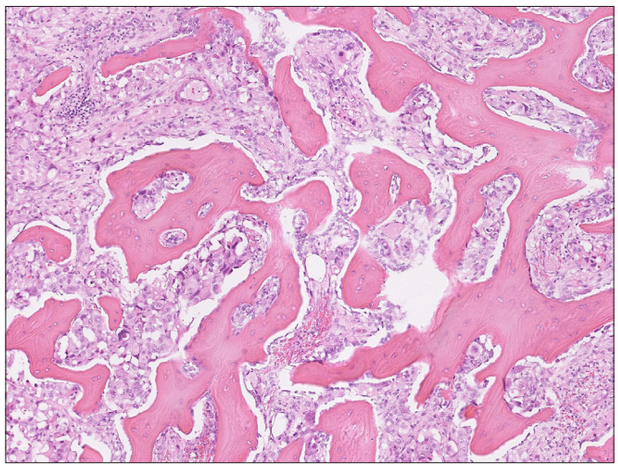

Figure 2

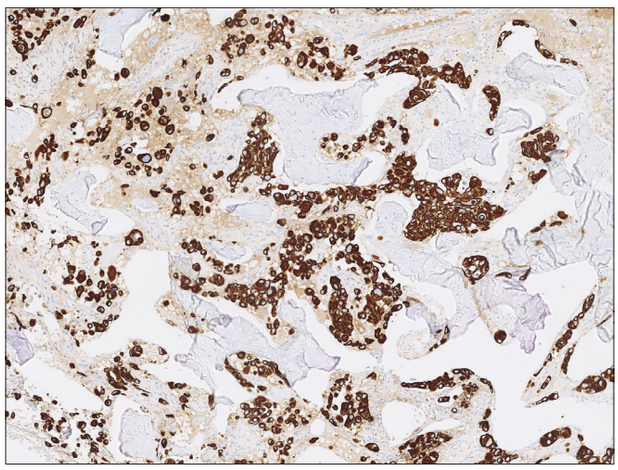

Figure 3

The patient and his wife were fully informed and a thorough discussion was held on the risks and potential benefits of palliative systemic therapy. The patient agreed to treatment with platinum-based chemotherapy in the form of carboplatin and gemcitabine, together with bisphosphonate therapy in the form of zoledronic acid. Chemotherapy was given with primary granulocyte colony stimulating factor (g-csf) support in view of the degree of marrow abnormality, in order to reduce the risk of febrile neutropenia. Despite this, he subsequently developed one episode of febrile neutropenia. This was associated with hypotension. A rapid infection screen showed no apparent focus of sepsis. He was treated immediately with intravenous piperacillin with tazobactam together with gentamicin as per the local febrile neutropenia protocol and he recovered promptly.

He was not able to tolerate carboplatin beyond three cycles due to myelosuppression but was able to continue single agent gemcitabine at reduced dose. He improved considerably in terms of pain and general well-being. Routine re-staging CT imaging six months after diagnosis showed many of the lytic bony lesions to have become sclerotic, indicating healing. However, an asymptomatic pathological fracture was now evident through the odontoid peg (figure 4), without neurological impairment. After spinal orthopaedic advice, he was treated with radiotherapy and wore a hard collar for several months. He later developed painful lower legs and X-rays confirmed tibial and fibula metastases – an unusual distribution (figure 5). He has been able to have significant breaks from chemotherapy, which remains gemcitabine given with four-weekly zoledronic acid, a potent bisphosphonate which reduces pathological fracture risk and treats tumour-induced hypercalcaemia. It is now over two years since diagnosis and he remains remarkably well and fully active.

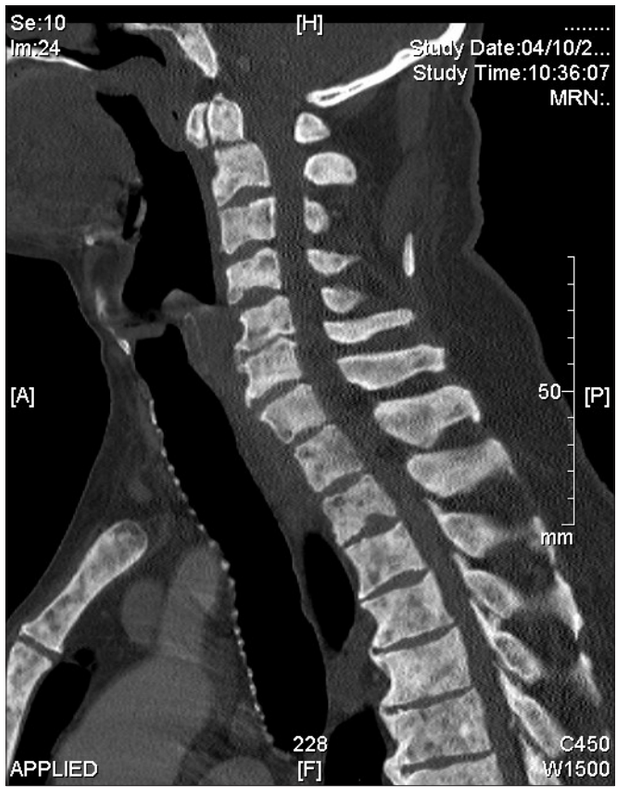

Figure 4

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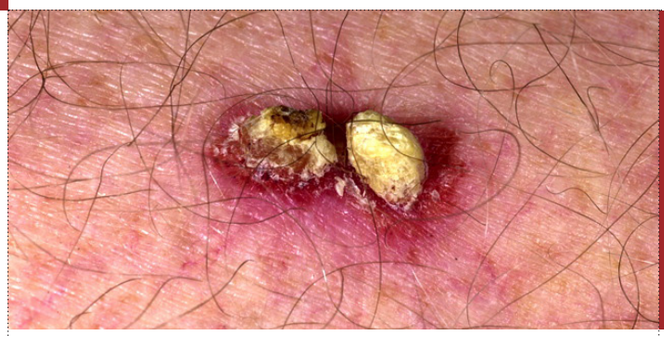

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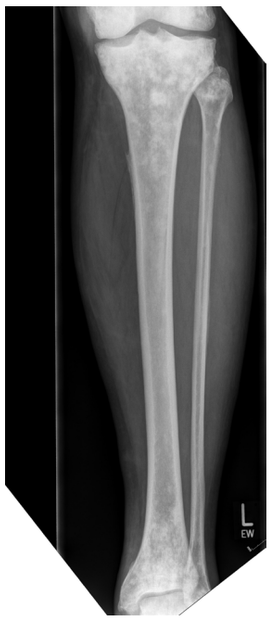

Figure 5

Discussion

Metastatic carcinoma of unknown primary (CUP) accounts for 3-5% of cancer diagnoses. Historically, in 15-25% of cases no primary site is found at post mortem examination. Investigation is guided by a thorough history and physical examination. Tumour markers are rarely diagnostic with the exception of PSA (prostate cancer). Alpha fetoprotein can be of use if hepatocellular carcinoma or germ cell tumour is suspected. Other markers such as CEA, CA19-9 and CA125 may be more helpful in monitoring response to treatment if initially elevated. Treatment is guided by the clinical scenario and the histopathological characteristics of the tumour. The recent National Institute for Health and Clinical Excellence (NICE) guidance (3) makes clear recommendations on the establishment of specific multi-disciplinary teams in hospitals with cancer units or cancer centres to ensure uniform expert management of such patients. NICE also recommended the establishment of a National Cancer Research Network (NCRN) clinical studies group for CUP with a comprehensive portfolio of relevant clinical trials to address the relative lack of research in this area to date.

Questions

1. What is the incidence of carcinoma of unknown primary among cancer diagnoses?

a. Less than 1%
b. 3 – 5%
c. 5 – 10%
d. 15%
e. 20%

2. Alpha-fetoprotein is useful in the diagnosis of

a. Colonic carcinoma
b. Adenocarcinoma of lung
c. Hepatocellular carcinoma
d. Endometrial carcinoma
e. Nasopharyngeal carcinoma

3. Bone metastases are more commonly associated with the following group of primary cancers?

a. Colon, pancreas, lymphoma, stomach, breast
b. Neuroendocrine, testicular, nasopharyngeal, lung, breast
c. Renal, bladder, pancreas, melanoma, thymus
d. Prostate, renal, lymphoma, glioblastoma, pancreas
e. Prostate, breast, lung, renal, thyroid

4. The following statements are correct regarding CUP

a. FDG PET- CT is the investigation of choice after initial laboratory blood tests
b. Serum tumour markers are often diagnostic in the investigation of CUP
c. Gene-expression based profiling is an essential investigation in the majority of patients
d. A panel of antibodies comprising CK7, CK20, TTF-1, PLAP, ER (women only) and PSA (men only) should be part of the immunohistochemical workup of all patients with adenocarcinoma of unknown primary
e. Upper and lower gastrointestinal endoscopy are essential for all patients under investigation for CUP

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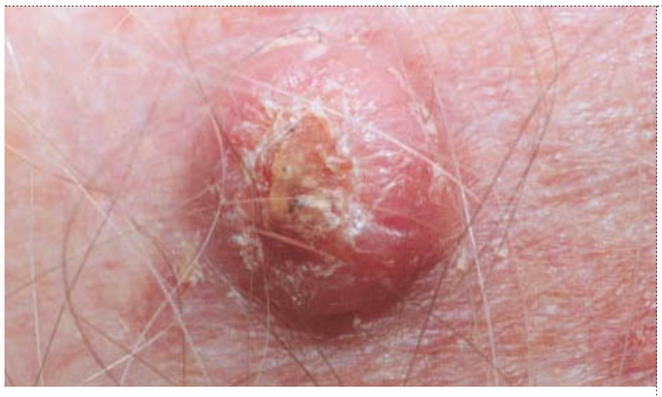

5. Patients with carcinoma replacing the bone marrow are may present with:

a. Anaemia and/or neutropenia
b. Pathological fractures
c. Hypercalcaemia
d. Raised alkaline phosphatase
e. All of the above

Answers

1. b.
In 3 – 5% of cancer diagnoses no proven primary site of origin is found despite extensive investigation. (4) Even in historical series where subsequent post-mortem examinations have been carried out, the primary site remains occult in 15-20% of these cases.

2. c.
In general, serum tumour markers are more useful in monitoring response to treatment or in assessing for relapse than in making a diagnosis. A few markers however, are relatively specific and can be of some benefit in the investigation of CUP. A good example is prostate specific antigen (PSA) when this is very high in men in the presence of bony metastases. Alpha-fetoprotein can be greatly elevated in hepatocellular carcinoma and can also be raised in some germ cell tumours.

3. e.
In the very advanced stages of metastatic disease, most cancers can spread to involve bone. However, typically prostate, breast, lung, renal and thyroid are those that most commonly do so.

4. d.
Currently a panel of antibodies comprising CK7, CK20, TTF-1, PLAP, ER (women only) and PSA (men only) are commonly used in the investigation of carcinoma of unknown primary. Additional tests are added according to the particular pattern of symptoms, signs and investigation results that all may point to one site being more likely than another as the primary site. Gene-expression-based profiling is likely to become used more widely in the future but is currently not a standard investigation.

5. e.
The answer is that all of these may occur when there is extensive bone marrow replacement by tumour. In such cases monitoring of serum calcium is essential and radiography of involved weight-bearing bones is important to assess the risk of pathological fracture.

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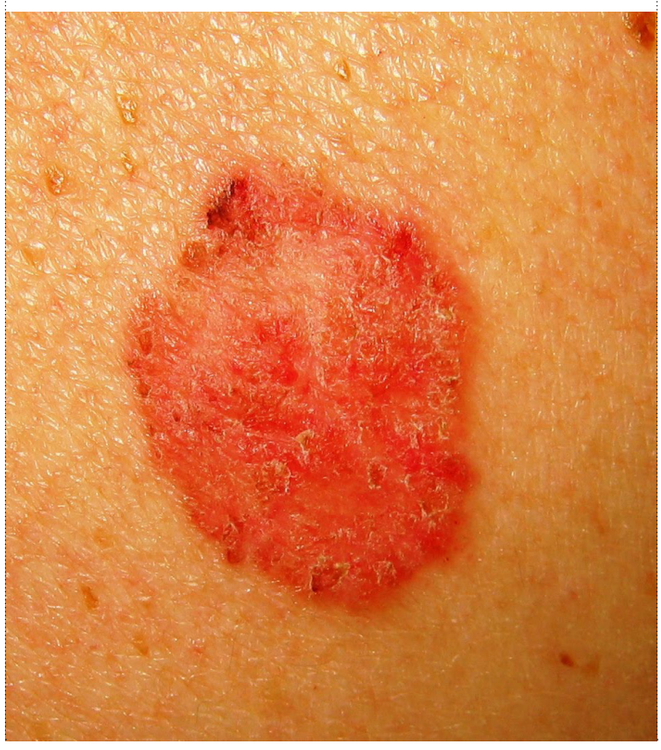

CASE BASED DISCUSSION: PARANEOPLASTIC SYNDROMES

K Thillai, J Waters

Case based discussion:
Paraneoplastic Syndromes
Patient Management

Abstract

Paraneoplastic syndromes encompass a heterogeneous group of rare disorders which exist as an indirect consequence of a primary tumour and its metastases. In some cases the syndrome may precede the diagnosis of cancer and an early and accurate recognition of the syndrome is therefore paramount. A case of the neurological paraneoplastic condition 'Lambert Eaton Myasthenic Syndrome' is presented here along with a discussion of the relevant investigations and subsequent management.

Clinical scenario

A 64-year-old woman presented to her primary care physician with a three-month history of reduced mobility, weight loss and fatigue. She described difficulty climbing stairs and complained of stiffness in her arms and legs. She also reported a dry mouth and intermittent facial flushing. A detailed neurological examination revealed a mild proximal weakness with depressed reflexes throughout but no other focal signs. Routine blood tests demonstrated elevated liver enzymes. An abdominal ultrasound scan revealed multiple liver lesions, consistent with metastatic malignancy. A staging computerised tomography scan of her chest, abdomen and pelvis highlighted a probable primary tumour in her small bowel, as well as confirming the presence of multiple liver metastases affecting both the right and left hepatic lobes. A subsequent liver biopsy demonstrated metastatic well-differentiated neuro-endocrine carcinoma (also known as a carcinoid tumour).

Neuroendocrine carcinomas arise from pleuripotent stem cells that originated within the epithelium of the embryological gut. These tumours can therefore develop in a number of sites, including organs derived from the embryological foregut (respiratory tract, stomach, first part of duodenum and pancreas), the embryological midgut (from the second part of the duodenum to the ascending colon, including the small intestine and appendix), and the embryological hindgut (transverse, descending and sigmoid colon, and rectum). The characteristic histological appearance of well differentiated neuroendocrine carcinomas is that of uniform cells with plentiful cytoplasm, often forming a nested growth pattern. The cytoplasm often contains secretory granules, which contain peptide or amine secretory products. Small bowel neuroendocrine carcinomas typically secrete 5-hydroxytryptamine (serotonin), tachykinins, prostaglandins and bradykinins, which give rise to the classical symptoms of the 'carcinoid syndrome' comprising facial flushing (largely mediated by tachykinins) and diarrhoea (largely mediated by 5-hydroxytryptamine).

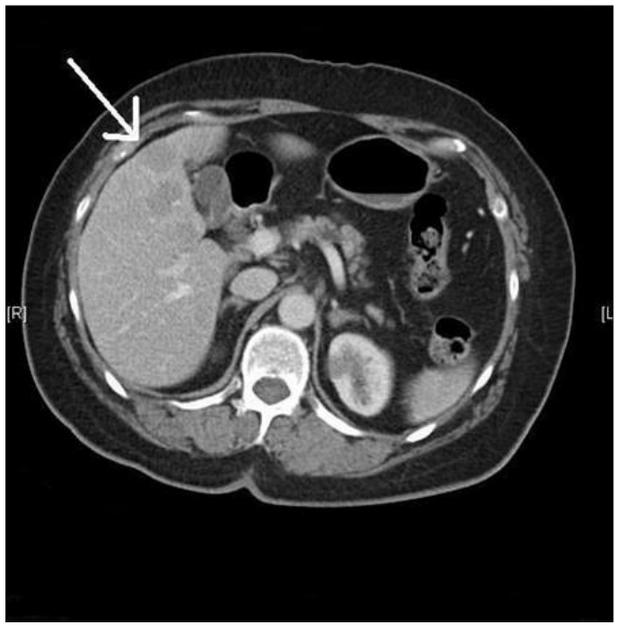

Figure 1: CT Scan. The arrow on this CT scan shows the hypervascular liver lesions that are typical for neuroendocrine liver metastases.

The patient was commenced on treatment with long-acting octreotide. This is a synthetic analogue of somatostatin, a naturally occurring peptide hormone, which acts by binding to somatostatin receptors on neuroendocrine tumour cells. This results in inhibition of multiple cellular functions including secretion, motility and proliferation, and is the first line of therapy for the control of the symptoms related to hormone secretion by the tumour cells. The patient experienced a rapid resolution of her symptoms of facial flushing. However, her neurological symptoms persisted, and further investigation was therefore instigated after referral for a neurological opinion.

She initially underwent electrophysiological studies which revealed a pattern of a reduced compound action potential, which transiently increased following repetitive stimulation. This suggested the diagnosis of Lambert-Eaton myasthenic syndrome (LEMS). The diagnosis was confirmed with serological tests that revealed the presence of antibodies against voltage gated calcium channels.

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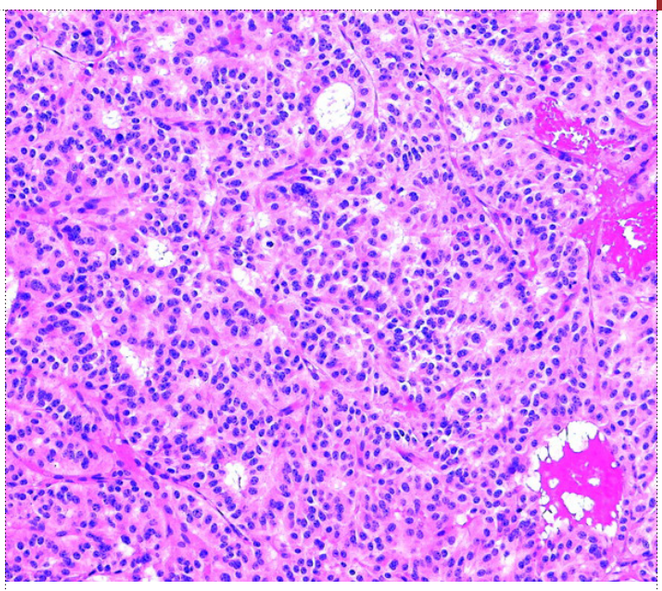
The management of metastatic neuroendocrine carcinoma focuses firstly on the control of disease-related symptoms with the aim of enhancing the patient's quality of life, and secondly on control of disease growth, aiming to prolong survival. The natural history of well differentiated neuroendocrine carcinomas is often very indolent, and therefore cytotoxic chemotherapy has a very limited role in their treatment. Surgical resection of limited metastatic disease is considered where feasible, but this is unlikely to result in cure. Somatostatin analogues have long been known to exert antiproliferative effects, as well as having an antisecretory function. This was confirmed in an elegantly designed trial in which patients with metastatic well differentiated midgut neuroendocrine carcinomas with no or minimal hormone-related symptoms were randomized between long-acting octreotide and observation. Patients randomized to octreotide had prolonged disease control with a median time to tumour progression of 14.3 months compared with the control group, which had a median time to tumour progression of 6 months. (1) Patients are therefore often initially treated with somatostatin analogues with the dual aim of disease and symptom control, and additional therapy only considered in the event of significant disease progression.

However, in the case of this patient, it was recognized that improvement in her neurological function would likely only result from control of the underlying malignancy. A specialist opinion was therefore requested for selective internal radiotherapy to treat her hepatic metastatic disease and achieve optimal control of her cancer. This technique involves the injection of radio-isotope-impregnated glass beads (microspheres) into the hepatic artery. Tumours growing within the liver receive the majority of their blood supply from the hepatic artery, whereas normal liver parenchyma receives a large proportion of its blood supply from the portal venous system. This results in delivery of a high dose of radiotherapy to the metastatic tumour deposits within the liver, while relatively sparing the normal liver tissue from the radiotherapy dose delivered by the injected microspheres.

Discussion

Paraneoplastic Syndromes

Paraneoplastic syndromes are symptoms arising as an indirect consequence of an underlying malignancy and not as a direct result of cancer cell invasion. The complex pathogenesis of these conditions is not yet fully understood. A current prevailing hypothesis is that they are caused by an immunological response to tumour cell antigens that cross react with antigens present within normal tissues, leading to immunologically-mediated destruction of the normal cells and tissues involved. Evidence in support of this hypothesis has been the demonstration of both T-cell and antibody responses against parts of the nervous system in some of the common neurological paraneoplastic syndromes. The four most common sub-groups of paraneoplastic syndromes are neurological (the most common), haematological, endocrine and cutaneous (see table 1).



Neurological	
Lambert Eaton Myasthenic Syndrome	Small cell lung cancer Neuroendocrine tumours
Cerebellar degeneration	Ovarian cancer Breast cancer Lung cancer
Polymyositis	Lung cancer Lymphomas Bladder cancer
Opsomyoclonus	Neuroblastoma Breast cancer Lung cancer
Sensory neuropathy	Small cell lung cancer
Limbic encephalitis	Small cell lung cancer
Stiff person syndrome	Breast cancer
Haematological	
Polycythaemia	Renal cell cancer Hepatocellular cancer
Non infective endocarditis	Lung cancer Breast cancer Ovarian cancer
Trousseau	Pancreatic cancer Lung cancer Breast cancer
Endocrine	
Cushings syndrome	Small cell lung cancer Pancreatic cancer
SIADH	Small cell lung cancer
Hypoglycaemia	Insulinoma Hepatocellular cancer
Carcinoid	Neuroendocrine tumours
Hypercalcemia	Lung cancer Breast cancer Renal cancer Ovarian cancer
Cutaneous	
Acanthosis Nigricans	GI cancer
Erythroderma	Lymphoma
Sweet's syndrome	Acute myelogenous leukaemia
Melanosis	Melanoma
Dermatomyositis	Lung cancer
Gardners' syndrome	Colorectal cancer

Table 1. Paraneoplastic syndromes and commonly associated malignancies.

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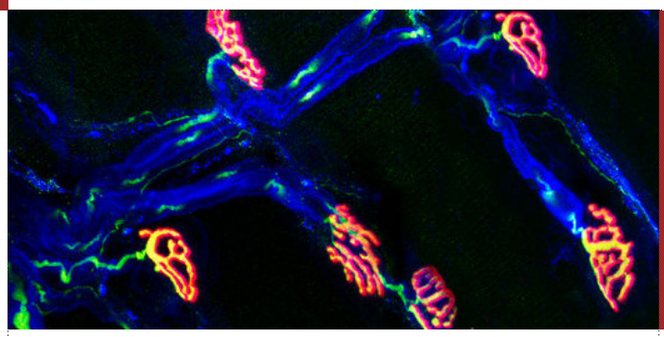

Case based discussion: Paraneoplastic Syndromes
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Lambert Eaton Myasthenic Syndrome (LEMS) is a disorder of the neuromuscular junction (NMJ) and is one of the most frequently observed neurological paraneoplastic syndromes. The prevalence of LEMS is approximately 0.2 cases per million and the most commonly associated malignancy is small cell lung cancer, of which approximately 3% of cases exhibit LEMS. It is also associated with neuroendocrine tumours but can sometimes manifest in conjunction with benign autoimmune diseases. In the clinical setting it is important to distinguish LEMS from myasthenia gravis. This is another disorder of the neuro-muscular junction, which is an autoimmune disease resulting from the development of antibodies to the acetylcholine receptor.

Pathophysiology

In LEMS, antibodies are produced against the presynaptic voltage-gated calcium channels in the NMJ. These cause depletion in the calcium concentrations in the nerve endings which are required for acetylcholine release. This reduced acetylcholine release results in the classical muscle weakness seen in the condition. In LEMS the number and appearance of acetylcholine vesicles remain normal, as does the postsynaptic sensitivity to acetylcholine.

Lambert's sign is the pathognomonic bedside clinical test used to distinguish LEMS from myasthenia gravis. In LEMS when a muscle group is tested repeatedly, strength can temporarily improve, a feature not seen in myasthenia gravis. This improvement is because repetitive nerve stimulation leads to a near continuous influx of calcium into the pre-synaptic nerve terminal. This allows more vesicles to attach to the nerve membrane and a sudden increase in acetylcholine, resulting in a transient marked improvement in muscle strength.

Clinical features

The most common clinical feature of LEMS is a symmetrical proximal weakness which becomes slowly progressive. Patients may describe difficulty arising from a chair and changes in their gait and they may have diminished reflexes. Sensory signs and cranial nerve involvement are less common. Autonomic symptoms such as dry mouth, constipation or blurred vision may also be present. In more serious cases, patients may display signs of respiratory muscle involvement leading to respiratory failure. As mentioned, Lambert's sign is useful in both diagnosing LEMS and differentiating it from myasthenia gravis.

Investigations

The diagnosis of LEMS is often made clinically in the context of an underlying malignancy and is then confirmed by the presence of antibodies against voltage gated calcium channels (VGCC). Antibodies against the P/Q-type VGCC are present in up to 80-95% of patients with LEMS. These can be tested for serologically but can also be identified in cerebrospinal fluid.

The majority of patients with LEMS have a distinct electrophysiological pattern on electromyography. The compound muscle action potential (CMAP) is a group of near simultaneous action potentials from several muscle fibers in one area that are evoked by stimulation of the supplying motor nerve. These are then recorded as one multi peaked action potential. In LEMS there is a reduced baseline CMAP which increases significantly but transiently with repetitive nerve stimulation or exercise (See Figure 2). This finding is diagnostic of LEMS.

Differential diagnosis

The main differential diagnosis for LEMS is myasthenia gravis. However LEMS tends to involve proximal muscle weakness and is less likely to involve the ocular muscles than myasthenia gravis. Other conditions which can present in a similar way include motor-neurone disease, myelopathys and cancer related fatigue.

Treatment

If LEMS is diagnosed in the absence of cancer an underlying malignancy must always be investigated for extensively. In cases of isolated paraneoplastic syndrome a cancer usually presents within 2 years and almost all patients have an identified cancer at 4 years after diagnosis. The mainstay of treatment is the management of the underlying malignancy. The best response is seen in cases of small cell lung cancer, which can be highly chemosensitive.

Specific treatments for LEMS include aminopyridines such as 4-Diaminopyridine (DAP), which prolong nerve depolarisation thus improving calcium entry and resulting in improved muscle strength. Another drug of choice is guanidine which inhibits voltage gated potassium channels and therefore enhances the amount of acetylcholine that is released. Acetylcholinesterase inhibitors such as pyridostigmine reduce the metabolism of acetylcholine therefore increasing the amount that is available for acetylcholine receptor binding.

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Intravenous immune globulin (IVIG) therapy has been proven to have some benefit, especially in patients with respiratory involvement but such patients may also need non-invasive ventilation in the acute setting.

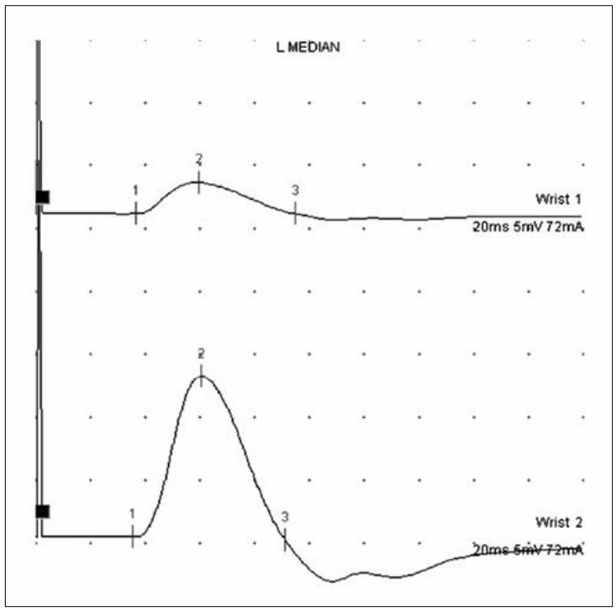

Figure 2: EMG results.

Thus the patient's median nerve is tested by stimulating the abductor pollicis brevis. The top tracing shows a low amplitude CMAP at baseline. The bottom tracing shows the same muscle group following exercise. This demonstrates a significant increase in amplitude which reflects the temporary improvement in muscle strength following a repetitive contraction.

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Summary

Lambert Eaton syndrome is one of the most common paraneoplastic syndromes. If it is diagnosed in isolation, intensive investigation to look for an underlying cancer should always be commenced. The diagnosis involves a combination of clinical findings such as proximal weakness and fatigue and is confirmed by serological antibody testing and electromyography. The most common differential diagnosis is myasthenia gravis. Treatment for paraneoplastic LEMS primarily involves management of the underlying malignancy, but medications to control symptoms can also be used.

Questions

Which of the following are true?

1. Paraneoplastic syndromes:

a) Paraneoplastic syndromes always occur after the diagnosis of malignancy
b) The four common sub-groups of paraneoplastic syndromes are neurological, haematological, endocrine and cutaneous
c) Paraneoplastic conditions can be caused by benign conditions
d) Paraneoplastic disorders are caused
by the local presence of cancer deposits
e) The mainstay of treatment for paraneoplastic
syndromes is treatment of the underlying malignancy

2. Lambert Eaton syndrome

a) In LEMS antibodies are produced against the post-synaptic voltage-gated calcium channels
b) A common clinical finding for LEMS is proximal weakness
c) Sensory signs are more prevalent than motor signs.
d) Lamberts signs is the improvement of weakness with repeated testing
e) LEMS is associated with weakness, brisk reflexes and autonomic symptoms such as dry mouth and constipation

Answers

1a) False.
Paraneoplastic syndromes can precede the diagnosis of malignancy but the cancer usually present with 2-4 years of the diagnosis.

1b) True.
There are many types of paraneoplastic syndromes but these four groups account for the most common.

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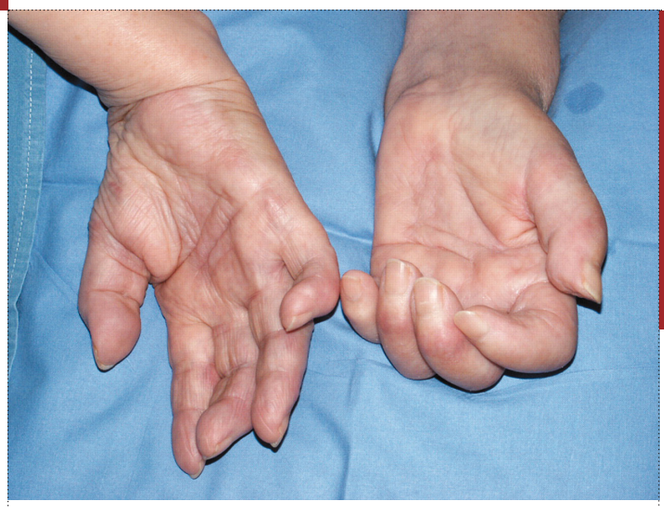

1c) False.
Although many conditions such as Lambert-Eaton syndrome may be caused by a benign cause, the term 'paraneoplastic syndrome' is always associated with malignancy.

1d) False.
It is not related to the local effect of the cancer cells, but by an immune response that is generated.

1e) True.
Although other directed therapies including anti-immune treatment can be effective, the most important treatment to control symptoms is the anti-cancer treatment.

2a) False.
Antibodies are produced against the pre-synaptic voltage-gated calcium channels.

2b) True.
Commonly a progressive proximal weakness is seen.

2c) False.
Motor signs are more common than sensory ones.

2d) True.
This is a classic sign of LEMS and can be used to differentiated LEMS from myasthenia gravis.

2e) False.
LEMS is associated with weakness, diminished reflexes and autonomic symptoms.

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MALIGNANCY IN TEENAGERS AND YOUNG ADULTS

R Goldspring, F Roberts

Malignancy in teenagers and young adults
Patient Management

Abstract

Cancer is the commonest medical related cause of death in teenagers and young adults. Overall, it is second only to accidents. (1, 2, 3) In the United Kingdom, six teenagers and young adults are diagnosed with cancer every day. (1)

In 2005, NICE Guidance on Improving Outcomes in Children and Young Adults with Cancer was published and there has been a significant improvement in services. There has been recognition that they require not only specialised care, but also psychological, social, educational and developmental support. (3, 4)

Here we report a case history of a young woman of 22 with metastatic breast cancer.

Case History

A 22 year old female presented to her GP with a 3 month history of a lumpy feeling in her left breast. She was referred on to the local breast clinic where she underwent standard triple assessment, which is clinical examination, radiology (mammography and ultrasound) and histopathology with core biopsy or cytology.

Clinical examination revealed a 14 x 14 cm mass in the left breast with an enlarged left axillary lymph node. There were no other abnormalities noted on examination.

A mammogram revealed a spiculate elongated mass in the 2 o'clock position in the left breast measuring 59 mm (see figure 1).

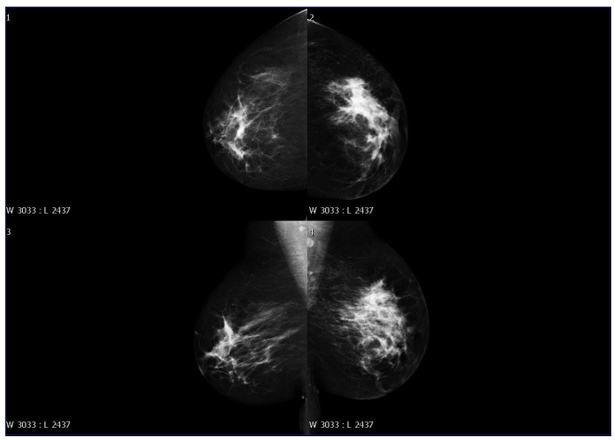

Figure 1: Clockwise from top left: right cranio-caudal (CC) view, left CC view, left mediolateral oblique (MLO) view, right MLO view. The elongated mass can be seen in the two right images.

An ultrasound of the left breast showed skin oedema in the lateral quadrant of the left breast with a large ill defined mass at the 3 o'clock position measuring 35 mm.

The core biopsy revealed a grade 2 invasive ductal carcinoma. This was oestrogen receptor (ER) positive, progesterone receptor (PR) positive and the HER2 (human epidermal growth factor receptor 2) result was positive. A fine needle aspiration of an enlarged axillary lymph node revealed metastatic carcinoma.

A panel of blood tests revealed raised cancer tumour markers. Her CA15.3 was 299 (normal <30), CEA 26.8 (normal <5) and her creatinine was 122 (normal 49-90). The other blood tests were normal. A CT scan of the thorax and abdomen revealed left axillary lymphadenopathy, the primary cancer in the left breast and destructive lesions in T4, T6, T10 and L1. The left kidney was small, measuring 33 mm on the long axis (see figure 2).

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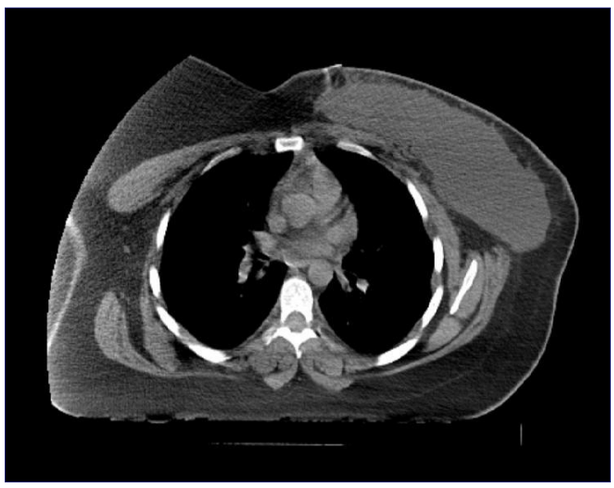


Figure 2: The CT scan shows the large left breast mass.

An MRI could not be performed due to pain and claustrophobia. This was to be used to characterise the lesion in the breast. A bone scan showed focal uptake at T5, L1 and in the right humerus, confirming the presence of bone metastases (see figure 3).

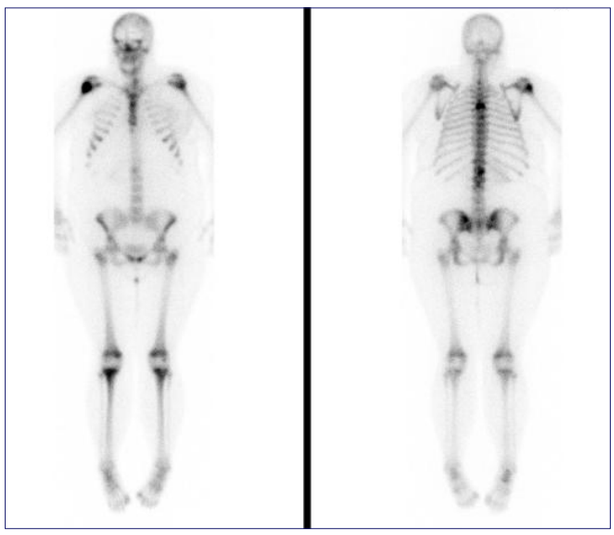
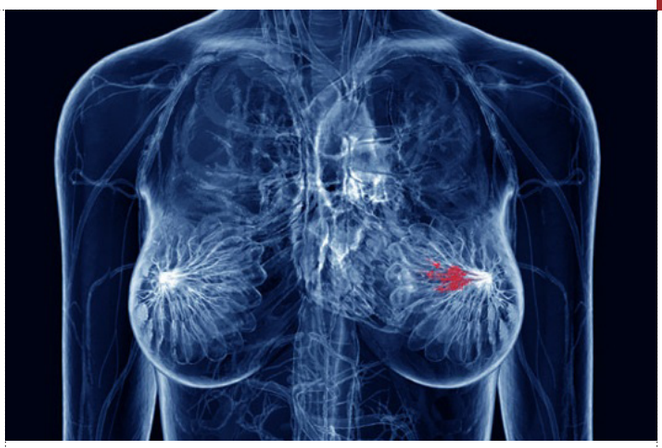


Figure 3: The bone scan shows uptake at T5, L1 and the right humerus.

The case was discussed at the local multidisciplinary breast cancer team meeting and she was referred for support to the Teenage and Young Adult Cancer (TYAC) Unit. She requested to be seen and treated at her local cancer unit rather than the principal treatment centre (the official name for the central cancer centre) as it was some distance away. She was seen by the visiting consultant clinical oncologist, the specialist nurse from the TYAC unit and the local breast cancer nurse specialist.



The diagnosis of metastatic breast cancer, which makes her disease incurable, was discussed as well as the role of palliative chemotherapy with epirubicin and cyclophosphamide (EC) agents. The benefits, being disease control, and side effects of the treatment were explained and consent obtained.

There was an in depth discussion regarding many issues surrounding teenagers and young adults with cancer. The location of chemotherapy delivery was discussed. Her local cancer unit was close to her home and family support, while the principal treatment centre's TYAC unit was a significant distance away. The patient made an informed decision to have her treatment at her local cancer unit. She understood that if she needed to be admitted due to complications of chemotherapy, such as neutropaenic sepsis, it would be to the principal treatment centre's TYAC unit, as there is no inpatient oncology care at her local hospital. There was a discussion about fertility. EC chemotherapy can increase the chances of infertility, either temporarily or permanently. Options such as embryo or egg storage were discussed. The patient decided against fertility preservation. The role of contraception was discussed to ensure that she would not become pregnant during her treatment, due to the risk to the foetus. During this time, and during her treatment, the specialist nurse from the TYAC unit kept in close contact to provide psychological support.

The management plan was to deliver chemotherapy prior to surgery to allow the possibility of tumour shrinkage. There would be a clinical review prior to each cycle to ensure there was no growth of the tumour, in which case surgery would be performed sooner. Surgery would be performed followed by which radiotherapy would be delivered. The other treatment options that are also considered and started at different points are antihormonal therapy, trastuzumab and bisphosphonates.

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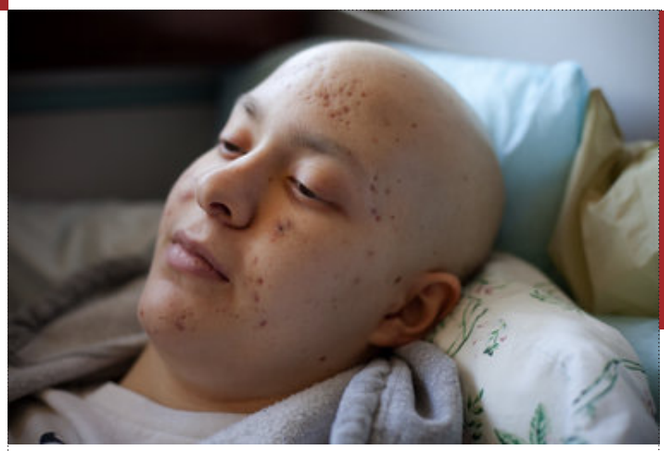

Tumour markers and clinical examination were used to assess the response to treatment. Both indicated a dramatic response during the treatment. A total of six cycles of 3 weekly EC chemotherapy were given, which is a standard regime for neoadjuvant (prior to surgery) chemotherapy. The chemotherapy was then changed to docetaxel to incorporate trastuzumab (Herceptin) into the chemotherapy regimen. This change was done to allow the incorporation of trastuzumab to ensure the patient had the best chance of tumour shrinkage and long term control. Unfortunately, her creatinine levels increased following the first cycle of docetaxel and this was converted to weekly paclitaxel.

A total of six cycles of weekly paclitaxel were given in replacement for the 3 weekly docetaxel. Trastuzumab was continued as maintenance treatment after the chemotherapy was completed. The tumour markers were normal at the end of chemotherapy. She was intolerant of bisphosphonates, which were given due to the bony me-tastases to prevent skeletal related events.

The patient then proceeded with surgery and underwent a left mastectomy and left axillary nodal clearance. The post operative histopathology revealed 70 mm of DCIS (ductal carcinoma in situ) with lymphovascular invasion, but no evidence of invasive cancer. There was a 0.5 mm micrometastasis in one of seventeen lymph nodes examined.

Post operatively she was placed on tamoxifen hormone therapy, which is standard maintenance treatment for ER/PR positive metastatic tumours, to decrease the risk of local recurrence. Radiotherapy was arranged to the left chest wall and left supraclavicular fossa with a dose of 40 Gy in 15 fractions. She will continue on trastuzumab indefinitely, which is common practice in the metastatic setting. She was also placed on zoladex to medically suppress her ovaries after her periods returned. She remains well and symptom free 15 months from diagnosis.

Discussion

Teenagers and young adults with cancer are a unique group that require specialised care that crosses the boundaries of paediatric and adult oncology. (5, 6) The care does not only incorporate cancer treatment, but also the growing recognition that these patients have special physical, social, psychological, developmental and educational requirements. (3) NICE Guidance on Improving Outcomes in Children and Young People with Cancer made specific requirements for providing care to this age group. The care of teenagers and young adults is now served by principal treatment centres that provide age-appropriate facilities and managed by dedicated multidisciplinary teams. There should be dedicated inpatient and day case facilities. (7)

TYAC units are designed to primarily treat patients in an age appropriate environment, but to also offer support for education, careers, finances, psychosocial needs and much more. The facilities on the unit include games rooms, relaxation areas and therapy rooms. The healthcare professionals on the unit include TYA nurse consultants, TYA nurse specialists, nursing sister, staff nurses, psychologists, social workers, hospital teachers, pharmacists, palliative care and youth support co-ordinators. The youth support coordinators organise activities for the patients and families. The diagnosis of cancer during an important time in their lives can often make teenagers and young adults feel isolated from their friends. The social events and activities allow them to spend time with people who are going through a similar experience, whilst still having a social life. These events can range from day trips to theme parks to ward based activities such as arts and craft workshops and halloween parties.

The range of cancers seen in teenagers and young adults is unique and different from those seen in children and adults. They can be grouped into three types: (i) late onset children's cancers, (ii) early onset adult cancers, and (iii) cancers only found in young people. (1) The commonest cancers in the teenage and young adult group in 2003 were: lymphoma (25.5%), carcinomas e.g. cervical (17.1%), germ cell tumours e.g. testicular, ovarian (13.8%), leukaemia (10.7%), central nervous system tumours (8.9%), melanomas (8.4%), bone tumours (5.7%) and soft tissue sarcomas (5.4%). The commonest cancer in young men in the United Kingdom is testicular cancer (27%) and in young women melanoma and Hodgkin's lymphoma (17%). (1, 8)

MALIGNANCY IN TEENAGERS AND YOUNG ADULTS

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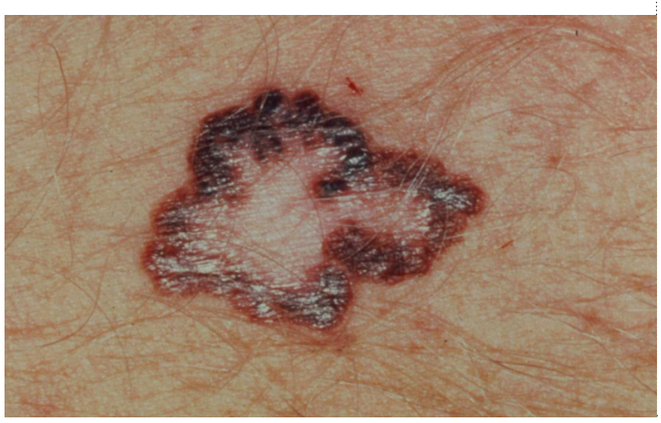
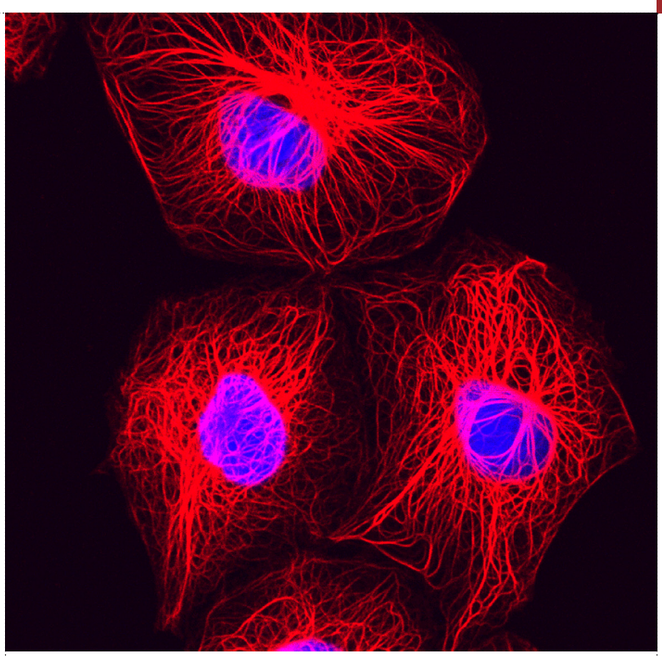
The survival of teenagers and young adults with cancer is worse than children and adults. (5) The overall 5 year relative survival improved from 63% in 1979-1984 to 77% in 1996-2001. (3) Unfortunately, there was not an improvement for all tumour sites, with no improvement among high grade brain tumours, bone and soft tissue sarcomas. Teenagers and young adults have not seen the improvements in overall survival that have occurred in children and adults. The reason for this is not understood, but it thought to be due to multiple factors. There are differences in biology, treatment, care facilities and clinical trials participation. (5) Between 2005-2007 56% of 5-14 year old were entered into clinical trials, compared to 20% of 15-24 year olds. (3)

When cancer treatment proves successful patients may still develop unintended long term consequences, such as infertility, organ dysfunction and secondary cancers. (3, 5) The awareness of the risk of late effects is extremely important when making a management plan in teenagers and young adults. The disruption to education and vocational training can have a large impact on their lives. (3, 4) As clinicians we recognise that teenagers and young adults are at a vital developmental stage of their lives and, alongside cancer treatment, they will be progressing through the usual developmental milestones, pursuing educational and career choices and establishing independence.

The long term follow up of patients is achieved through the National Cancer Survivorship Initiative. This is a new aftercare pathway that aims to improve the follow up of teenagers and young adults after they have completed potentially curative treatment. Approximately 60% of long term survivors experience at least one co-morbid health condition. (9) The aim is to ensure that each patient has the most appropriate level of clinical and non clinical aftercare. This can range from self management to late effects clinics. This is achieved through risk stratification and individual patients will have a personalised pathway of aftercare. The transition from teenage and young adult services to adult oncology is important to allow continuity of care. (10)

Our patient was highly unusual in developing metastatic breast cancer at such a young age and in choosing to have her treatment at the local cancer unit with support from the TYAC unit at the principal treatment centre. However, the support from the TYAC unit was valued by the patient and her treating clinicians.





Acknowledgement

I would like to thank Dr. D. Stark, Consultant Medical Oncologist, for his helpful on this article.

Questions

1. What percentage of breast cancer patients are HER2 positive?

a) 5-10%
b) 10-15%
c) 15-20%
d) 20-25%
e) 25-30%

2. What is the age range for the NHS breast screening programme?

a) 45-65
b) 47-68
c) 47-73
d) 50-73
e) 50-75

MALIGNANCY IN TEENAGERS AND YOUNG ADULTS

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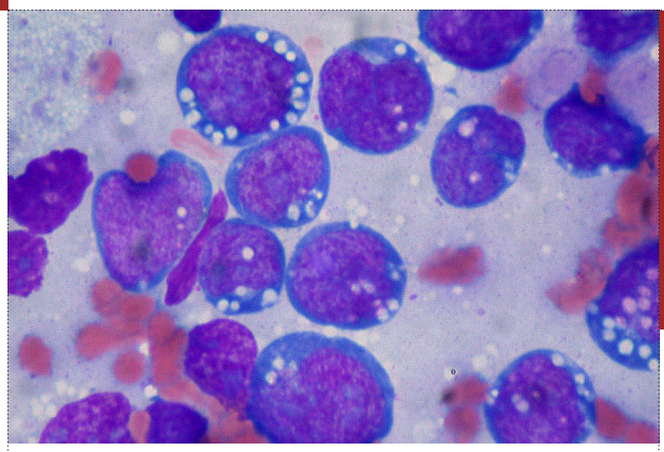

3. What are the commonest cancers in young men and women in the United Kingdom?

a) Testicular (men) and Malignant Melanoma (women)
b) Testicular (men) and Breast (women)
c) Malignant melanoma (men) and Breast (women)
d) Bone tumours (men) and Hodgkin's lymphoma (women)
e) Hodgkin's lymphoma (men) and cervical (women)

4. What are the three principles of the triple assessment?

a) history, examination, mammogram
b) examination, mammogram, biopsy
c) examination, mammogram, ultrasound scan
d) history, cytology, biopsy
e) cytology, biopsy, ultrasound scan

5. How many teenagers and young adults are diagnosed with cancer each day?

a) 6
b) 16
c) 26
d) 36
e) 46

Answers

1. Answer: d
Approximately 20-25% of patients will be HER2 (human epidermal growth factor receptor 2) positive. HER2 is a gene that makes the HER2 protein, which is located on the surface of the breast cells. It controls the growth of healthy breast cancer cells. Growth factors attach to the HER2 receptor to allow cell growth and division. Patients that are HER2 positive have a gene that continues to amplify and make extra HER2 protein.

This allows growth factor to attach to the amplified receptor and means the breast cells grow out of control. HER2 positive breast cancers can be treated with trastuzumab (Herceptin), a monoclonal antibody directed against the HER2 receptor.

2. Answer: c
The NHS Breast Screening Programme was set up in 1988 by the Department of Health. The age range was traditionally 50-70, however in 2010 the screening programme began phasing in the new age range of 47-73. The screening programme works on a rolling system and therefore patients may not be called on their 47th birthday, but they will have their first mammogram within three years of this date.

3. Answer: a
The commonest cancer in young men is testicular cancer. It accounts for approximately 27% of diagnosed cancer cases. The commonest cancers in young women are malignant melanoma and Hodgkin's lymphoma. They individually account for 17% of cancers diagnosed in young women.

4. Answer: b
The three basic principles of the triple assessment are (1) clinical examination, (2) radiology (mammography and ultrasonography) and (3) histopathology (cytology ± core biopsy). The grading system starts with a letter (e.g. E - examination, R - radiology, M - mammography, U - ultrasonography, C - cytology and B - biopsy) followed by a number (1 - normal, 2 - benign, 3 - probably benign, 4 - probably malignant, 5 - malignant and in the biopsy category 5a - non-invasive and 5b - invasive)

5. Answer: a
Approximately 6 teenagers and young adults will be diagnosed with cancer each day in the United Kingdom. It is the commonest disease related cause of death. Before the age of 20, approximately 1 in 312 males and 361 females will be diagnosed with cancer.

MALIGNANCY IN TEENAGERS AND YOUNG ADULTS

R Goldspring, F Roberts

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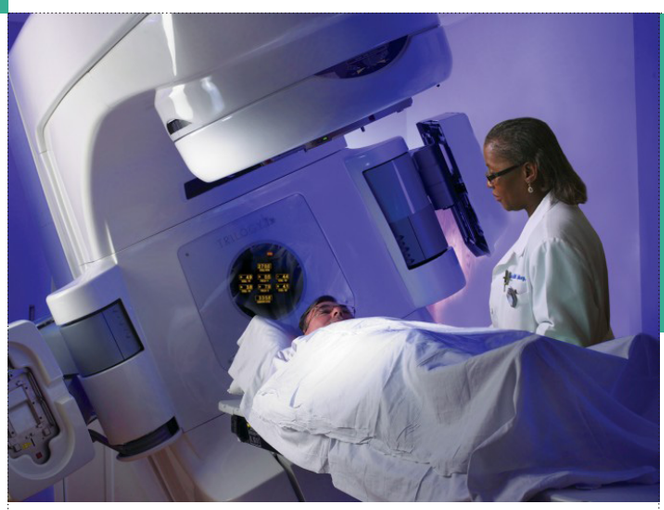
A CAREER IN ONCOLOGY: YOUR QUESTIONS ANSWERED

C Thompson, A Choudhury



What is an oncologist?

Oncologists are physicians trained in the non-surgical management of cancer, using systemic drugs such as chemotherapy, hormonal therapy, molecular-targeted therapy, and radiotherapy. In the UK, the speciality is divided into medical oncology (specializing in systemic cancer treatment) and clinical oncology (specializing in both systemic cancer treatment and radiotherapy). (1, 2)

How many oncologists are there in the UK?

The Royal College of Physicians (RCP) Consultant Census in 2010 identified 298 medical oncologists working in the UK (280 full time equivalent). (3, 4) The Royal College of Radiologists (RCR) Clinical Oncology UK Workforce Report 2010 states there are 687 clinical oncologists (650 full time equivalent) (5), based in one of 50 large specialist cancer centres. Each has an average list of 2,000 patients under his or her care. (2)

Around 309,527 people were diagnosed with cancer in the UK in 2008. This statistic equates to around 504 cases per 100,000 people. Incidence rates for Great Britain increased in males from 368 per 100,000 in 1979 to 416 per 100,000 in 2008, and in females from 273 per 100,000 to 365 per 100,000. (6) There is a continuing increase in cancer incidence, increasing complexity and personalization of cancer treatment, improving prognosis of cancer and more public awareness of cancer services.

These factors have led to a rapid expansion of oncology relative to other medical specialties in recent times.

What leads people to choose to train in oncology as a speciality?

I choose clinical oncology as a speciality because it offers such a variety of different challenges. It is both technical and scientific, requiring detailed knowledge of cell biology, pharmacology, statistics and anatomy, as well as awareness of surgical techniques and an ability to interpret radiology. Clinical oncology training also offers the opportunity to learn more about medical physics in relation to radiotherapy.

A career in oncology: Your questions answered
Teaching & Training

Oncologists are involved in delivering treatment both to cure cancer and extend survival or, even if cure cannot be offered, to help with symptoms and improve quality of life for the patient. We are responsible for discussing extent of disease, treatment options and prognosis with patients and their relatives. Decisions regarding the withdrawal of active treatment and the initiation of best supportive or end of life care is often communicated by the Oncology team since a relationship has built up with both the patient and their family. This is an emotionally demanding aspect of the job but one which many oncologists find extremely rewarding.

We treat a diverse patient group. Cancer can happen to patients of any age, gender, ethnicity and background leading to many different challenges within the job. Patients may have difficult social problems or emotional needs requiring support, whilst others are very well informed about their cancer and come with many questions often arising from internet research. Younger patients may struggle with both their diagnosis and its impact on aspects of their life, including driving, working and personal relationships. There can be long term issues regarding sexual function, fertility and increased risk of secondary malignancy. Some oncologists may be involved with the care of their patients for many years, offering continuity throughout the disease pathway.

Oncology also offers the opportunity to be involved in medical research. Cancer research attracts a huge amount of interest from the public and the scientific community. There is a constant search for new developments, to improve prognosis. New treatments are constantly emerging and oncologists are an integral part of this quest. Some oncologists, particularly those holding academic posts with a dual contract between the NHS and university, will participate in translational medical research. A higher proportion of consultants hold academic contracts in oncology than in other medical specialities (a third of consultants in medical oncology). (1)

A CAREER IN ONCOLOGY: YOUR QUESTIONS ANSWERED

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Those who are not involved in academia will recruit patients to clinical trials, where the monitoring and reporting of toxicity and response whilst on treatment is crucial. The practice of oncology is heavily rooted in evidence based medicine, and an important aspect of the job for all oncologists is to read and appraise the latest evidence about new treatments, interpret statistical and clinical benefit and to incorporate this into their clinical practice where appropriate.

Oncologists work as part of a network of health professionals involved in a patient's care, throughout their disease pathway. This team will include general practitioners, district and community nurses, professionals from the local hospice and other specialists in the hospital, such as surgeons, physicians, radiologists, pain management teams, palliative care teams, pharmacists, medical physics and radiotherapists.

What does the training involve?

There are 13 clinical oncology training schemes in England, as well as schemes in Wales, Scotland and Northern Ireland. (2) In both clinical and medical oncology, specialist training begins after completion of core medical training and entry is dependent on achieving Membership of the Royal College of Physicians (MRCP). Trainees spend much of their time in outpatient clinics but are also involved with inpatient care. Multidisciplinary team (MDT) meetings, where patient care plans are often decided, are an important part of training. As clinical oncology trainees, we spend time in the radiotherapy department with a minimum of one session per week of technical radiotherapy planning. (2)

Clinical oncology training is five years of full time training (or equivalent). During this time, we must complete Fellowship of the Royal College of Radiologists (FRCR) in clinical oncology. The examinations are in 2 parts. FRCR part 1 consists of four papers, with a "best of five" multiple choice question format, in cell biology and radiobiology, physics, statistics and pharmacology. The final FRCR examination is taken after a minimum of three years of training and is divided into a written paper (in best of five format), and two clinical examinations, one in viva format and one in an OSCE style. Medical oncology involves a minimum of four years of training and now, like many other medical specialities, involves an examination, in best of five format, the Specialty Certificate Examination (SCE). This is usually taken in the penultimate year of higher specialist training, leading to the postnominal MRCP (UK) (medical oncology). (1) Many trainees, in both clinical and medical oncology, take time out of their clinical training (out of programme experience or OOPE) to do clinical fellowships either in the UK or abroad or formal post graduate research, often as an MD or PhD.

What does a consultant oncologist do?

Oncologists are usually based either in a dedicated cancer centre, or in a large teaching hospital environment, with some clinical work at peripheral centres. We usually sub-specialise in up to three cancer sites. The majority of patients are seen and receive treatment in the outpatient setting. Clinical work includes assessment of new patients, review of patients on treatment with chemotherapy or radiotherapy, management of treatment-related toxicity and follow up of patients following treatment completion. Although oncology is an outpatient based speciality, some patients do require admission, for oncological emergencies, management of treatment-related toxicity and occasionally for treatment itself. These patients are often acutely unwell and have complex needs.

There were between 1.7 and 3.2 inpatient admissions per new cancer diagnosis in 2008/09, according to the National Audit Office. The NHS Atlas of Variation in Healthcare states that this represents from 40 bed-days per 1000 population to 65 bed-days per 1,000 population, varying between primary care trusts (PCT)(7). These figures have led to increasing emphasis on day-case services for treatment delivery, avoiding admissions, reducing their duration and improving the management of these patients. (8) An increasing number of hospital trusts are now employing consultant oncologists to provide an acute oncology service. This takes the form of dedicated consultant sessions as part of the job plan.

Oncologists are usually also part of an on call system, which will vary between hospitals but which usually involves non-resident on call for at least a 24 hour period. This will include management of patients presenting with oncological emergencies and treatment-related complications. In addition, clinical oncology consultants are involved in the acute management of patients with malignant spinal cord compression where radiotherapy is often an essential part of treatment.

Alongside clinical work, research and MDT commitments, most oncologists are involved in education, from medical student teaching to registrar training and education for other health care professionals. We will also frequently have management roles, including involvement in committees, steering groups, boards, working parties, professional societies or colleges, locally or nationally.

A CAREER IN ONCOLOGY: YOUR QUESTIONS ANSWERED

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A career in oncology:
Your questions answered
Teaching & Training

What is radiotherapy and what are the indications for its use?

Radiotherapy is the use of ionising radiation to treat malignant disease by delivering a measured dose of radiation to a defined tumour volume with minimal dose to surrounding tissues. This is most commonly achieved through the use of external beam radiotherapy. Other ways of delivering radiotherapy include the use of radioisotopes (given orally as a drink or capsule or by intravenous injection) and brachytherapy (internal radiotherapy, which involves putting a solid radioactive material close to, or inside, the tumour).

Radiotherapy is used at some point in the treatment of nearly two thirds of cancer patients. It is usually given as a course of daily treatments (called fractions), with no treatments at weekends. It takes between five and twenty minutes to give each day. It can be used as radical (curative) treatment for example in the treatment of head and neck, lung, and prostate cancers amongst others It is also used in the adjuvant setting (to reduce the risk of recurrence locally) for example in breast cancer and soft tissue sarcoma or to palliate symptoms, most commonly pain from bone metastasis or bleeding from the tumour. Palliative radiotherapy is very effective for relief of pain from bone metastasis. A systemic review of randomised controlled trials looking at palliative radiotherapy given in single or multiple fractions, showed improvement in pain relief for over 80% of patients. (9) The effectiveness of radiotherapy in both curative and palliative settings makes it a rewarding aspect of the job of an oncologist.

What aspects of radiotherapy involve an oncologist?

There are many steps involved in treating patients with radiotherapy. Firstly, the oncology team must assess the patient to determine if they will benefit from radiotherapy, considering the risks and benefits. We must identify the area to be treated. We identify the area involved with tumour, using information from clinical examination, operation findings, and radiology. This is called the gross tumour volume (GTV). Next we decide the area around this that may contain microscopic cancer cells. This is called the clinical target volume (CTV). Finally a bigger area than this must be included in the total volume to be treated to allow for movement of the tumour. This is called the planning target volume (PTV) (figure 1).

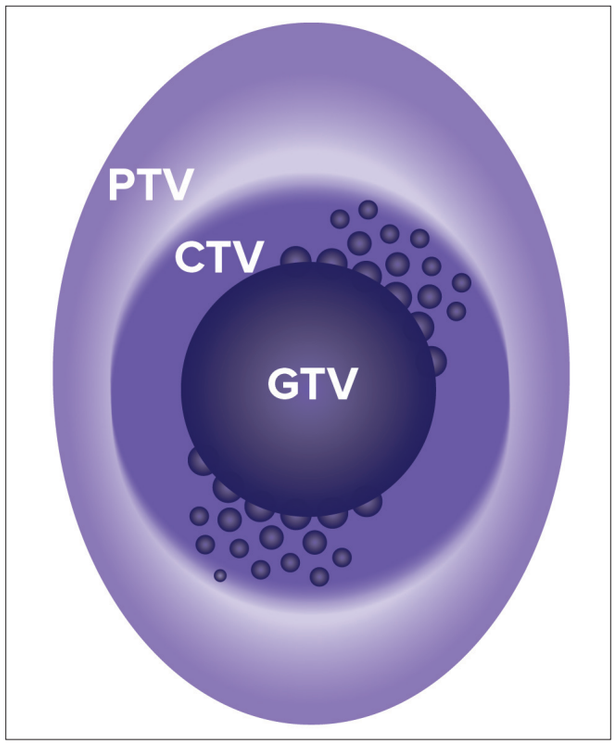

Figure 1: Treatment volumes. GTV=Gross Tumour Volume, the tumour apparent on clinical examination, operation or radiological investigation. CTV= Clinical Target Volume, the area at risk of microscopic involvement from the tumour. PTV= Planning Target Volume, the clinical target volume plus a margin to allow for potential movement.

We must then decide if the radiotherapy will be potentially curative or palliative. This relates in part to the amount of radiotherapy to be given (the dose, measured in Gray) and the number of treatments to be given (the number of fractions). Next, we decide on the type of radiation to be used (usually photons or electrons) and the way in which this will be designed and delivered. The simplest way to deliver radiotherapy is with a single radiation beam, aimed in a single direction at the area to be treated, with the tumour at the centre (figure 2).

A CAREER IN ONCOLOGY: YOUR QUESTIONS ANSWERED

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This type of radiotherapy is usually designed by inspecting and marking out the area to be treated on a patients skin e.g. as in skin cancer treatment, or on a simulator film (like a plain X-ray) e.g. in palliative treatment for bone pain or spinal cord compression.

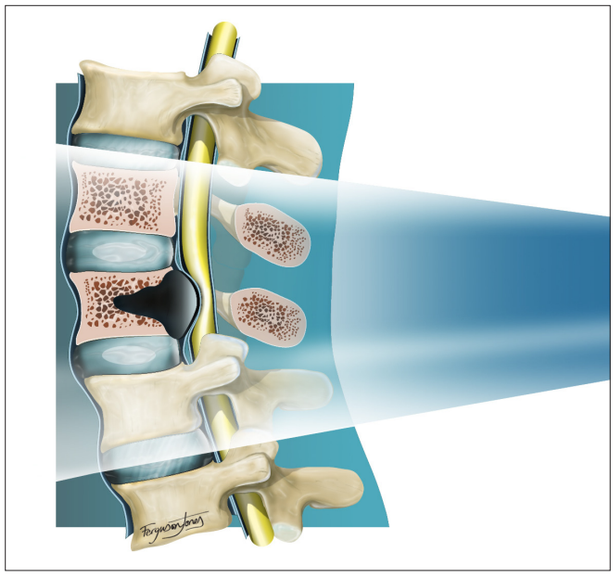

Figure 2: Single posterior beam used to treat a bony metastatis in the spine.

A more complex way to deliver radiotherapy is to use multiple radiation beams, aiming in different directions so that their combined effect creates an area of high dose over the area to be treated, with the tumour at the centre. This type of radiotherapy is usually planned using CT scans. Radiotherapy techniques have advanced to use increasingly complex arrangements of beams and to vary the amount of radiotherapy delivered within the beam, sculpting the radiotherapy more precisely to the shape of the tumour (Figure 3).

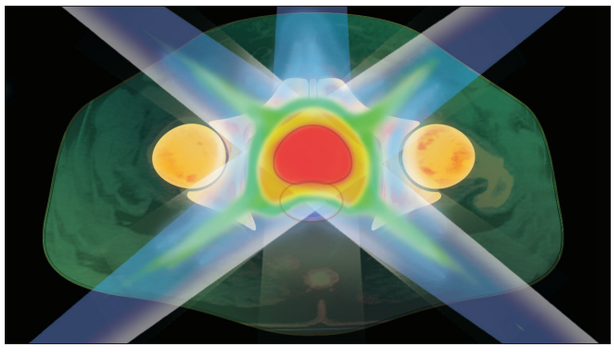

Figure 3: Radiotherapy plan for prostate cancer treatment, using 5 beams to create a high dose region (shown in red) which is shaped to minimise dose to the rectum.

Potential side-effects both short and long term are discussed with the patient and consent obtained. The oncology team monitors the patient through treatment, assessing side effects. If necessary, adjustments to treatment can be made in conjunction with the physics, planning and radiotherapy treatment staff.

How would you summarize the skills required to become an oncologist?

Oncology is an exciting and rewarding speciality. It offers a unique combination of challenges, from technical aspects of delivering complex treatments, to involvement in cancer research and providing continuity of care for patients throughout a disease pathway with many emotional and psychosocial implications. If you enjoy team work, have good communication skills and want to apply knowledge of basic sciences and new developments in cancer research to treating patients in the clinical setting and have the opportunity to be involved in medical research, this is the career for you!

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Illustrations provided by Philip Ferguson Jones

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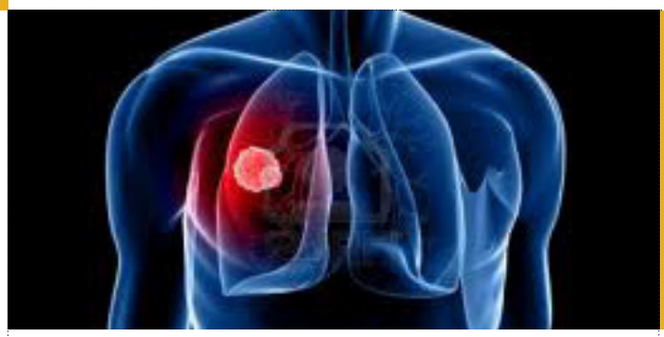
CASE BASED DISCUSSION: MANAGMENT OF METASTATIC LUNG CANCER

D Muthukumar, Z Helman



Case Based discussion:
Managment of Metastatic lung cancer
Good Clinical Care

Abstract

Lung cancer is the most common cancer worldwide, and the second most common cancer among men in the UK, accounting for around 14% of all new cases of cancer in males. It is the third most common cancer among women, responsible for more than 11% of all new cases of cancer in females. It has been estimated that the lifetime risk of developing lung cancer in 2008 is 1 in 14 for men and 1 in 19 for women in the UK. It is estimated that, at any one time, there are 65,000 people living with lung cancer in the UK.

The vast majority of lung cancers present with symptomatic disease. The presenting features of lung cancer can be related to the primary tumour causing cough and haemoptysis. Local spread, chest wall and mediastinal lymph node involvement can cause chest pain and a hoarse voice. Occasionally patients can develop complications such as superior vena cava obstruction from locally advanced disease or Horner's syndrome from a Pancoast tumour.

Lung cancer can metastasize to liver, bone, brain and to the adrenal glands. Bone metastases, in addition to causing pain can result in pathological fractures or spinal cord compression.

The management of advanced and metastatic lung cancer is a combination of supportive care with systemic chemotherapy and/or palliative radiotherapy. Novel targeted agents can be used in a select group of patients. The aim of these treatments is to control the symptoms, delay disease progression and maximise quality of life. Symptoms developed during the course of a metastatic cancer can sometimes be debilitating. Therefore, recognition and management of these symptoms by a multidisciplinary team is essential.

Case history

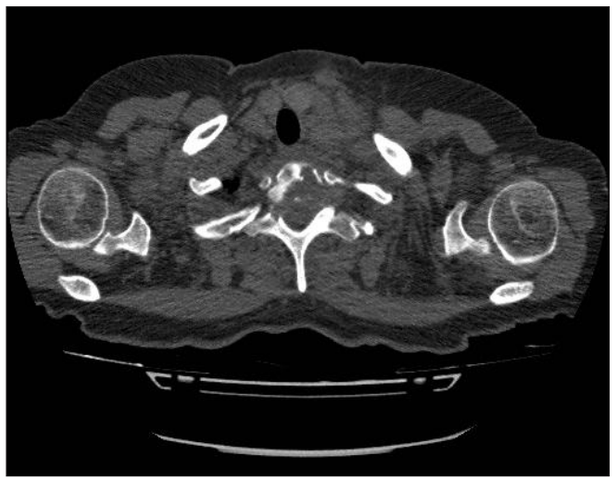
A seventy two year old lady presented with severe pain in the left arm for the past two months. She describes the pain to be sharp, felt in the left shoulder and left forearm. The pain was severe enough to wake her from sleep. She also noticed a burning sensation in her fingers. She could not perform tasks like buttoning her dress or tying laces. She recently noticed thinning of muscles of her hand and a weak grip. She had lost a stone in weight in the last few months. She noticed shortness of breath on moderate exertion and a cough but no haemoptysis. Regular paracetamol did not relieve the pain.

How would you assess her?

A detailed history including the duration and severity of pain and weakness is essential. The symptoms of shortness of breath and cough need to be explored further. Occupational history including exposure to chemicals, radiation and smoking history should be elicited.

This should be followed by clinical examination. General examination should include palpation of lymph nodes in the neck and supraclavicular and axillary regions. A thorough chest examination is essential followed by neurological examination including examination of power, sensation, and reflexes in all four limbs. Local spinal tenderness should be elicited.

Initial blood tests full blood count, urea and electrolytes, liver function tests including alkaline phosphotase, calcium and LDH should be taken. A chest X-ray would also be needed.



Picture 1: Axial image of CT chest showing lytic lesion in the thoracic vertebra.

CASE BASED DISCUSSION: MANAGMENT OF METASTATIC LUNG CANCER

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Results

Clinically, she had large hard lymph nodes palpable in both cervical and supraclavicular areas. Chest auscultation was essentially normal. Neurological examination revealed small muscle weakness of all muscles in the left hand. Sensations were diminished in C8, T1 nerve root distribution.

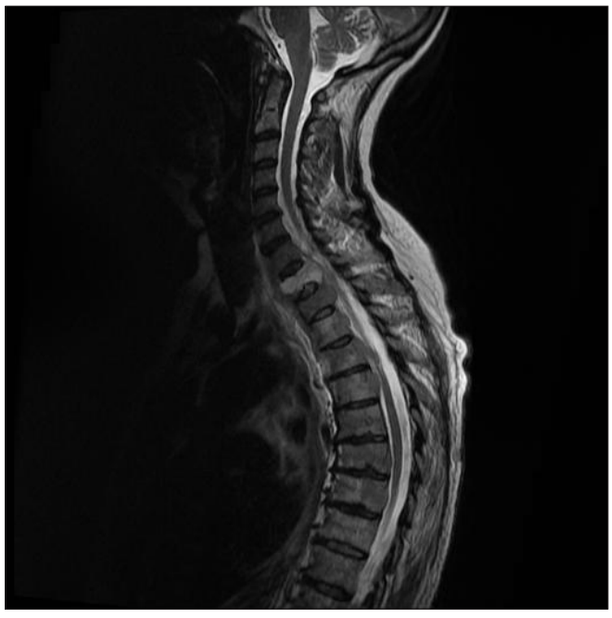
Chest X-ray showed slight widening of mediastinum, in the right para-tracheal region.

Full blood count and biochemical profile were normal except for elevated alkaline phosphotase.

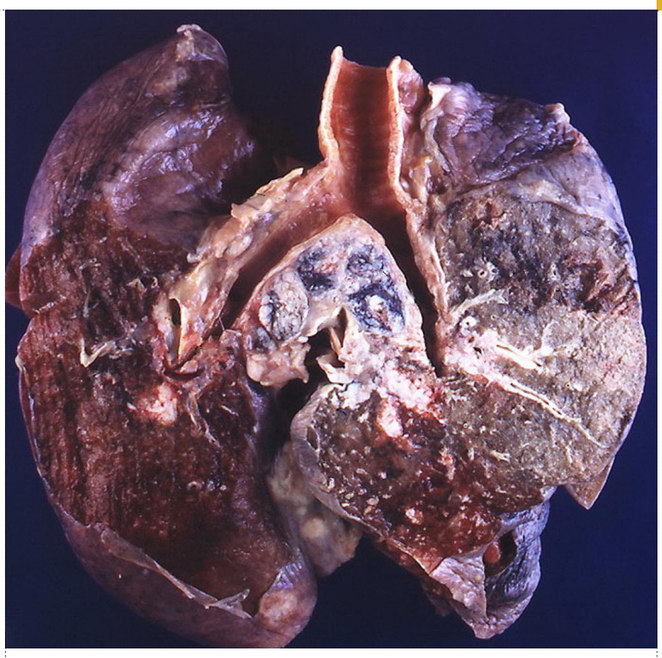
What would be the next investigations?

Abnormal chest X-ray and palpable supra-clavicular hard lymph nodes should arouse the suspicion of metastatic lung cancer. A contrast enhanced CT scan of the chest and upper abdomen and MRI of the cervico-thoracic spine are essential.

Fine needle aspiration of the lymph node should be performed and cells sent for cytological analysis.



Picture 2: Saggital image of T2 weighted MRI scan showing vertebral metastases.



Results

The CT scan of the chest revealed 2 cm soft tissue mass in the medial segment of the right middle lobe. A 28 mm nodule is seen in the left adrenal gland. Osteolytic lesions were seen in C7, T1, T2 and T5 spine. MRI spine revealed abnormal bone marrow signal from C7 to T6 spine. There was narrowing of the AP diameter around C7-T1 with involvement of the both pedicles. Fine needle aspirate of the lymph nodes confirmed malignant cells.

What further investigations are needed and how do you interpret them?

The results of the imaging and FNA of the lymph nodes suggested a disseminated cancer. She proceeded to have lymph node biopsy of the supra-clavicular node on the left. Histology revealed moderately differentiated adenocarcinoma. Immunohistochemistry shows the tumour cells stain with CK 7 and thyroid transcription factor. There was no reactivity with cytokeratin 20 or Ca-125.

The above pattern of immunohistochemical stains would suggest a non-small cell lung cancer. This is supported by the radiological appearance of a lung lesion and mediastinal lymphadenopathy.

CASE BASED DISCUSSION: MANAGMENT OF METASTATIC LUNG CANCER

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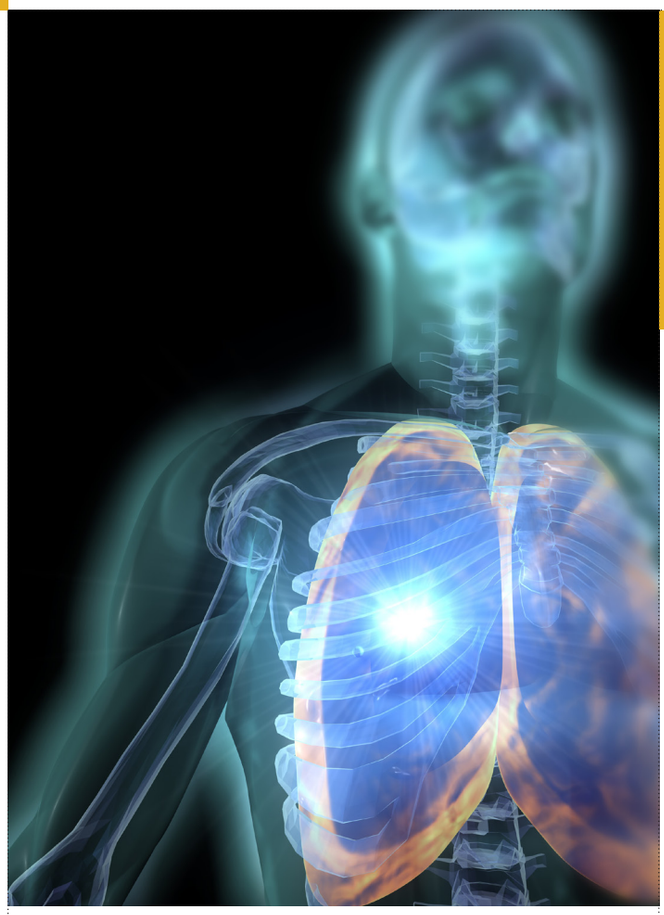

Cytokeratin (CK) is one of the components of the intracytoplasmic cytoskeleton. The CKs constitute a family of more than 30 polypeptides and are distributed in a tissue-specific manner. Immunohistochemistry of certain cytokeratins are useful for the determination of tissues of origin in several types of tumours.

CK7 is expressed in 97%–100% of primary lung adenocarcinoma cases and in 5%–27% of primary colon adenocarcinoma cases. In contrast, CK20 is expressed in 7%–10% of primary lung adenocarcinoma cases and 92%–100% of primary colon adenocarcinoma cases. Thyroid transcription factor is positive in 75% of adenocarcinoma of lung, and is a useful marker for adenocarcinoma of lung. The pattern of cytokeratin expression and the presence or absence of thyroid transcription factor staining would help to differential adenocarcinoma of lung from other cancers.

Systemic treatment of adenocarcinoma is changing and testing for EGFR and ALK mutations is becoming standard. Tumours positive for these mutations respond well to new targeted agents which are replacing first-line chemotherapy where they have been shown to be better tolerated and more effective, e.g. gefitinib and erlotinib, which are taken orally indefinitely until the tumour progresses, whereas chemotherapy is generally intravenous, once every 3 weeks and for a maximum of 6 doses.

Case Based discussion: Managment of Metastatic lung cancer Good Clinical Care

Discussion on further management

A prompt inpatient oncology referral should be made. If there is an acute oncology service, this should be utilised. The oncologist's review recommended the patient would benefit from palliative radiotherapy to the cervico-thoracic spine. She underwent a radiotherapy planning CT scan and received five fractions of palliative radiotherapy. This was followed with systemic platinum-based chemotherapy.

The description of her pain was consistent with neuropathic pain. Neuropathic pain results from damage or dysfunction of the peripheral nervous system, that normally signals pain. It may arise from a heterogeneous group of disorders that affect the peripheral and central nervous systems. Non-malignant examples include painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia. People may experience altered pain sensation, areas of numbness or burning, and continuous or intermittent evoked or spontaneous pain. Neuropathic pain is an unpleasant sensory and emotional experience that can have a significant impact on quality of life.

Neuropathic pain can be difficult to treat and is not typically responsive to simple and opiate analgesia alone. If pain is thought to be related to nerve root or spinal cord compression then dexamethasone may be started after discussion with the oncology team. Management of neuropathic pain, particularly in the context of metastatic disease is challenging and is best managed by specialist palliative care services. As this pain is often severe it can significantly impact on quality of life hence a holistic approach is so important.

A number of drugs are used to manage neuropathic pain, including antidepressants and anti-epileptic agents, opioids and topical treatments such as capsaicin and lidocaine. Many people require treatment with more than one drug, but the correct choice of drugs, and the optimal sequence for their use, has been unclear. Medications that care used can include Gabapentin, Pregabalin and Amytriptyline. Gabapentin is titrated up from an initial dose of 300 mg OD to 300 mg. three times daily over the first 3 days, and further if necessary more gradually up to 600 mg tds. Pregabalin is titrated up from 75 mg twice daily. Amitryptyline is usually started at 10 mg at night though a higher dose is usually necessary and is particularly useful if patients cannot take pregabalin or gabapentin due to renal impairment. With all of the above medications, on-going review of response and side effects is essential.

CASE BASED DISCUSSION: MANAGMENT OF METASTATIC LUNG CANCER

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Palliative chemotherapy in metastatic lung cancer can help to delay disease progression and improve symptoms. In the past, there was considerable pessimism about the role of chemotherapy in the treatment of non-small cell lung cancer. A qualitative meta-analysis of clinical trials, by Cochrane has revealed, by using systemic chemotherapy, 27% reduction in the risk of death equivalent to a 10% improvement in survival at one year could be achieved. Chemotherapy agents are tailored to the patient's needs and to the histological type of lung cancer. For example, Pemetrexed based chemotherapy has been proven effective for adenocarcinomas and large cell carcinomas but were inferior for squamous cell cancers.

Targeted therapy of lung cancer refers to using agents specifically designed to selectively target molecular pathways responsible for, or that substantially drive, the malignant phenotype of lung cancer cells. As they work in selective cellular pathways, they do not cause the adverse effects like myelosuppression normally seen with cytotoxic chemotherapy. Targeted agents are designed to be selective in their effects by modulating the activity of enzymes driving the uncontrolled growth, angiogenesis, invasiveness, and metastasis of malignant tumours.

In lung cancer, inhibitors of epidermal growth factor receptor (EGFR) include Erlotinib and Gefitinib. Monoclonal Antibody against EGFR like Cetuximab and inhibitors of vascular endothelial growth factor like Bevacizumab (Avastin) are the targeted agents that have proved effective.

As with all cases of metastatic cancer, a holistic approach to assessment and management with effective communication with the patient are essential. Management by the multidisciplinary team, including specialist palliative care can together produce the best outcome for an individual patient.

Learning points

1. Lung Cancer is one of the most common cancers in the UK and often presents at an advanced stage. The treatment of metastatic lung cancer can involve a combination of chemotherapy, radiotherapy and palliative care.
2. Neuropathic pain is a common and challenging symptom and could be resistant to conventional analgesics. Early input from oncologists, the palliative care team and the pain team is essential to guide on appropriate use of analgesics.
3. Histological confirmation is essential to identify the type of lung cancer and to tailor the treatment accordingly.
4. Immunohistochemistry is a valuable tool to differentiate the different types of cancer and to choose the appropriate treatment.

Questions

1. Bone secondaries could be associated with:

a. Bone pain
b. Neuropathic pain
c. Pathological fracture
d. Spinal cord compression
e. All of the above

2. Non malignant causes for neuropathic pain include

a. Diabetes mellitus
b. Shingles
c. Trigeminal neuralgia.
d. Bells palsy.

Answers

1. E.

Bone metastases can produce local symptoms of pain. However, some bone secondaries are prone for pathological fractures, particularly lytic lesions. Pressure symptoms would include nerve root compression causing radicular pain and epidural compression causing spinal cord compression. Palliative radiotherapy is an effective treatment for bone secondaries, with at-least 60% getting a pain relief within three weeks.

2. A, B, C.

Non-malignant examples include painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia. Bells palsy produces lower motor neuron lesions of the facial nerve.

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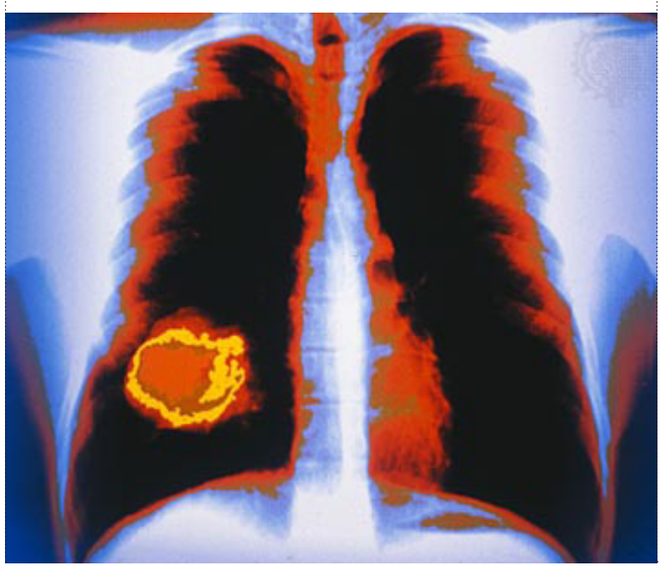

CASE BASED DISCUSSION: FERTILITY AFTER CHEMOTHERAPY

JJ Sacco, SM O'Reilly

Abstract

A significant proportion of patients who undergo chemotherapy for cancer become infertile as a result. Following substantial improvements in the management of several solid tumour types, increasing numbers of patients are surviving cancer and chemotherapy. The average age at which people start their families is also increasing, and both factors have led to greater numbers of patients facing chemotherapy related infertility, and the associated social and psychological stress.

Here we present two illustrative cases, one involving a woman undergoing adjuvant chemotherapy for breast cancer, and the second a man undergoing chemotherapy for testicular cancer. We will discuss the salient points raised by each case, and in particular, the options currently available for fertility preservation.

Scenario 1

AB, a 35-year old woman, underwent wide local excision and axillary node sampling for a 3 cm, grade 3, node negative, oestrogen receptor (ER) negative, HER2 negative, breast cancer. On discussion in the specialist Multidisciplinary team (MDT), a decision was made to recommend adjuvant Epi-CMF (epirubicin followed by cyclophosphamide, methotrexate and 5-fluorouracil) chemotherapy and radiotherapy to the breast. AB did not have any children and was not currently in a relationship.

She was very distressed about the possibility of becoming infertile as a result of the chemotherapy, and wished to consider fertility preservation options. Following discussion, she opted to have oocyte cryopreservation, but while this was being set up she phoned to cancel, as she did not wish to further delay her treatment. She underwent chemotherapy and radiotherapy uneventfully. However, approximately three years later, she attended clinic early at her request. She had missed her last menstrual period, and a pregnancy test was positive. She was reassured that her previous chemotherapy would be unlikely to increase the risk of congenital defects. The pregnancy was uneventful, and AB and her daughter both remain well a year later.

Case based discussion: Fertility after chemotherapy
Patient Management

Scenario 2

A 22 year old man (CV) in a stable relationship was referred to the urologists with a testicular lump and found to have a stage I seminoma. Following an orchidectomy, he was referred to the medical oncologists for adjuvant chemotherapy to reduce the risk of recurrence. As this adjuvant treatment was associated with a small risk of infertility, he elected to undergo sperm cryopreservation, which was performed prior to chemotherapy. He received one cycle of carboplatin, which he tolerated with few side effects. Two years after this, he and his partner decided to start a family. However, attempts at natural conception were unsuccessful. He was referred to the fertility clinic and was found to be azoospermic. IVF with banked sperm was attempted and was successful on the second cycle. His partner subsequently underwent a normal pregnancy and delivery. CV remains disease free, 5 years after diagnosis.

Discussion

Infertility is relatively common in cancer survivors and is a cause of significant psychosocial morbidity. Cancer is a devastating diagnosis, with consequences for all aspects of life, and the ability to have children is a major determinant of emotional well-being. Patients are also frequently afraid of the risks of pregnancy complications or congenital abnormalities in their offspring should they conceive after cancer treatment. It is therefore important that these issues are explored. Unfortunately, surveys have shown that this frequently does not occur, and patients do not receive adequate information. (1, 2)

Chemotherapy induced infertility is most commonly a problem where curative chemotherapy is used routinely in younger patients. This includes the two examples above (breast cancer and germ cell tumours of the testis), as well as others such as haematological malignancies, the lymphomas and childhood malignancies. Chemotherapy induced infertility mainly occurs through loss of ovarian follicles in women or disruption of spermatogenesis in men. In women, temporary amenorrhoea may be caused by destruction of maturing follicles, while depletion of primordial follicles may lead to permanent amenorrhoea. While most chemotherapy agents can induce infertility, this is most likely to occur with the alkylating agents, examples of which include cyclophosphamide, ifosfamide and procarbazine. Notably other treatment modalities may also impact on infertility including surgery (oophorectomy) or pelvic radiotherapy.

CASE BASED DISCUSSION: FERTILITY AFTER CHEMOTHERAPY

JJ Sacco, SM O'Reilly

Assessing the likelihood of female infertility following chemotherapy is imprecise, and depends on both the type and duration of chemotherapy and age of the patient. Three groups may be thus defined, low, intermediate and high. (3) In the case of AB, the likelihood of infertility would fall into the intermediate group, (3) which encompasses a risk of permanent amenorrhoea of between 20 and 80%. However, a variable decrease in fertility is likely, most commonly manifested by early menopause.

Fertility preservation in women

The main options available for mitigating chemotherapy-induced infertility in women include embryo or oocyte cryopreservation, ovarian cryopreservation and transplantation, and ovarian suppression during chemotherapy. Of these, embryo cryopreservation is the best established technique. This involves ovarian stimulation over a two-week period, induction of ovulation by HCG injection and subsequent oocyte collection by ultrasound guided transvaginal follicle aspiration under sedation. Oocytes may then be fertilised in vitro and embryos cryopreserved. Embryo cryopreservation has a relatively high success rate. However, this technique requires a partner (or sperm donor). Alternatively, for women like AB who are without a partner, oocytes may be directly cryopreserved and fertilisation performed at a later date. Oocytes are less able to withstand cryopreservation and historically this has a very low success rate. (4) However recent technical advances show promise in increasing pregnancy rates. (5)

Cryopreservation of ovarian tissue involves the laparoscopic removal of ovarian tissue, which is cryopreserved. Completion of chemotherapy can then be followed by heterotopic implantation of this cryopreserved ovarian tissue (e.g. in the abdominal wall, forearm or chest wall) or orthotopic implantation (e.g. to remaining ovarian tissue or pelvic peritoneum). Cryopreservation of ovarian tissue is the only option available to prepubertal girls and can be performed directly after diagnosis. However the technique remains mainly experimental, and only a small number of live births have been reported to date. (6)

A further strategy that has been investigated is the suppression of ovulation during chemotherapy with gonadotrophin-releasing hormone (GnRH) analogues. This strategy remains experimental, and a recent meta-analysis suggested an increase in resumption of menses and ovulation, but no improvements in pregnancy rates. (7)

The choice made by AB, to forgo fertility preservation, is very common. In a recent survey performed in the US, only 4% of patients who were eligible for fertility preservation, went ahead with it. (1) Several barriers lead to this low uptake of embryo or oocyte cryopreservation. These include the time taken for the procedures (3-6 weeks), the potential risks involved in oestrogen stimulation in ER positive breast cancers, and cost. Each of these factors may be partially mitigated. Firstly, pre-surgical identification of patients who are likely to undergo adjuvant chemotherapy allows early discussion and planning of ovarian stimulation/oocyte harvesting.

Secondly, 'natural-cycle IVF' may be used to harvest oocytes without ovarian stimulation, or aromatase inhibitors and tamoxifen may be used in conjunction with follicle stimulating hormone. (8) Finally, several fertility preservation techniques are funded by the NHS. Provision of these is however variable and subject to local guidelines.

AB's subsequent pregnancy illustrates the fact that many women go on to conceive normally following chemotherapy. Patients are frequently concerned about the risk of congenital defects following chemotherapy in the parents. However, most studies have shown the risk to be similar to that in the general population. (9, 10) On the other hand, tamoxifen does appear to be associated with an increase in congenital abnormalities. (11) It is therefore imperative that, for breast cancer patients with oestrogen positive breast cancer, conception is avoided during tamoxifen treatment. Patients should be advised to use non-hormonal (barrier) methods of contraception while on tamoxifen. Due to the pharmacokinetics of tamoxifen a washout period of two months prior to conception is advisable. (11)

CASE BASED DISCUSSION: FERTILITY AFTER CHEMOTHERAPY

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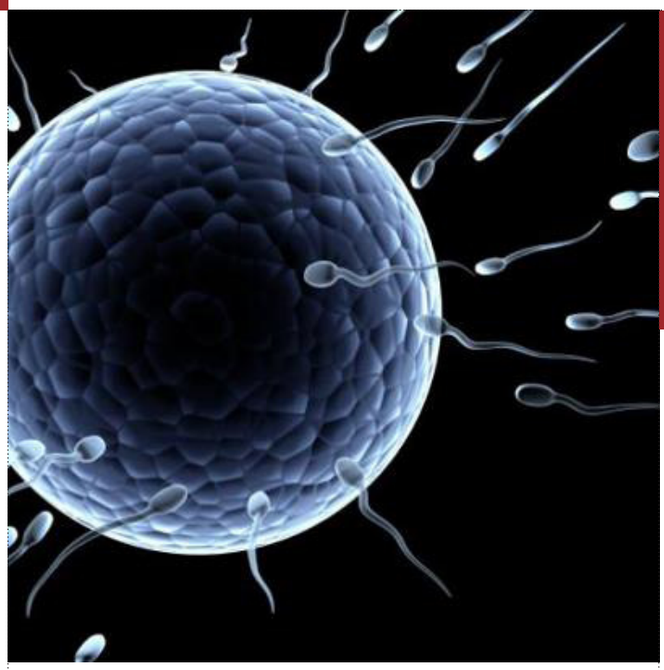

Male fertility preservation

Preservation of fertility in men is generally much more straightforward and involves cryopreservation of sperm after masturbation. If no sperm are found in the ejaculate or if the patient is unable to ejaculate, alternative methods such as direct epididymal or testicular sperm aspiration can be used. However, even for men with extremely low sperm counts and/or motility, advances in IVF procedures such as intracytoplasmic sperm injection (ICSI) of the partner's oocytes can result in successful pregnancy. Thus, collection of sperm prior to chemotherapy, as was done in CV's case, should be attempted wherever feasible.

Cryopreservation of semen is not an option for pre-pubertal boys. Ongoing studies are evaluating the feasibility of cryopreservation of testicular tissue for autotransplantation.

Prolonged azoospermia is rare after single agent carboplatin. However low sperm count and quality is relatively frequent in patients with testicular germ cell tumours, which likely contributed to CV's infertility.

Questions

1. Which following procedure is most likely to result in a successful delivery after chemotherapy?

A: Oocyte cryopreservation
B: Ovarian cryopreservation
C: Suppression of ovulation during chemotherapy
D: Embryo cryopreservation
E: None of the above

Case based discussion: Fertility after chemotherapy
Patient Management

2: Which of the following is not associated with an increased rate of infertility after cancer treatment?

A: Younger age
B: Chemotherapy regimes that include alkylating agents
C: Pelvic radiotherapy in women
D: Gynaecological surgery
E: Patients with germ cell tumours (GCTs) of the testis

Answers

1: D.

Frozen embryos survive freeze-thawing better than oocytes, leading to a better success rate with embryo cryopreservation. While cryopreservation of ovarian tissue has several potential advantages, only a small number of live births have occurred with this technique. The efficacy of ovarian suppression during chemotherapy in fertility preservation remains unproven.

2: A.

A younger age at presentation decreases the likelihood of infertility after chemotherapy. Alkylating agent chemotherapy commonly results in infertility. Pelvic radiotherapy and gynaecological surgery both increase the risk of infertility. Low sperm count and quality is relatively frequent in patients with testicular germ cell tumours.

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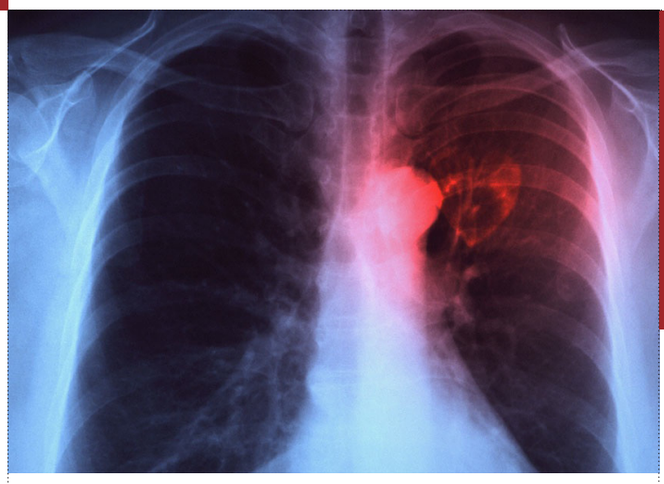
CASE BASED DISCUSSION: MANAGEMENT OF NEUROENDOCRINE TUMOURS

S Ellis, T Hickish, T Geldart



Abstract

A 55 year old gentleman with a long history metastatic Bronchial Carcinoid developed signs and symptoms of Right Heart Failure over a 6 week period. Despite curative surgery ten years previously he had relapsed both in the chest and liver, and had subsequently received a variety of treatments to try to control his disease which had continued to slowly progress. He was admitted as an emergency with increasing shortness of breath and found to have severe stenosis of his right pulmonary artery caused by the growing tumour mass in his chest.

The case discusses the subsequent management of this problem and the specialists involved, and also the diagnosis, management and treatment of neuroendocrine tumours.

Case History

A 55 year old gentleman was admitted on the acute take with a 6 week history of increasing shortness of breath, fainting episodes and new peripheral oedema. His past medical history included a diagnosis of primary bronchial carcinoid 10 years ago, for which he had undergone a left pneumonectomy. Five years later his disease recurred in his chest and liver and he was treated with chemotherapy and subsequent radiotherapy to his mediastinum.

After 18 months on a somatostatin analogue he was given funding on compassionate grounds for a Everolimus which inhibits signal transduction in cancer cells to treat his slowly advancing disease, this had stopped 4 months prior to presentation, and he was awaiting further specialist treatment in a London tertiary referral centre .

On examination he was clinically in right heart failure with a raised JVP, and pitting oedema to the sacrum. There was a parasternal heave and a pansystolic murmur loudest at the lower left sternal edge. Blood pressure ranged from 70-90 systolic with heart rate 100-150 beats per minute. Liver function tests showed raised ALP, ALT and bilirubin, renal tests showed new acute renal failure. Chest X-ray (image 1) showed a left pneumonectomy with complete white out of the left lung field and mediastinal shift, right lung field was clear.

Case based discussion: Management of Neuroendocrine Tumours
Patient Management

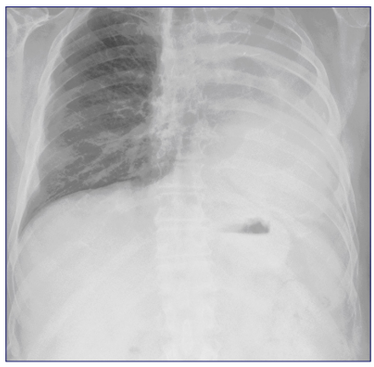


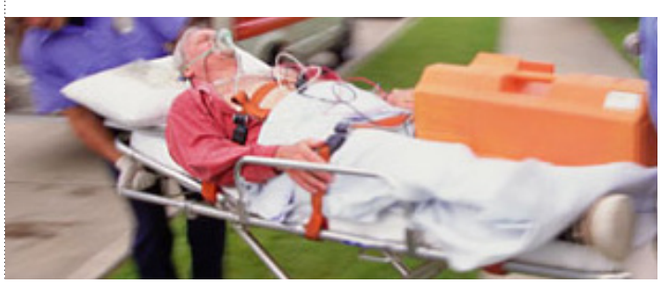
Image 1: CXR on admission to hospital.

In order to preserve blood pressure he was given small fluid boluses, and Hydrocortisone due to a history of chronic steroid use and concern about resulting adrenal insufficiency. He was placed on daily subcutaneous Octreotide in case of carcinoid crisis after discussion with his Oncologist, see table 1.

Signs of Carcinoid Crisis
Flushing
Bronchospasm
Tachycardia
Widely/rapidly fluctuating blood pressure

Table 1: Clinical signs of Carcinoid Crisis.

An echocardiogram was requested which demonstrated a grossly dilated right ventricle and atrium, severe right ventricular systolic dysfunction and moderate to severe Tricuspid regurgitation with accompanying severe pulmonary hypertension.



CASE BASED DISCUSSION: MANAGEMENT OF NEUROENDOCRINE TUMOURS

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He was reviewed by the cardiology team who recommended starting 40 mg IV Frusemide BD, a transoesophageal echo (TOE), and a CTPA to look for the underlying cause of his pulmonary hypertension, and examine the cardiac valves for evidence of carcinoid heart disease. A subsequent CTPA (image 2) showed no pulmonary emboli but did demonstrate a critical narrowing of his right pulmonary artery secondary to external compression from tumour mass. After MDT discussion he was transferred to a tertiary referral centre with a view to pulmonary artery stenting. The stent was inserted percutaneously under radiological guidance. Image 3 shows the improvement in pulmonary artery calibre after stent insertion.

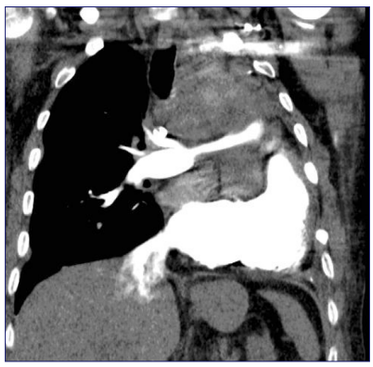

Image 2: CTPA, coronal reconstruction demonstrating severe narrowing of Right Pulmonary Artery by surrounding tumour mass.

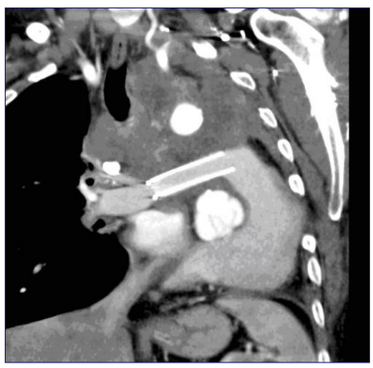

Image 3: Arterial phase CT Thorax with coronal reconstruction demonstrating Pulmonary Artery Stent.

It was followed by rapid improvement in his symptoms, and laboratory results over the following few days. Three days post procedure he walked out of hospital without breathlessness and resolution of peripheral oedema.

Discussion

Neuroendocrine tumours (NETs) are a rare and diverse collection of cancers that share a variety of pathological features. They originate from epithelial cells in many different organs such as the gut, pancreatic islets, lungs and thyroid (see table 2). They represent only 0.5% of all cancers, with an incidence of approximately 2 in 100,000, which has been slowly rising over the last few decades. (1)

Type of NET	Most common primary site	Hormones secreted
Carcinoid	GI Tract/Lungs	Serotonin
Oat Cell(Small Cell)	Lung	ACTH, ADH
Gastrinoma	Pancreas/Duodenum	Gastrin
Glucagonoma	Pancreas	Glucagon
Insulinoma	Pancreas	Insulin
VIPoma	Pancreas	VIP
Medullary Carcinoma	Thyroid	Calcitonin
Paraganglioma	Within Sympathetic nervous system	Catecholamines
Phaeochromocytoma	Adrenal	

Table 2: Types of Neuroendocrine Tumours.

Their exact aetiology is unknown but a number of familial cancer syndromes are seen to increase risk of NETs. (2) As their name suggests they are capable of producing a variety of hormones and peptides which depending on their location and extent of spread can lead to systemic sequelae. Despite this many NETs pursue an indolent course and are found incidentally. Carcinoid syndrome consisting of dry flushing, palpitations, diarrhoea and abdominal pain can be the presenting feature of jejunal and ileal NETs, but is rare in other NETs without metastasis to the liver which normally metabolises the circulating hormones. Diagnosis involves a variety of imaging techniques including CT, MRI, and radio-labelled octreotide (Octreoscan).

Examples of the patient's Octreoscan images are included in image 4.

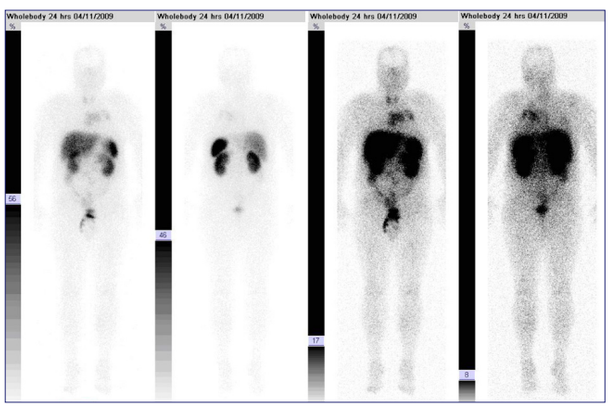

Image 4: Whole body images from an Indium Octreotide scan performed in 2009 on the patient demonstrates avid uptake of Indium octreotide in the mediastinum and left side of chest consistent with recurrent disease.

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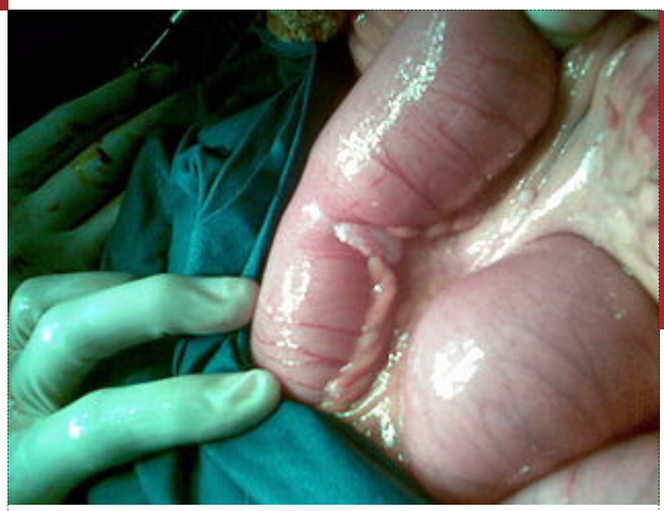

Biopsy for histology is important to confirm diagnosis, and give information about the differentiation and proliferation rate (as indexed by the Ki67 score) of the tumour as this effect prognosis. (3) Blood tests are also useful as the secretory products of the tumours can be measured. Chromogranin A and B can be found in high concentrations in the blood, as can Pancreatic Polypeptide in gastroenteropancreatic NETs. Urinary 5-HIAA, a metabolite of serotonin can also be measured by 24 hour urine collection. Chromogranin levels in the patient had been rising over the preceding few months as his disease progressed.

Surgical resection is the mainstay of treatment when the tumour is localised, the patient had undergone a pneumonectomy, but unfortunately this is not always curative and he later relapsed. Where surgical cure is not feasible de-bulking of tumour with symptom control with hormonal manipulation and other supportive medications is advised.

Octreotide is a somatostatin analogue used to reduce the symptoms of carcinoid syndrome, it can be given daily or monthly in longer acting preparations to treat the symptoms of excess neuropeptide secretion by the tumours. By binding to and blocking the somatostatin receptors it may also act to slow tumour growth. (2)

Any instrumentation of the tumour can lead to carcinoid crisis. Peri-operatively an octreotide infusion is advised, as was started in this case. Drugs which activate the sympathetic nervous system must be avoided and antihistamines, steroids and adrenoreceptor blocking drugs must be available.

Monitoring of the heart with echocardiograms for those with carcinoid is also advised as it may be affected. Elevated levels of serotonin produced by the tumour are believed to lead to damage to the tricuspid and pulmonary valves. In addition, as this case graphically shows, the tumour itself may be the cause.

Case based discussion: Management of Neuroendocrine Tumours
Patient Management

After 48 hours the patient was able to come off of the continuous octreotide infusion back onto daily subcutaneous injections. The stenting of his pulmonary artery relieved the severe pulmonary hypertension, and resulting haemodynamic compromise. The CTPA confirmed further progressive disease in his chest so his referral to London was expedited.

The case demonstrates that neuroendocrine tumours present a variety of challenges to the physician. They require a multidisciplinary approach with the input of Radiologists, Surgeons, Gastroenterologists, Endocrinologists, and Oncologists. New techniques and treatments mean that patients are living longer, but can develop new complications requiring novel approaches in order to treat them.

Questions

1. With regard to Neuroendocrine tumours:

a) Neuroendocrine tumours are found only in the gut
b) All neuroendocrine tumours cause carcinoid syndrome
c) The genetic familial cancer syndrome MEN-1 is not associated with an increased risk of NETs
d) Chemotherapy is used for metastatic disease
e) 55% of those with Stage II disease are alive at 5 years

2. With regard to carcinoid heart disease

a) It is caused by metastasis of the NET to the heart
b) It more commonly affects the left side of the heart
c) It cannot be treated with surgery
d) It can be treated with Somatostatin analogues
e) A pan-systolic murmur at the lower left sternal edge may be heard

Answers

1. Answer: d

Neuroendocrine tumours are found throughout the body, although most commonly within the digestive tract. A significant proportion of neuroendocrine tumours are non-functioning, their clinical picture will vary according to the hormones released by the tumour for instance pancreatic insulinomas will cause intermittent hypoglycaemia.

CASE BASED DISCUSSION: MANAGEMENT OF NEUROENDOCRINE TUMOURS

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Many carcinoids do not cause symptoms until they have metastasised to the liver as prior to this the enterohepatic circulation would allow liver enzymes to degrade the circulating amines and peptides before they reached the rest of the body. Multiple Endocrine Neoplasia Syndrome Type 1 is an autosomal dominant condition associated with an increase risk of NETs. The MEN 1 gene is located on chromosome 11 and likely works as a tumour suppressor, defects in the gene lead to tumours in the pancreatic islets, parathyroid and pituitary glands.

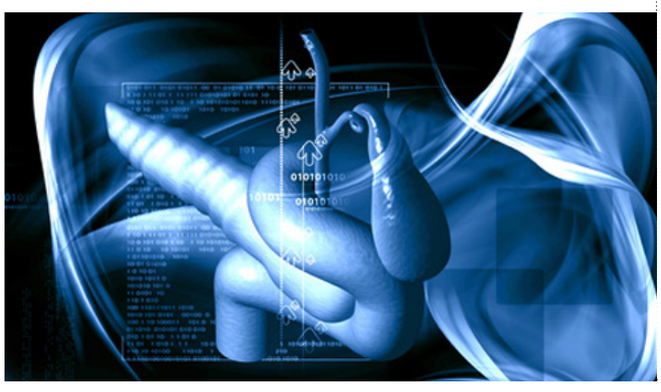
Chemotherapy with platinum and streptozocin based drugs is used in the palliative setting (2) and numerous trials are ongoing, newer drugs aimed at targeting specific enzymatic pathways in cancer cells such as Sunitinib and Everolimus are also being investigated with some evidence of benefit. (2) Prognosis can be estimated using the TNM staging criteria, but must be used in conjunction with information about the Grade and proliferation rate of the cancer, as more aggressive poorly differentiated tumours can have a significantly poorer prognosis. (3) Five year survival for all patients diagnosed with NETs is shown in Table 3.

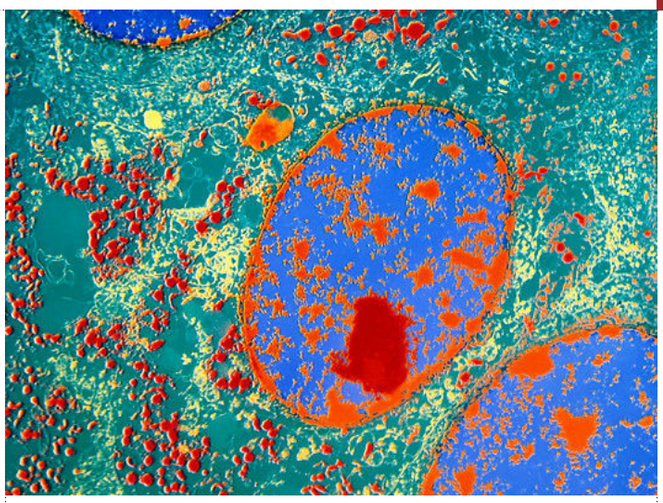
Stage at presentation	Percentage survival 5 years from diagnosis
Stage I	100%
Stage II	90%
Stage III	79%
Stage IV	55%

Table 3: Five year overall survival for NETs according to Stage at presentation (2).

2. Answer: e

Around 50% of patients with carcinoid syndrome will go on to develop carcinoid heart disease. (4) It is not caused by metastasis to the heart but is thought to be secondary to circulating vasoactive peptides produced by the tumours. Fibrous plaques are seen to preferentially involve the right side of the heart, presumably as the circulating peptides are inactivated by the lungs before they reach the left -sided valves and chambers. This can lead to valvular stenosis or regurgitation , and if this occurs the pan-systolic murmur of Tricuspid regurgitation may be audible on the left sternal edge. Surgical valve replacement can be an option along with medical treatments for heart failure. Somatostatin analogues are not seen to improve the condition. (4) Regular echocardiograms for those with Carcinoid are recommended.





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NUTRITION IN CANCER PATIENTS

M A Zohree Ali, P Ross

Abstract

Patients with cancer suffer a variety of symptoms. Cancer-associated malnutrition is one of the most common symptoms encountered. It can result from the systemic and local effects of a tumour, the host response to the tumour or advanced anticancer therapies (surgery, chemotherapy, radiotherapy, biological immunotherapy and hormonal treatment). Cachexia often occurs in advanced cancer. It is a multifactorial syndrome characterized by anorexia accompanied by generalized host tissue wasting, skeletal muscle atrophy, immune dysfunction, and metabolic derangements. Cancer patients therefore have the double burden of fighting cancerous cells and finding ways of replacing damaged cells.

Although cancer patients often have reduced food intake, alterations in metabolism and resting energy expenditure may also contribute to their nutritional status. Several agents produced in response to the tumour, such as pro-inflammatory cytokines and hormones, have been implicated in the pathogenesis of malnutrition and cachexia.

Case scenario

A 78 years old male with a long standing history of tobacco chewing and smoking was admitted to the hospital with history of progressive hoarseness of voice, loss of appetite and weight loss. For a few months, he noticed intermittent difficulty in swallowing, especially solid food. He also noticed sharp pain radiating to the right ear. The patient was unable to swallow food 15 days before admission. He immediately vomited after eating solid food.

Nutrition in cancer patients
Good Clinical Care

The patient was referred to a dietician for nutritional support. A trial of nasogastric tube feeding failed because of poor tolerance. Parenteral nutrition started whilst the patient underwent investigation of his symptoms. Laryngoscopy and biopsy proved stage II squamous cell carcinoma of the larynx (T2 N0 M0). CT scan showed no evidence of spread to the local lymph nodes. The patient was referred to the oncologist, who recommended radiotherapy with curative intent. Percutaneous endoscopic gastrostomy tubes (PEGs) prior to the start of treatment was indicated and it improved his nutritional status during the course of radiotherapy.

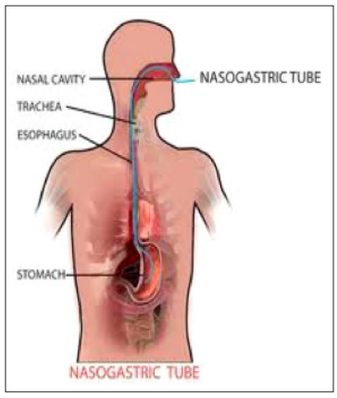


Figure 1: Case Study 1.

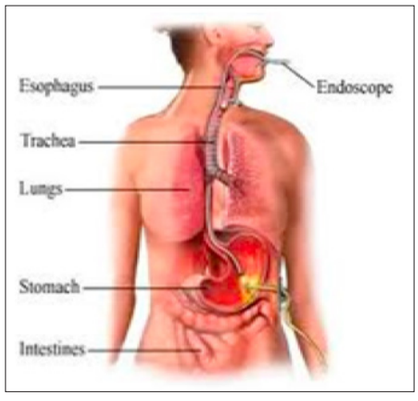


Figure 2: Case Study 2.

NUTRITION IN CANCER PATIENTS

M A Zohree Ali, P Ross

Nutritional screening and assessment

Nutritional support is required to reduce the consequences of cancer-associated nutritional decline. The development and implementation of screening and assessment tools is essential for effective nutritional intervention and management of patients with cancer. A number of screening and assessment tools are currently available for use. An example of a screening and assessment procedure is the Patient-Generated Subjective Global Assessment (PG-SGA).The caregiver completes sections on weight history, food intake, symptoms, and function. A member of the healthcare team evaluates weight loss, disease, and metabolic stress and performs a nutrition-related physical examination. A score is generated from the information collected. The need for nutrition intervention is determined according to the score.

Patients identified through screening require referral to a dietician for an in-depth nutritional assessment. This may involve taking medical, dietary, psychological and social history. Physical examination, anthropometry and biochemical testing will be also required. Interventions initiated after nutritional assessment should be tailored to the individual and take into consideration the patient's prognosis.

Method of nutrition

The preferred method of nutritional support is the oral route. Enteral nutrition is indicated when the gastrointestinal (GI) tract is functional but oral intake is insufficient to meet nutritional requirements. Common situations in which enteral nutrition may be needed include malignancies of the head and neck regions, oesophagus, and stomach.

The use of appetite stimulants such as steroids and medroxyprogesterone can help increase the food intake and weight gain. Recommendations during treatment may focus on eating foods that are high in energy, protein, and micronutrients. Supportive treatment might be required to help overcome alteration in taste, xerostomia, mucositis, nausea, or diarrhoea that are common side effects of chemotherapy and radiotherapy. Increasing the number of meals that include high-energy and high-protein snacks may help the overall outcome.

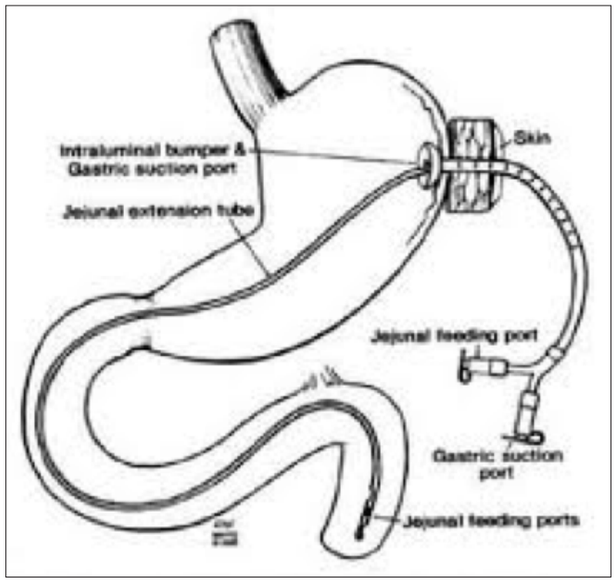


Figure 3: Method of nutrition.

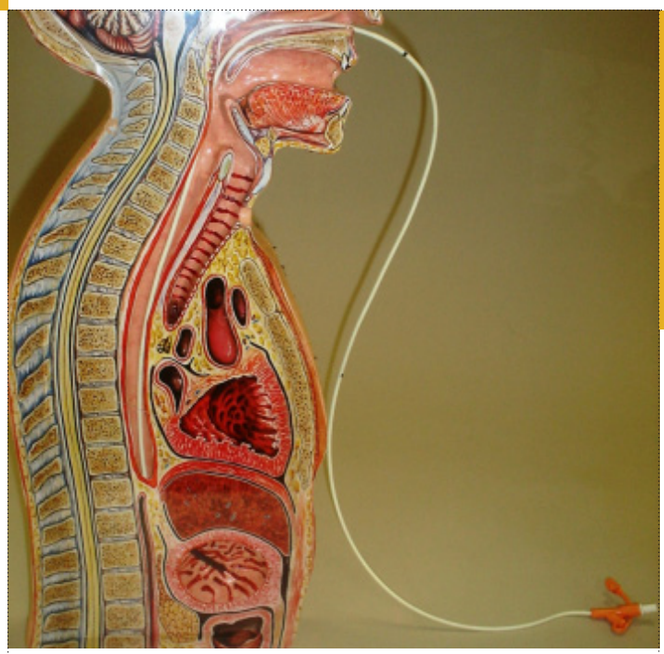
Enteral nutrition continues to use the gut especially in cases of gastrointestinal tract cancers and also where there are severe complications of chemotherapy or radiotherapy that prevent oral nutrition. Enteral nutrition is associated with certain complications such as infection and diarrhoea but is easier to administer than parenteral nutrition. Contraindications for enteral nutritional support include a malfunctioning gastrointestinal tract, malabsorption, mechanical obstructions, severe bleeding, severe diarrhoea, intractable vomiting, gastrointestinal fistulas in locations difficult to bypass with an enteral tube and inflammatory bowel processes. Thrombocytopenia and general pancytopenic conditions following anticancer treatments may also prevent placement of an enteral tube.

Percutaneous endoscopic gastrostomy tubes (PEGs) and percutaneous endoscopic jejunostomy tubes (PEJs) are generally used for long-term enteral feedings (>2 weeks). The placement further down in the gastrointestinal tract has a number of advantages:

- the diameter of the tube is larger (15F-24F catheters), which allows easier and faster passage of formulas and medications;
- the risk for aspiration is lower because of the decreased chance of migration of the tube up into the oesophagus;
- the risk for sinusitis or nasoesophageal erosion is lower; and this route is more convenient and aesthetically pleasing to the individual because of the ability to conceal the tube.

NUTRITION IN CANCER PATIENTS

M A Zohree Ali, P Ross



Assessment of need and ease of delivery are best done early. If the malnourished individual requires surgery for an unrelated event, a PEG or PEJ may be placed at that time to avoid an additional procedure.

Parenteral nutrition may be indicated for individuals who are unable to use the oral or enteral route. Contraindications for use of parenteral nutrition are an inability to obtain intravenous access and poor prognosis not warranting aggressive nutritional support. Complications arising from parenteral nutrition can be categorized as mechanical (vein thrombosis, pneumothorax, and catheter tip misplacement) or metabolic (hyperglycemia/hypoglycemia, hypokalemia, and elevated liver function tests). The constitution of parenteral nutrition and administration schedule needs careful supervision by personnel familiar with undertaking same. Consequently, many hospitals have specialist teams comprising a physician interested in nutrition, dietitian and pharmacist.

Goals of nutritional assessment and intervention

The goals of nutritional therapy are to prevent or reverse nutrient deficiencies, preserve lean body mass, help patients to tolerate treatments, minimize nutrition-related side effects and complications, maintain strength, boost immune function, aid in recovery and healing and improve quality of life.

Questions

1. Cancer-associated malnutrition results from?

A: Systemic and local effects of a tumour
B: The host response to the tumour
C: Anticancer therapies
D: Alterations in metabolism and resting energy expenditure
E: All of the above

Nutrition in cancer patients
Good Clinical Care

2. Enteral nutrition is indicated in the following situation?

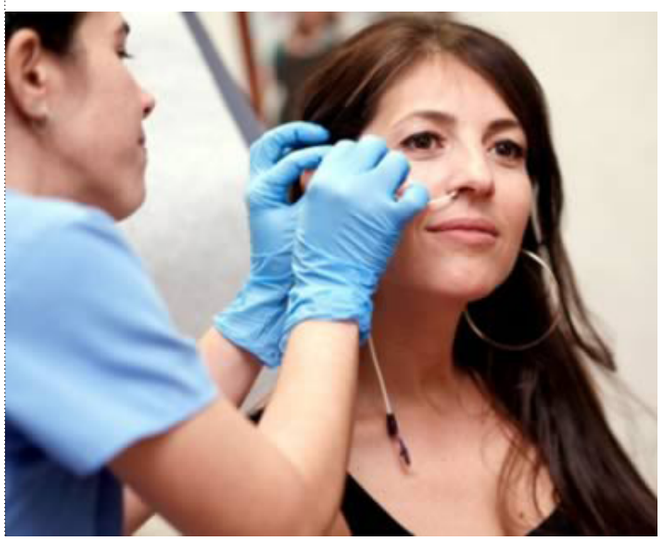
A: when the gastrointestinal (GI) tract is non-functioning
B: when oral intake is insufficient to meet nutritional requirements
C: when gastrointestinal (GI) tract is functional
D: B&C together
E: When oral intake is sufficient to meet nutritional requirements

3. Which of the following is a known complication of parenteral nutrition?

A: Vein thrombosis
B: Pneumothorax
C: Metabolic syndrome
D: Elevated liver function tests
E: All of the above

4. Contra-indication of parenteral nutrition includes?

A: Functioning gut
B: A need for nutritional support for less than 5 days
C: An inability to obtain intravenous access
D: Poor prognosis not warranting aggressive nutritional support
E: All of the above



NUTRITION IN CANCER PATIENTS

M A Zohree Ali, P Ross

5. Common side effects of chemotherapy that can affect nutritional status are?

A: Nausea, vomiting and diarrhoea
B: Xerostomia
C: Mucositits
D: Diarrhoea
E: All of the above

Answers

1. Answer E

2. Answer D

3. Answer E

4. Answer E

5. Answer E

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BRAIN TUMOUR TREATMENT OPTIONS

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Abstract

As with almost any cancer presentation, brain tumours are a diverse group of diseases with widely varying morbidities, prognoses and treatment options. The most common tumours found in the brain are metastases from an extracranial site (1) - approximately 8.3 per 100,000 compared with 6.6 per 100,000 for primary brain tumours. However, primary brain tumours are the second most common childhood cancer and the most common solid tumour in children (2), with different treatment options and a superior prognosis compared to adult tumours.

Treatment modalities for brain tumours include surgery, chemotherapy, radiotherapy and supportive care. This article will give an overview of the care of adult patients with central nervous system (CNS) metastatic disease and some of the more common primary brain tumours including high and low grade gliomas.

Presentation and assessment

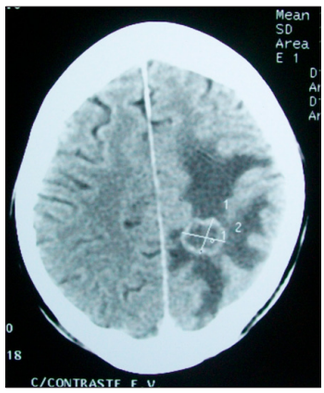
The most common presenting symptom of a patient with a CNS malignancy is headache (3), although at the time of diagnosis most patients also display other symptoms such as focal neurology, generalised neurological deficit, personality change or seizure. There are no signs which are diagnostic of a tumour over, for example, a stroke, but the onset of symptoms (rapid or gradual) or features of raised intracranial pressure may well give a clue as to the aetiology. Sometimes the only presenting feature is new onset of seizures.

Tumours at any site, especially the posterior fossa, blocking the flow of CSF through the ventricles, can lead to hydrocephalus and raised intracranial pressure. Symptoms of this include headaches and vomiting (worse in the morning) cognitive deterioration, visual changes and unsteadiness. (4) Cranial nerve, spinal cord or cauda equina symptoms may make the diagnosis of meningeal disease (malignant meningitis) more likely (5), and sometimes CSF sampling (for cytology) is required if no evidence is found on imaging.

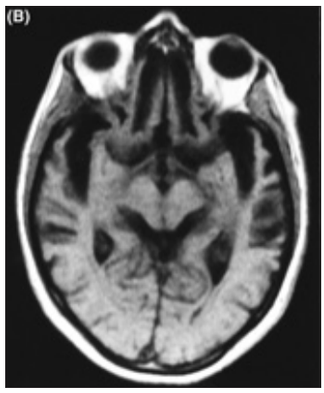
Patients with CNS symptoms will usually undergo a CT scan from which a provisional diagnosis may be made. In those with no prior history of malignancy, the CT may be followed by MRI scan, and CT of the chest, abdomen and pelvis may be performed to ensure the neurological findings are not due to metastatic disease.

Further investigations would then be considered to provide a histological diagnosis. It should be noted that approximately 10% of tumours are not picked up on an initial CT scan (3), so if there is still a strong clinical suspicion of a neoplasm, a contrast enhanced MRI should be considered. If access to CT and MRI brain scans is equal, a primary MRI scan is the investigation of choice.

Figure 1: Space-occupying lesion in left temporo-parietal region associated with peritumoural oedema. Source: Wikimedia. Author: Bobjgalindo.



CT scan.



MRI scan (T1 weighted).

BRAIN TUMOUR TREATMENT OPTIONS

T Simmons, C Bridgewater, M Hatton

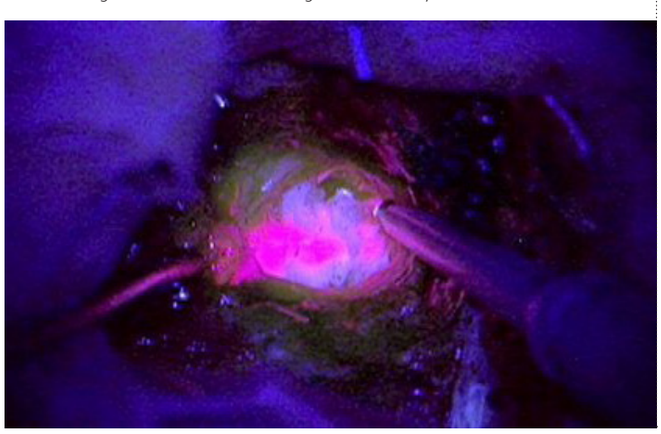
When assessing any patient with cancer, especially those with cerebral disease, an assessment of the fitness of the patient is vital, including both comorbidities and symptoms attributable to the tumour. All the treatments described below require the patient to be able to tolerate the procedure and the associated short and long-term toxicities. An accurate assessment of performance status is invaluable in assessing patients for treatment. The ECOG (Eastern Cooperative Oncology Group) has developed a performance status score as below (6) and the Karnofsky score can also be used.

Score	Description
0	Fully active, able to carry on all pre-disease work without restriction
1	Restricted in physically strenuous activity, but able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of limited selfcare, but confined to a bed or chair for more than 50% of waking hours
4	Completely disabled, bedbound or chair bound
5	Dead

Table 1: Source: ECOG.

These scores are prognostic predicting survival and the severity of treatment side effects. Fitter patients (score of 0-1) are likely to benefit from most treatments, where someone with a score of 3-4 may have a short survival time and be better managed with supportive care only. However, a common theme throughout this article is that each patient should be individually assessed as to what treatments should be offered.

Any patient with a suspected primary brain tumour, or metastatic CNS disease where aggressive treatment options are being considered, should be discussed in a neuro-oncological multidisciplinary team meeting. The MDT, containing neurosurgeons, oncologists, pathologists, radiologists, nurses and allied health professionals, will advise on immediate management and, if appropriate, arrange further investigations and ongoing treatment. To enable a productive discussion to occur, the referral should include details of the patient's symptoms, performance status and any co-morbidities. Unless contraindicated, MRI scanning is often requested before the discussion due to its much greater resolution and diagnostic accuracy.



When a patient is diagnosed with a brain tumour, there are various legal aspects to consider, especially that of driving. The UK has strict guidelines concerning driving following the diagnosis of a brain tumour (7), and all patients should be instructed to inform the DVLA, who will revoke their licence. WHO grade III and IV tumours would mean a 2 year driving ban, where a lower grade primary tumour or metastatic deposit will mean a year's ban. After this time, a medical assessment is made regarding fitness to drive, and whether seizures and both local and systemic disease remain controlled. It is not a certainty the licence would be reinstated after this time. This can have a major impact on the lifestyle of a previously fit person, and the loss of independence can be difficult to cope with.

Treatments

Emergency Treatment: CNS tumours can develop rapidly progressive disabling or life threatening symptoms which, depending on the aetiology, may be readily reversible. The management of seizures and the need for corticosteroid treatment is outlined below. If hydrocephalus is found, surgical intervention such as a ventricular / peritoneal shunt or ventriculostomy may be indicated urgently.

Corticosteroids: While lower grade or slow growing tumours may cause little or no oedema, the more rapidly progressing primary or secondary CNS tumours are often oedematous, adding to the mass effect, and this can be relieved by corticosteroids. In any patient presenting with a brain tumour, the addition of steroids may dramatically improve symptoms within a few days and is well tolerated. Some of the side effects of steroids such as increased appetite, energy and weight gain may be seen as beneficial for many of the patients in this situation, but care should be taken to titrate to the lowest tolerated dose (ideally stopping as other treatments take effect) to delay or prevent longer term toxicities such as skin changes and proximal myopathy.

The most usual choice of corticosteroid in the UK is dexamethasone, with starting doses of 4-8 mg recommended for mild to moderate, and up to 16 mg daily for severe symptoms. (8) Steroids should be given with a gastroprotective agent such as a proton pump inhibitor or ranitidine.

One special case to consider is lymphoma. Corticosteroids are an effective anti-lymphoma agent, and are used in a large number of lymphoma chemotherapy regimens. (9) Lymphoma classically presents in a peri-ventricular location (10), and the diagnosis may be suspected by the reporting radiologist. If steroids are given before a biopsy is taken, a subsequent biopsy may not contain any viable tumour precluding a diagnosis, thereby delaying definitive chemotherapy. Where possible, good practice would be to discuss the case with the neurosurgical team before initiating steroids, but it is recognised that in an emergency situation this is not always possible, or steroids have already been started before the possibility of lymphoma is raised.

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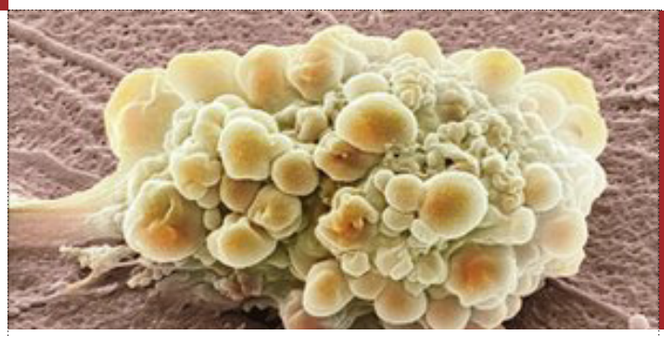

Brain tumour treatment options
Patient Management

Anticonvulsants: Seizure is a common complication of CNS tumours, and is often the presenting complaint. Control of seizures may be achieved using the same principles as any other cause of epilepsy. The main difference when considering the choice of anti-epileptic agent in this situation is the potential for interactions with subsequent chemotherapy. Certain anti-epileptics either inhibit or induce cytochrome P450, which can significantly alter the exposure to cytotoxic chemotherapy, either increasing toxicity or decreasing effectiveness. Phenytoin, for example, is an enzyme inducer. Levetiracetam does not significantly interact with P450, and is a commonly used alternative. (11) If in doubt, the case should be discussed with the neurology team. The prophylactic use of anticonvulsants in patients without a seizure history is controversial, and evidence is that it is unlikely to be of benefit. (12)

Supportive care: The diagnosis of a CNS tumour is both physically and emotionally devastating, and many of the treatments are associated with significant toxicity. For this reason, professionals such as physiotherapists, occupational therapists, speech therapists, neurologists, specialist nurses and the palliative care team all provide vital services key to the management of these patients. They should be involved at an early stage, to aid rehabilitation during and after initial treatment, and throughout the disease progress.

Surgery: Resection is the quickest way to obtain relief of symptoms from a space occupying lesion, and recovery can be rapid. With some notable exceptions, the aim of the neurosurgeon is to remove as much of the tumour as possible without causing unacceptable ongoing morbidity. The extent of resection influences outcome (13), and the aim is a complete resection while keeping the patient neurologically intact. When considering surgery, the fitness of the patient, location of the disease and the diagnosis are all taken into account. Surgery is rarely undertaken in areas where an operation may cause a significant, permanent functional deficit such as the motor strip, speech areas or brainstem and if there is doubt, functional MRI can help (14) or awake craniotomy is performed. (15)

In the context of a suspected primary brain tumour where the disease is not resectable, biopsy should be obtained whenever possible (16). While radiological techniques can generally identify that a tumour is present, and modern techniques such as MRI spectroscopy are improving accuracy, predicting grade or tumour subtype from radiology remains unreliable, but if a histological diagnosis is not possible, a working diagnosis can be made on clinical and radiological grounds. The uptake of contrast implies a glioma is high grade. Biopsy is rarely required from metastatic disease from a known primary.

Radiotherapy: Radiotherapy is the use of ionising radiation to cause DNA damage in cells, resulting in cell death. While some rarer CNS tumours can be cured with radiotherapy, for most indications the aim is to shrink the tumour and achieve long-term local control of the disease. When radiotherapy is being given for metastatic disease, the entire brain is considered to be at risk, so the whole brain is treated. In the case of malignant meningitis, radiotherapy may be targeted at the most likely site to be causing symptoms (including spine or skull base). (5)

Radiotherapy takes a few minutes to give each day, but regimens can last up to six weeks. While receiving radiotherapy is a similar experience to having a scan, there are both short and long-term toxicities. Short term toxicities include fatigue, hair loss, headache and sickness. Longer term, cognitive effects can become apparent (especially in children), hair loss may be permanent depending on the radiotherapy dose received and endocrine problems such as pituitary dysfunction can occur years later.

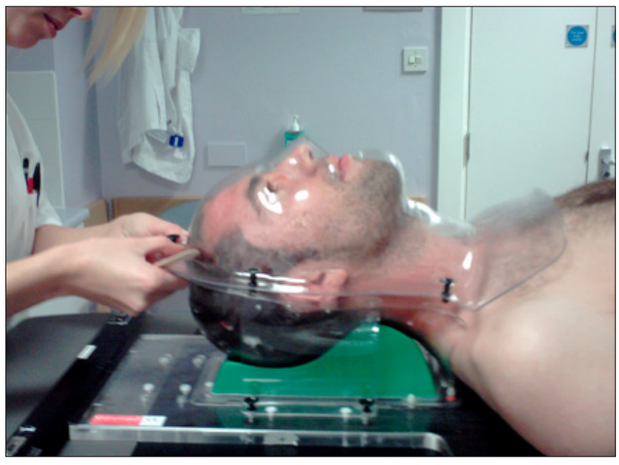

Figure 2: Patient being fitted into a custom-made head shell prior to radiotherapy. Picture reproduced with the permission of Jenna Styan.

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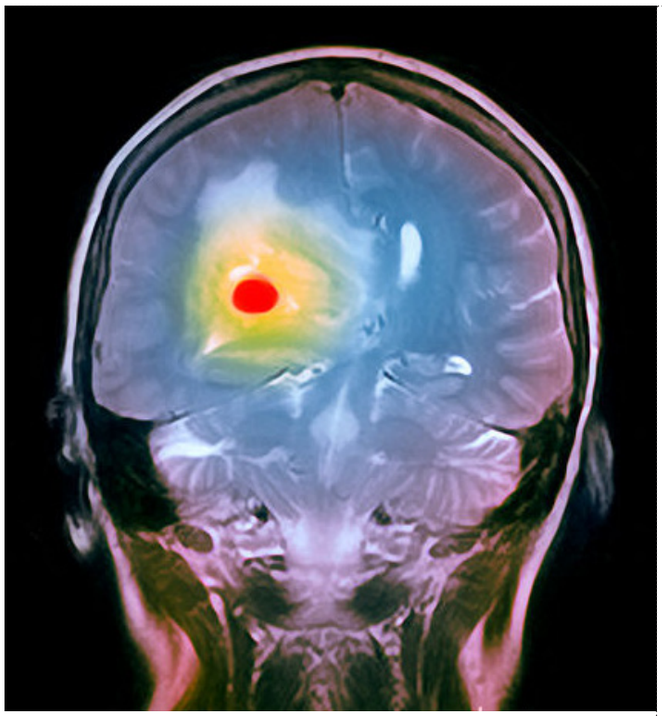


Stereotactic Radiosurgery: Radiosurgery also uses radiation to treat CNS tumours, but instead of using a small number of beams to treat a large tumour, many (over a hundred) beams are focussed on a small tumour. Treatment is to a much higher dose than conventional radiotherapy, ablating abnormal tissue without damaging surrounding tissue. Very precise positioning and targeting is required for this treatment, sometimes involving the use of a stereotactic frame attached directly to the skull. As with other treatments, patient selection is very important, and typically up to three small lesions can be treated at any one time, although precise criteria vary. (17)

Chemotherapy: Cytotoxic chemotherapy causes irreparable damage to DNA resulting in cell death. Indications for chemotherapy vary widely but for the most part chemotherapy is used to control the disease and delay progression rather than cure. A notable exception is that of CNS lymphoma, for which chemotherapy (alongside radiotherapy) is used as part of a curative regimen. (18) While some oral chemotherapy preparations are available, the toxicity associated with these is not necessarily any less than with intravenous preparations. Chemotherapy carries significant toxicity including fatigue, nausea, vomiting and bone marrow suppression, which can in turn lead to neutropenic sepsis or other potentially life threatening complications.

Tumour types

Metastatic disease: The most common aetiology of CNS tumour is that of metastatic disease from a systemic malignancy. The most common primary sites are lung, breast, melanoma and lower gastrointestinal cancers. While brain metastases generally carry a very poor prognosis (median survival may be as short as 4 months (19)), aggressive treatment for selected patients can result in long-term survival.

Management of a patient with cerebral metastases is highly individualised. Having said this, patients with brain metastases fit into three main categories;

1. Single (or very low number of) cerebral metastases in an otherwise fit patient with systemic disease well controlled.

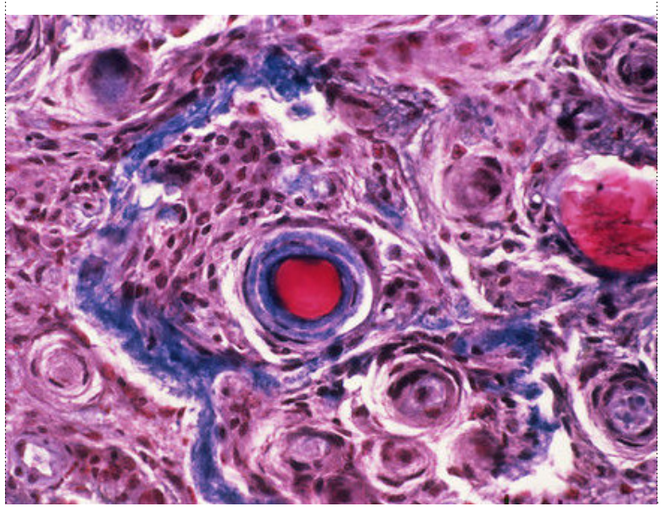
These are patients where aggressive surgical or radiosurgical management plays an important role. Once again, patient selection is vital, but where possible, resection or ablation of oligometastatic disease improves both quality of life and prognosis. (20) Another role for surgery is to obtain a tissue diagnosis (either through excision or biopsy) where none is obtainable from another site to guide further management. The treatment of 2-3 metastases in this situation is more controversial, but surgery may still be appropriate. Following surgery, whole brain radiotherapy should be considered (21), as once the cancer has shown a propensity to metastasise to the brain, the entire CNS is felt to be at risk. (12) Whole brain radiotherapy is given over two weeks or less.

2. Multiple cerebral metastases or metastasis not amenable to surgical or radiosurgical treatment in an otherwise fit patient.

For this group of patients, steroids and whole brain radiotherapy are the mainstay of treatment. While the response to steroids may give an indicator of response to radiotherapy, as long as a patient is fit enough, radiotherapy can increase survival. (22) For patients where the systemic disease is not controlled, especially for particularly chemosensitive tumours such as small cell lung cancer, chemotherapy may also be an option. (23)

3. Cerebral metastases in an unfit patient.

Unfortunately, the scenario where a patient with cerebral metastases is unfit (PS 3-4), not improved by the use of corticosteroids and interventions such as a shunt have been excluded, carries a very poor prognosis, usually of weeks. For these patients, supportive and palliative care is key, and radiotherapy is not usually appropriate.



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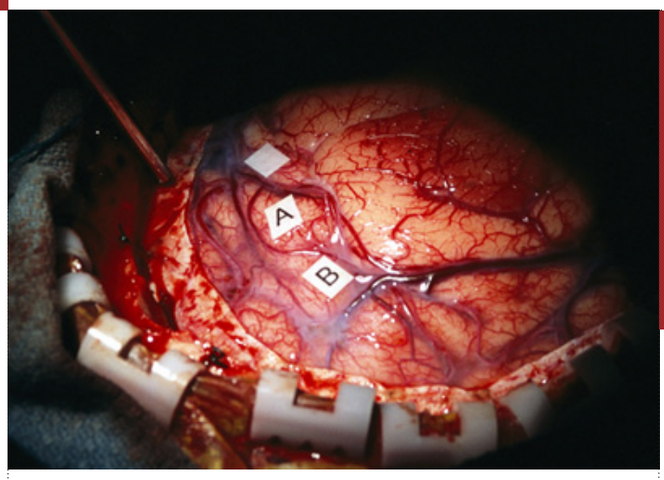

There is currently a trial underway looking into the grey area between the last two categories in non-small cell lung cancer. Interim results have not yet shown differences in survival or quality of life between radiotherapy and no radiotherapy (in addition to steroids and best supportive care). The trial is still recruiting, and significant differences may emerge between the two strategies. (24)

Primary brain tumours: The World Health Organisation grades primary brain tumours from I to IV (25), with grade IV tumours being the most aggressive. 54 differing tumour entities are classified, and it is beyond the scope of this article to analyse the treatment of each type in detail, but an overview of the treatment of the more common high and low grade tumours is provided. As can be expected, there are some significant exceptions to the rules below.

High grade glioma(WHO III and IV): Until relatively recently, long-term survival from glioblastoma (WHO IV) was rare, with a 2 year survival of under 10%. Until this time, surgical resection of the tumour followed by radiotherapy (for 6 weeks) was standard treatment. In 2004 a trial showed that the addition of temozolomide (an oral chemotherapy) both during and after radiotherapy significantly improved the survival to 27.2% at 2 years and 9.8% at 5 years. (13) The current standard of care for glioblastoma patients who are performance status 0-1 is therefore maximal surgical de-bulking, six weeks of radiotherapy and chemotherapy and finally six months of adjuvant chemotherapy (taken for 5 days every month). This regimen has potential to be toxic and is currently not felt to be suitable for elderly patients, or those who are unfit, and sometimes a shorter course of radiotherapy, or possibly supportive care and corticosteroids alone is most appropriate.

Grade III gliomas (such as anaplastic astrocytoma) have a better prognosis than glioblastomas. (26) They are treated in a similar manner, but current practice is not to use adjuvant chemotherapy, although trials are ongoing.

Despite the recent improvements in survival, high grade gliomas still recur in almost all patients. At recurrence, repeat surgery is considered, and is would be the treatment of choice if possible. Other chemotherapy regimens, such as PCV (procarbazine, lomustine and vincristine – intravenous chemotherapy) are used, but response rates are well under 50%. (27)

Low grade glioma (WHO I and II): Low grade gliomas are approached in a rather different way to WHO III and IV tumours, and there is less agreement regarding optimal management. This slow growing group of tumours presents more frequently with seizures (80%). Surgery can be curative for grade I tumours such as pilocytic astrocytomas. Treatment options include adoption of a watch and wait policy (for asymptomatic, unilateral, small tumours without mass effect in young patients) to resection, or radiotherapy if resection is not appropriate (28). At resection or biopsy, some tumours which were previously thought to be low grade based on clinical and radiological assessment may have higher grade features, in which case they are treated according to the pathology. The evidence for the use of chemotherapy for low grade tumours is very limited at present but trials are ongoing.

Summary

CNS tumours are a heterogeneous group of diseases with widely varying treatments and prognoses. An individualised approach to the disease is vital, with the fitness of the patient, histology of the disease and location of the tumour all influencing management. As well as physical symptoms, the diagnosis of a brain tumour can have a significant psychological impact and carry loss of independence. The multiprofessional team should be involved early, and be available to the patient throughout the course of their illness. It should not be forgotten that there are legal implications associated with the diagnosis of a brain tumour, especially regarding driving.

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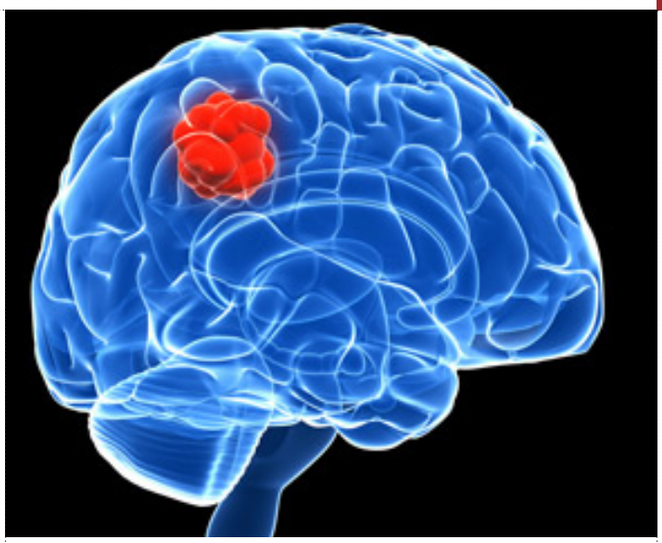

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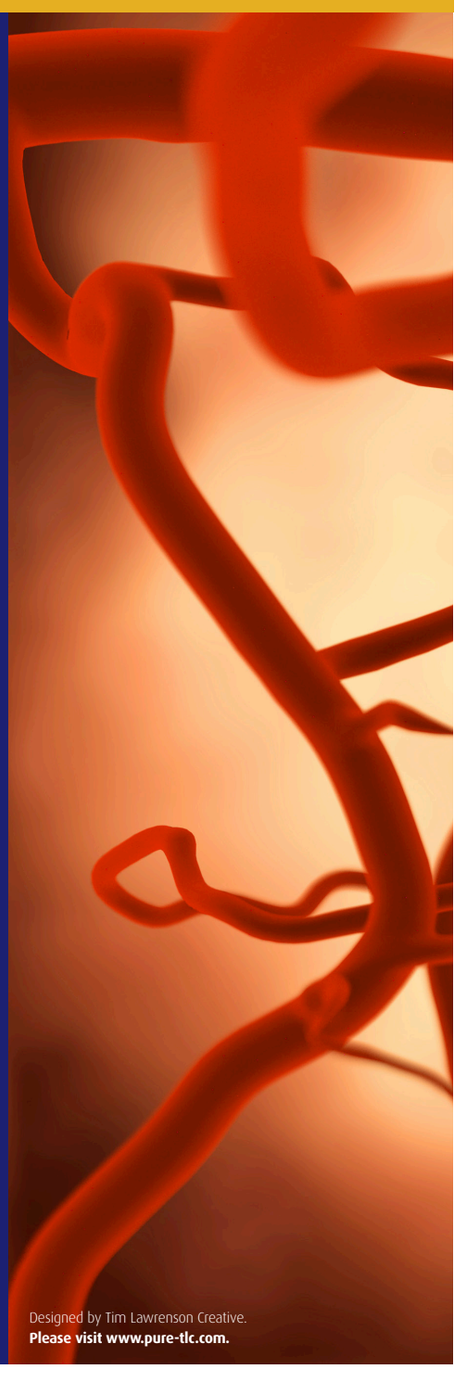

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