SELF ASSESSMENT QUESTIONS

Answers on p 736.

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Visual disturbances and weight gain

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A 51 year old man presented with a two year history of gradually deteriorating vision in his left eye, accompanied by 34 kg weight gain, easy bruising, and hypertension which was relatively resistant to conventional treatment. The patient denied any history of headaches. On examination, his general appearance was as shown (fig 1). On ocular examination his visual

acuity was 6/6 in the right and 6/12 in the left eye. A left relative afferent pupillary defect was present and fundoscopically there was left optic nerve atrophy. Numerous investigations were performed, including Humphrey's field analysis (fig 2), and a cerebral magnetic resonance imaging (MRI) scan (fig 3). Eye positions on left lateral gaze were as shown (fig 4).

Figure 1 Appearance of patient on presentation (reproduced with patient's permission).

Figure 2 Overview of Humphrey's visual field analyses over three years (FL = fixation losses, GHT = glaucoma hemifield test, MD = mean deviation, PSD = pattern standard deviation; SITA was the program used).

Figure 3 MRI scan: axial and coronal sections.

Figure 4 Eye position on left lateral gaze (reproduced with patient's permission).

Questions

- (1) Explain the ocular findings, and give the differential diagnosis.
- (2) What further investigations would you perform?
- (3) What does his MRI reveal?
- (4) Outline initial management, and, should this fail, what alternative treatment options exist?

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Acute myeloid leukaemia with tell-tale computed tomography scans

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Answers on p 737.

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A 36 year old man with acute myeloid leukaemia presented with recurrent episodes of fever and a three day history of right sided pleuritic pain and left upper abdominal pain after two cycles of chemotherapy. The patient had received several broad spectrum antibiotics with no clinical improvement. On examination, his temperature was 40.2°C and there was no evidence of Hickman catheter infection both in terms of local evidence and catheter blood cultures. Coarse crackles were noted over the base of the right lung. The liver, spleen, and peripheral lymph nodes were not enlarged. Bone marrow examination showed hypocellular marrow with no excess of blast cells. The neutrophil count was less than $0.05 \times 10^9/l$ for three weeks. Cultures of the blood were repeatedly negative. Chest radiography after two courses of chemotherapy was normal. Computed tomograms of the thorax and abdomen are shown in figs 1 and 2.

Questions

- (1) What do the computed tomograms show?
- (2) What is the most likely cause of the persistent fever in this patient and how would you confirm the diagnosis?
- (3) What is the treatment for this condition?

Figure 1 Computed tomogram of the thorax.

Figure 2 Computed tomogram of the liver and spleen

Failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient

S J McNulty, K J Hardy

Answers on p 739.

An 18 year old woman presented with a two week history of polyuria, polydipsia, and accelerated weight loss. On examination she was thin, dehydrated, hypotensive (blood pressure 88/58 mm Hg), and tachycardic (pulse 130 beats/min). Random blood glucose concentration was 20.2 mmol/l and she had hyponatraemia, hyperkalaemia, and mild uraemia (consistent with diabetic ketoacidosis); however, she was not ketoacidotic (box 1). She was diagnosed as having diabetes (subsequent testing confirmed a diagnosis of type 1 diabetes mellitus) and treated with intravenous insulin and intravenous fluid. On further questioning, she admitted to a 13 month history of easy tanning, weight loss, generalised weakness, reduced appetite, and several episodes of collapse with abdominal pain.

Questions

- (1) What test may be used to confirm a diagnosis of type 1 (as opposed to type 2) diabetes mellitus?
- (2) Given this patient's history before this admission; what other condition are the urea and electrolytes results in box 1 consistent with and how is the diagnosis confirmed?
- (3) What may be the explanation for this profoundly unwell patient with type 1 diabetes and hyperglycaemia not to have developed diabetic ketoacidosis?

Box 1: Investigations at presentation. Note the low sodium, high potassium, and urea consistent with diabetic ketoacidosis, but the absence of acidosis and significant ketosis (reference ranges in parentheses)

Sodium: 118 mmol/l (135–145)
 Potassium: 5.2 mmol/l (3.5–5.3)
 Urea: 10.9 mmol/l (2.5–7.5)
 Creatinine: 87 µmol/l (50–110)
 Glucose: 20.2 mmol/l
 Glycated haemoglobin: 9.0% (4.6–6.2%)
 Urinalysis: ketones ++
 pH: 7.4 (7.36–7.44)
 Arterial carbon dioxide tension: 4.99 kPa (37 mm Hg) (4.6–6.0 kPa)
 Arterial oxygen tension: 12.7 kPa (95 mm Hg) (11.3–13.3 kPa)
 Bicarbonate: 23.4 mmol/l (20–28)
 Saturated oxygen: 97.4%

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Diabetes and rapidly advancing pneumonia

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Answers on p 740.

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A 20 year man, who was known to have had type 1 diabetes for the past one year, had high grade fever with chills and rigors, and cough with expectoration for 15 days. He was admitted with epigastric pain, vomiting, and tachypnoea after not taking insulin for four days before admission.

On examination, he was moderately dehydrated but well oriented. His pulse was 120 beats/min regular, blood pressure 110/70 mm Hg, and he was febrile. His chest revealed fine crepitations in the left interscapular region. Other systemic examination was normal.

On investigation, his spot capillary blood glucose was 24.3 mmol/l, pH 7.25, bicarbonate 4 mmol/l, anion gap of 37 mmol/l, arterial oxygen pressure 13.3 kPa, and arterial carbon dioxide pressure 1.2 kPa. Urine ketones were

strongly positive (4+). His serum sodium concentration was 134 mmol/l, potassium 3.8 mmol/l, urea 10.5 mmol/l, and creatinine 45 µmol/l. Haematology investigations showed a haemoglobin of 101 g/l, total leucocyte count 18.9×10^6 /l with 81% polymorphs. Chest radiography showed left mid and lower zone infiltrates. Blood and sputum cultures were sterile. He received intravenous saline, appropriate insulin infusion with potassium supplementation, amoxycillin-clavulanic acid, amikacin, and metronidazole. He recovered from ketoacidosis within 24 hours and the pH went up to 7.47, arterial oxygen pressure was 13.10 kPa, arterial carbon dioxide pressure 2.27 kPa, bicarbonate 13 mmol/l with saturation of 98%. However, his fever did not abate. His arterial oxygen pressure and oxygen saturation

dropped to 6.93 kPa and 90% respectively. The arterial oxygen pressure/fractional inspiratory oxygen ratio was <150 mm Hg suggestive of acute respiratory distress syndrome (ARDS). His chest radiograph revealed bilateral pulmonary infiltrates, left more than right (fig 1). He was put on assisted ventilation and the antibiotics were changed to ceftizidime, netilmycin, cloxacillin, and metronidazole. Subsequently, he had an upper gastrointestinal bleed, which was managed with blood transfusion and intravenous ranitidine. He remained hypoxic despite an inverse ratio ventilation and developed respiratory acidosis. The lung lesion did not respond to the treatment and he died of his illness. Postmortem lung biopsy was done.

Figure 1 Chest radiograph of the patient showing bilateral pneumonia.

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Questions

- (1) What are the possible diagnoses and how would you investigate this patient?
- (2) How would you manage the condition?

Cutaneous gangrene in a renal dialysis patient

L Pantanowitz, A Harton, B Beckwith

Answers on p 741.

A 54 year old obese man with end stage renal disease secondary to membranous and crescentic glomerulonephritis, receiving haemodialysis, was admitted for painful necrotising abdominal and left groin wounds. He had hyperlipidaemia, coronary artery disease, peripheral vascular disease, and a 35 pack year smoking history. He was on warfarin sodium for a deep venous thrombosis. His vital signs were normal and a physical examination was remarkable for pitting pedal oedema, carotid bruits, weak left pedal pulses and large, tender, erythematous, and ulcerating subcutaneous masses of the lower abdominal wall. Blood tests revealed a glucose concentration of 6.5 mmol/l, total serum calcium 2.4 mmol/l, albumin 36

g/l, and phosphate 1.9 mmol/l. Parathyroid hormone (PTH) levels were normal and antineutrophil cytoplasmic antibody and antinuclear antibody were negative. Radiographs of his lower legs showed bilateral subcutaneous calcifications. Methicillin resistant *Staphylococcus aureus*, *Escherichia coli*, and streptococci were isolated from his wounds. A biopsy specimen (fig 1) was taken from these lesions to help make the diagnosis.

Questions

- (1) What is the diagnosis?
- (2) What are the risk factors for this condition?
- (3) Can this condition occur in patients without renal disease?

Figure 1 Photomicrograph showing circumferential and artefactually fragmented medial calcification of an arteriole with accompanying fibrointimal proliferation, both causing occlusion of the vessel lumen, with ensuing necrosis of adjacent subcutaneous fatty tissue (original magnification $\times 400$).

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SELF ASSESSMENT ANSWERS

Visual disturbances and weight gain

Q1: Explain the ocular findings, and give the differential diagnosis

Figure 4 (see p 732) shows decreased abduction of the left eye consistent with a left abducens nerve lesion. The clinical finding of a left relative afferent pupillary defect denotes a deficit of the afferent visual pathway, anywhere from the retina to the optic tract. However a lesion causing optic nerve atrophy can be due to a primary retinal problem, optic nerve tumour, or asymmetric lesion of the optic chiasm. Usually a lesion of the chiasm or posterior to it (tracts to the lateral geniculate nucleus) will affect the optic discs bilaterally. Here the retina appeared normal on fundoscopic examination, hence the lesion must be of the optic nerve, or an asymmetric lesion of the chiasm. This is confirmed as the Humphrey's field analysis deficit affects only the left eye.

The Humphrey's field analysis reveals a unilateral defect affecting the left eye, but sparing the inferior temporal quadrant, at the time of initial presentation. Subsequent analysis performed after treatment, revealed that this lesion was localised to the superior half of the visual field. This would suggest that the lesion affects the inferior fibres of the optic nerve. As the pituitary gland is anatomically beneath the optic chiasm, this finding would be consistent with a pituitary tumour. Pituitary macroadenomas most commonly cause a bitemporal hemianopia, which in 8% progress to complete loss of vision in one eye. Nine per cent have a single eye defect, most commonly superior temporal. Bitemporal scotomas or monocular losses such as central scotomas may also occur. Through invasion of the cavernous sinus, ocular palsies may occur. The oculomotor nerve is most commonly affected.^{1 2}

The differential diagnoses that must be considered in a patient who presents with an optic nerve lesion include trauma, tumour, multiple sclerosis, a vascular event such as a central retinal artery occlusion, a hypertensive vasculopathy, or temporal arteritis. However in this patient who experienced a gradual onset of his symptoms, which were found to be unilateral on examination, the most likely differential diagnosis is a tumour. A pituitary macroadenoma, applying pressure from below, would account for the optic nerve findings. The abducens nerve findings, however, may be due to raised intracranial pressure due to an expanding mass within the cranium, or due to direct pressure of the tumour on the abducens nerve as it passes through the cavernous sinus. In this case, the computed tomogram revealed asymmetric involvement of the chiasm and involvement of the left cavernous sinus by the mass.

Q2: What further investigations would you perform?

Based on the moon facies and centripetal obesity visible in fig 1 (see p 732), and a history of recent weight gain, easy bruising and hypertension, a diagnosis of Cushing's syndrome should be suspected. With the associated ocular manifestations primary pituitary pathology is the most likely cause, namely Cushing's disease.

The screening test of choice for Cushing's syndrome is a 24 hour urinary free cortisol, or a 0800 plasma cortisol after 1 mg of dexamethasone at midnight. If raised, a low dose, 0.5 mg dexamethasone suppression test six hourly for two days is performed. If cortisol is not suppressed, the diagnosis of Cushing's syndrome is made. Localisation is further achieved by a high dose dexamethasone suppression test, plasma adrenocorticotrophic hormone concentration and radiology, in the form of coronal and axial MRI scan sections through the pituitary fossa.

Q3: What does his MRI scan reveal (see fig 3, page 733)?

The MRI scan shows a large pituitary mass, which extends anteriorly towards the left optic canal. The mass is encasing the siphon of the left internal carotid artery and appears to involve the left cavernous sinus.

With regards to pituitary dependent Cushing's disease, up to half of those who have a microadenoma may have no perceivable abnormality on MRI. In this patient, however, a large macroadenoma with extrasellar extension was detected, which is seen in about 10% of pituitary dependent Cushing's disease.

Q4: Outline initial management, and, should this fail, what alternative treatment options exist?

For a pituitary macroadenoma, the treatment of choice is trans-sphenoidal or frontal resection. This corrects hormonal overproduction within 24 hours in about 70% of patients with Cushing's disease.³ However in pituitary macroadenomas, success rates are much lower with regards to surgical intervention alone. Recurrence of visual field defects occurs in 85% over 10 years, but this figure drops to 15% if radiotherapy is combined with surgery. In patients with recurrence of the tumour, further radiotherapy and surgery may be useful to control the tumour bulk, and medical therapies may be used in an attempt to control endocrine manifestations.

The most commonly used medical therapeutic agent is ketaconazole, which acts by inhibiting steroidogenesis, but may cause abnormalities of liver function tests. If this fails, other options include metyrapone and aminoglutethimide. Metyrapone was found to control hypercortisolaemia and clinical features in up

to 83% of 24 patients after pituitary irradiation.⁴ However all the aforementioned medications have a temporary suppressive action and lack a permanent ablative action on the adrenal gland. Mitotane (O,p'DDD) is an exception,⁵ as it may be curative in Cushing's disease if used for six months to two years at doses of 2 g per day. The usual concerns with side effects which arise when 12 g per day is used in the treatment of adrenal carcinoma do not appear to be of concern at such low doses. Another therapeutic modality is octreotide, however this maybe of use only when a patient's cortisol level is adequately suppressed; such that an upregulation of somatostatin receptors in the pituitary tumour occurs. Thus, when octreotide is introduced, there are more receptors to bind with and hence a shrinkage of tumour bulk can be achieved. Bilateral adrenalectomy is another therapeutic option, however the possibility of a patient developing Nelson's syndrome (an increase in pituitary tumour bulk due to a loss of the cortisol negative feedback system) is a major concern.

Our patient initially underwent a transfrontal resection. Despite two further surgical resections and two courses of radiotherapy, the tumour continued to grow and the patient experienced a recurrence and progression of his clinical symptoms. Unfortunately the ketoconazole had to be stopped because of an increase in his hepatic enzymes after starting treatment. Subsequently he was started on mitotane, with normalisation of plasma and urinary cortisol levels. In our patient, whose eye symptoms are particularly symptomatic and continuing to progress, octreotide is also being considered as adjuvant treatment with mitotane, for its potential benefit in decreasing tumour bulk.

Final diagnosis

Cushing's disease.

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Acute myeloid leukaemia with tell-tale computed tomography scans

Q1: What do the computed tomograms show?

Computed tomography of the thorax (fig 1, see p 733) showed multiple nodules of varying sizes in the lung parenchyma. There is also a mass measuring 3 × 4 cm at the apical segment of the right lower lobe with adjacent consolidation. These findings were not seen in the chest

Box 1: Stratification of episodes and definitions of invasive aspergillosis¹

(1) Proven

- Positive tissue biopsy with typical filamentous fungi + positive culture for aspergillus species from the same site, or
- Positive culture for aspergillus from an otherwise sterile body fluid (not including bronchoalveolar lavage fluid).

(2) Probable

- Positive bronchoalveolar lavage test for aspergillus (direct examination and/or culture) + suggestive thoracic computed tomography (halo or air crescent signs)*.

In patients without positive culture or cytology:

- Computed tomography evidence of invasive infection of the nasal passage, sinuses, or central nervous system in high risk patients.
- Typical clinical signs and symptoms (for example, pleuritic chest pain) in the presence of characteristic features on computed tomography of the thorax.

(3) Possible

In persistently neutropenic patients with negative cultures for bacteria and without evidence of viral illness (with or without pulmonary infiltrates):

- Fever not responding to five days of adequate broad spectrum antimicrobials.
- Relapsing after initial defervescence.

*Highly probable of invasive pulmonary aspergillosis

radiograph that was performed one day earlier. However repeat radiography that was done one week after the computed tomography of the thorax showed a cavitating mass at the apex of the right lower lobe and two nodules measuring 1-2 cm at the right middle and left lingular lobes. Computed tomography of the abdomen (fig 2, see p 733) revealed numerous small non-enhancing lesions in the spleen.

Q2: What is the most likely cause of the persistent fever in this patient and how would you confirm the diagnosis?

The clinical and radiological findings were strongly suggestive of deep seated fungal infection. Although pulmonary tuberculosis can present as cavitating lesions, nodules are an unusual presentation. Tuberculous granuloma of the spleen and liver may produce similar radiological appearances but it is less likely with persistent fever that is not responsive to broad spectrum antibacterial agents in a profoundly neutropenic patient. Opportunistic infection of the liver and spleen due to *Pneumocystis carinii*, *Candida albicans*, and aspergillus can produce a similar radiological appearance. *P. carinii* infection is less likely as the patient was given co-trimoxazole prophylaxis and the lung changes are not suggestive of this condition. In the present case, *Aspergillus fumigatus* was identified in the splenic aspirate. Aspergillus antigen was also detected in the

Learning points

- Persistent fever in a neutropenic host suggests an occult fungal infection.
- *Aspergillus pneumonia* is the most common fungal pulmonary infection in immunosuppressed patients.
- Invasive aspergillosis can be suggested by the clinical picture in an appropriate setting.
- In leukaemic patients who have been neutropenic for more than seven days and remain febrile despite broad spectrum antibacterial therapy, any nodular infiltrate is highly suggestive of invasive aspergillosis.
- Blood culture and plain chest radiograph are insensitive means of making a diagnosis of invasive aspergillosis.
- In neutropenic patients, thoracic computed tomography is a major tool for the diagnosis of invasive pulmonary aspergillosis.
- The successful management of invasive aspergillosis depends on earlier initiation of antifungal therapy (within 96 hours of onset).
- Computed tomograms allow earlier diagnosis of invasive aspergillosis and thereby could improve the prognosis dramatically among febrile neutropenic patients.

serum samples using latex particle agglutination test. Stratification of definitions of invasive aspergillosis is summarised in box 1.¹

Q3: What is the treatment for this condition?

Amphotericin B is the standard treatment for invasive aspergillosis but has limited success.² There are numerous regimens for the administration of this drug but in neutropenic patients, it is important to give the full dose from the outset. High dose must be used (at least 1.0 mg/kg/day of conventional amphotericin B). The optimum duration of treatment has not been established, but amphotericin B should be continued at least until the neutrophil count is $>0.5 \times 10^9/l$. Thereafter treatment should be continued until symptoms resolve and radiological (on radiography and computed tomography) abnormalities disappear. Consolidation therapy with itraconazole is often appropriate, often for long periods. Relapse occurs even after months of treatment if patients remain immunocompromised. If renal dysfunction is likely to be a major problem or the fungal infection progresses despite treatment with an adequate dose of conventional amphotericin B, then one of the lipid associated preparations of amphotericin B or itraconazole is appropriate.³ Our patient received amphotericin B, resulting in resolution of the symptoms two weeks later. The lesions in the lung and liver cleared while residual nodules were noted in the spleen after a total of 1.3 g of conventional amphotericin B. The patient declined further inpatient treatment and was discharged with itraconazole 400

mg/day and currently awaiting allogeneic stem cell transplantation.

Discussion

Invasive aspergillosis is an increasingly recognised condition in immunocompromised hosts. Patients with prolonged and severe neutropenia after chemotherapy for haemato-oncological disorders and steroid treated allogeneic bone marrow transplant recipients are particularly at risk. Its prognosis remains poor in leukaemic patients, despite amphotericin B treatment. The crude mortality rate of invasive aspergillosis approaches 100% and results at least partly from difficulties in obtaining a reliable diagnosis at an early stage of the disease.⁴ Improvement of prognosis needs early recognition of invasive aspergillosis and effective antifungal treatment. Confirmation of such infection by clinical and laboratory examination can be extremely difficult. Definite proof of invasive aspergillosis implies the demonstration of hyphal invasion in tissue specimens with a positive culture for species from the same specimen.⁵ Cultures may require days or weeks to grow, while the histopathological examination of tissue specimens obtained by invasive procedures is often precluded by profound cytopenia. Consequently, in daily clinical practice, physicians combine clinical, radiological, and/or microbiological criteria to define the level of probability of invasive aspergillosis. However, these criteria either lack sensitivity and specificity or depend largely on a high fungal burden.⁶ The detection of circulating fungal antigens had been advocated as a promising indirect diagnostic method to overcome these drawbacks. Serial determination of serum galactomannan (a major *Aspergillus* exoantigen released during invasive disease) at a lower threshold should allow earlier diagnosis of invasive aspergillosis.^{1,7} Caillot *et al* analysed the course of invasive pulmonary aspergillosis in 37 patients with haematological malignancy and demonstrated that systematic computed tomography allows earlier diagnosis of invasive pulmonary aspergillosis and thereby improves overall survival among these patients.⁸ The computed tomography features that were identified as indicators of invasive pulmonary aspergillosis included angiotropic nodular parenchymal lesions (>0.5 cm), the halo sign, air crescent sign, and wedge shaped, pleural based infiltrates. The computed tomography halo sign is described as a mass-like infiltrate with a surrounding halo of ground glass attenuation and it occurs early in the course of invasive pulmonary aspergillosis. The air crescent sign is a cavitating pulmonary lesion. We have demonstrated in this case that computed tomograms are useful for making an early diagnosis of invasive aspergillosis and it had significantly influenced the outcome of the treatment. Performance of high resolution pulmonary computed tomography as early as possible is warranted in neutropenic patients presenting with non-resolving fever even if the chest radiograph is normal.

Final diagnosis

Invasive aspergillosis in the lungs, spleen, and liver.

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- 8 Caillot D, Casanovas O, Bernard A, *et al.* Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997;15:139–47.

Failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient

Q1: What test may be used to confirm a diagnosis of type 1 (as opposed to type 2) diabetes mellitus?

The intravenous glucagon stimulated C-terminal peptide test is considered the gold standard in confirming that a patient has type 1

(insulin dependent) diabetes mellitus. The insulin precursor proinsulin is released from the pancreas and then broken down into insulin and C-peptide. One milligram of glucagon is given intravenously, the subsequent rise in blood glucose stimulates the pancreas to release proinsulin, and thus pancreatic reserve can be measured by assaying C-peptide levels. In this patient type 1 diabetes was confirmed by a maximal response of 127 pmol/l at five minutes (adequate insulin reserve: >500 pmol/l, borderline insulin reserve: 200–500 pmol/l).

Q2: Given this patient's history before this admission; what other condition are the urea and electrolytes results in box 1 (see p 734) consistent with and how is the diagnosis confirmed?

Addison's disease is a deficiency in both glucocorticoids and mineralcorticoids. Glucocorticoid deficiency may lead to hypoglycaemia, while mineralcorticoid deficiency leads to hypoaldosteronism, thus producing a biochemical picture similar to aldosterone antagonising diuretics: hyponatraemia, hyperkalaemia, and uraemia.

Adrenal sufficiency may be tested with either the insulin tolerance test or the short Synacthen (tetracosactrin) test (standard or low dose). The insulin tolerance test is unpleasant for the patient, potentially hazardous in patients with a history of seizures or coronary heart disease, and requires medical supervision—making it relatively expensive. The short Synacthen test is a safe and easy test to confirm the diagnosis of Addison's disease. An intramuscular injection of 250 µg of synthetic adrenocorticotrophic hormone (ACTH) is given and serum cortisol concentration is measured at time 0 and 30 min. In our patient Addison's disease was diagnosed by a cortisol at 0 min of 15 mmol/l and at 30 min of 16 mmol/l (cortisol at 30 min >550 excludes the diagnosis). She also had a raised ACTH of 239.6 pmol/l (reference range 2.0–11.3) and was strongly positive for adrenal cortex antibodies. Her recovery appeared to be accelerated by glucocorticoid replacement therapy.

Q3: What is the explanation for this profoundly unwell patient with type 1 diabetes and hyperglycaemia not to have developed diabetic ketoacidosis?

While this patient was profoundly unwell with newly presenting type 1 diabetes mellitus and hyperglycaemia, we believe that she failed to develop diabetic ketoacidosis because her insulinopenia was offset by her hypoadrenalism.

Discussion

Multiple pathologies should always be considered, especially in endocrine disorders. Addison's disease (secondary to adrenal antibodies) and type 1 diabetes are both organ specific autoimmune diseases and are associated. Approximately 10%–18% of patients with Addison's disease have type 1 diabetes, but Addison's disease is rare in type 1 diabetes.^{1–3} A number of interactions have been reported

Figure 1 The metabolism of triglyceride to ketone bodies. Note the directly antagonising roles of insulin and cortisol (DKA = diabetic ketoacidosis; NEFA = non-esterified fatty acid).

between these two diseases, with perhaps the best described being reduced insulin requirements and severe unpredictable hypoglycaemia in established type 1 diabetic patients, who develop Addison's disease.^{4 5}

Insulin and catabolic hormones (catecholamines and cortisol) have antagonising effects on fat metabolism (see fig 1). In adipose tissue, insulin inhibits hormone sensitive lipase leading to reduced metabolism of triglyceride to non-esterified fatty acid (NEFA) and reduced ketone body formation, whereas catecholamines and cortisol stimulate the lipase leading to increased metabolism of triglyceride to NEFA with subsequent ketone body formation. In health, activity of this lipid pathway depends on a dynamic interaction between insulin suppressing the pathway and catecholamines and cortisol stimulating it. In newly diagnosed type 1 diabetes, profound hypoinulinaemia combined with relative catabolic hormone excess favours NEFA production and subsequent ketogenesis which leads to presentation as diabetic ketoacidosis in 10% of newly diagnosed patients. In this woman, the lipolytic and ketogenic effects of insulinopenia were offset by glucocorticoid deficiency and the normal drive towards ketogenesis was much reduced. The absence of diabetic ketoacidosis in this ill woman with newly diagnosed type 1 diabetes illustrates the importance of glucocorticoid sufficiency and insulinopenia in the development of diabetic ketoacidosis.

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Diabetes and rapidly advancing pneumonia

Q1: What are the possible diagnoses and how would you investigate this patient?

The diagnosis is diabetic ketoacidosis in type 1 diabetes mellitus, which was precipitated by fulminant chest infection and omission of insulin. He survived four days without insulin so there was possibly some endogenous insulin production. At presentation, he had metabolic acidosis with high anion gap (pH 7.25, bicarbonate 4 mmol/l, anion gap 37 mmol/l). In addition he had respiratory alkalosis (arterial carbon dioxide tension 1.2 kPa) caused by compensatory mechanisms and lung infection. He recovered from the diabetic ketoacidosis but pulmonary infection worsened leading to ARDS (arterial oxygen pressure/fractional inspiratory oxygen ratio <150 mm Hg). Preterminally, he had a stress induced upper gastrointestinal bleed.

Bacterial infection of the respiratory tract is a common precipitant of diabetic ketoacidosis in diabetes. In addition to the usual organisms

(*Streptococcus pneumoniae*, *Haemophilus influenzae*), *Staphylococcus aureus*, *Klebsiella* species, and *Pseudomonas* species (*Pseudomonas pseudomallei*) cause pneumonia more often in diabetics.¹ Curiously, pneumococcal pneumonia is not common in diabetics.² Acute tuberculous pneumonia in such a setting is another differential diagnosis. However, diabetic subjects more often have cavitary disease and a non-segmental distribution.³ Other important organisms, which usually result in fulminant infection in those with diabetic ketoacidosis, are fungi of the family mucoraceae.¹ Mucormycosis has a special predilection for diabetics especially during diabetic ketoacidosis. Lee *et al* reviewed 87 cases of pulmonary mucormycosis over the last 30 years, and observed that diabetes mellitus was the most common underlying predisposition (56%) and, of these patients, 20% had diabetic ketoacidosis at presentation.⁴ Failure to isolate the organism and lack of response to appropriate antibiotics were clues to the suspicion of fungal infection in this patient. Repeated sputum examination for hyphae, pleural fluid culture, bronchoalveolar lavage, and transbronchial lung biopsy should be done for establishing aetiological diagnosis.⁴

Q2: How would you manage the condition?

Treatment of pulmonary mucormycosis consists of prompt control of blood glucose, ketoacidosis, and administration of amphotericin B in doses of 0.5 to 1 mg/kg/day with a total dose of at least 2.5 to 3 g and aggressive surgical resection.^{4 5}

Discussion

Pulmonary mucormycosis is a life threatening complication of diabetic ketoacidosis. Mucor belongs to the class zygomycetes, a ubiquitous fungus whose commonest route of entry is the respiratory tract.¹ Other predisposing conditions for this fungus include neutropenia, lymphoma or leukaemia, and patients on high doses of corticosteroids and desferrioxamine therapy.⁴

Pulmonary mucormycosis presents as a rapidly progressive pneumonia having symptoms similar to a bacterial infection such as cough, dyspnoea, or pleuritic chest pain and often with haemoptysis. The radiological picture is not specific and includes lobar or multilobar consolidation, solitary or multiple infiltrates, mediastinal widening, bronchopneumonia, cavitation, and fungal ball and occasionally pleural effusion.¹ Lesions due to mucorales may expand very rapidly particularly in the immunocompromised host as in this patient.⁴

The outstanding characteristics of mucormycosis are: (i) ferrophilia and (ii) angioinvasion. During diabetic ketoacidosis, free iron is relatively increased due to impaired binding of iron with transferrin, thereby favouring growth of mucor.¹ Because of its angioinvasive property, it produces tissue infarction and a characteristic blackish inflammatory exudate, thereby producing obstruction in major airways and haemoptysis.¹

Figure 1 Microphotograph of the lung tissue showing broad aseptate fungal hyphae (arrows) with early right angled branching in a necrotic tissue background (haematoxylin and eosin $\times 550$).

The only method for diagnosing pulmonary mucormycosis, is histological demonstration of the fungus in lung biopsy material.¹ Cultures of sputum and biopsy material for mucor frequently are unhelpful with a high false negative rate.¹ There are no serological methods for measuring either antibody to the organism or antigen. Frequently, the organism is identified only at necropsy. In this patient postmortem lung biopsy showed right angled branching hyphae consistent with mucormycosis (fig 1).

Treatment of pulmonary mucormycosis rests on good glycaemic control, management of ketoacidosis, and intravenous amphotericin B. Correction of ketoacidosis is vital for successful outcome.⁶ It has been shown that serum of diabetic patients with ketoacidosis is conducive to the growth of rhizopus in contrast to the normal human serum.⁷ Amphotericin B is relatively less effective because of: (i) impaired drug delivery to the site of infection due to vascular occlusion and (ii) higher rates of amphotericin B resistance.⁵ Therefore, aggressive surgical resection of the diseased lobe and amphotericin B therapy is most useful, when the infection is localised. Survival of patients with mucormycosis has improved with this combined approach, as mortality in

surgically treated was 11% compared with 68% in those treated medically alone.⁵

Final diagnosis

Type 1 diabetes mellitus, diabetic ketoacidosis, and pulmonary mucormycosis with acute respiratory distress syndrome.

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- 5 Tedder M, Spratt JA, Anstadt MP, et al. Pulmonary mucormycosis: results of medical and surgical therapy. *Ann Thorac Surg* 1994;57:1044–50.
- 6 Lehrer RI, Howard DH, Sypherd PS, et al. Mucormycosis. *Ann Intern Med* 1980;93:93–108.
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Cutaneous gangrene in a renal dialysis patient

Q1: What is the diagnosis?

The diagnosis is calciphylaxis, also known as the uraemic gangrene syndrome, vascular calcification cutaneous necrosis syndrome, azotaemic calcific arteriolopathy, or calcifying panniculitis.

Q2: What are the risk factors for this condition?

Significant risk factors include white race, female gender, morbid obesity, recent severe weight loss, prolonged dialysis, insulin dependent diabetes mellitus, warfarin therapy, the use of calcium carbonate or corticosteroids, hypoalbuminaemia, iron overload, polycythaemia, peripheral vascular disease, Crohn's disease, AIDS, and hypotension. In a subset of patients, a hypercoagulable state may underlie the development of the disorder. A mathematical formula ($2 \times [\text{CaPO}_4 \text{ in mmol/l} - 5] \times \text{alkaline phosphatase in IU/l} \times \text{PTH value} \div \text{upper limit of normal PTH reference range}$) was empirically developed to aid in the identification of high risk patients (those with results greater than 1000).¹

Q3: Can this condition occur in patients without renal disease?

Although calciphylaxis occurs predominantly in patients with end stage renal disease, or those who have recently received a renal transplant, this entity can infrequently be seen with any cause of hypercalcaemia including primary hyperparathyroidism, vitamin D intoxication, the milk alkali syndrome, idiopathic neonatal hypercalcaemia, metastatic bone disease, various haematological malignancies, as well as end stage liver disease and after excess parenteral phosphate infusions during the treatment of sepsis.

Learning points

- In a patient with diabetic ketoacidosis and rapidly advancing pneumonia, other than bacterial infection, mucormycosis is an important consideration.
- Histological demonstration of the fungus either on bronchoalveolar lavage or lung biopsy material is obligatory to diagnosis.
- Effective treatment of diabetic ketoacidosis combined with amphotericin B and surgical resection of the lesion yields better results.

Discussion

Calciophylaxis, first described by Hans Selye in 1962, is a rare, potentially life and limb threatening condition of progressive tissue necrosis related to microvascular calcification.² In severe cases, there may be associated metastatic calcification of the subcutaneous fat, lungs, kidneys, stomach, pancreas, and heart. The pathogenesis of calciophylaxis is poorly understood.³ It evolves rapidly from a multitude of predisposing and/or sensitising events that are commonly present in the uraemic milieu. Some factor(s) other than renal failure, raised PTH, calcium and/or phosphate appears to be involved in its pathogenesis, since these parameters do not always accurately predict its development or severity.⁴ Recent observations suggest that infection by certain novel microorganisms (nanobacteria) may provide a nidus for pathological calcification.⁵ For reasons that are still unclear, factors in addition to calcific arteriolopathy must trigger calciophylaxis, because calcification of arteries (Monckeberg's sclerosis) commonly occurring in uraemic patients alone rarely results in tissue ischaemia. Possible mechanisms to account for reduced blood flow include complete obliteration of vessels by calcium salts, intimal fibrosis and proliferation, thrombosis, acquired protein C or S deficiency, a direct vasoconstrictive effect of calcium, and autonomic dysfunction. Precipitating events may include local skin trauma, injections, decreased systemic and local blood flow, ultraviolet light, albumin infusions, corticosteroids, oral phosphates, radio-opaque contrast media, and blood transfusion products. Calciophylaxis after renal transplantation may be due to immunosuppression.

Calciophylaxis manifests with livedo reticularis and/or painful violaceous skin plaques that typically progress to deep non-healing ulcers with underlying tissue necrosis and eschars of the trunk or limbs. Gangrene of digits may require amputation. Blood flow is usually demonstrable distal or deep to the necrosis. Involvement of the penis may also occur. Digital (peripheral) ischaemia has a better prognosis than proximal (central) necrosis. Infrequent complications include ischaemic myopathy, pancreatitis, and gastrointestinal haemorrhage. Superinfection is the primary cause of the high mortality (up to 60%–80%) associated with this condition. Clinically, calciophylaxis may simulate atherosclerotic peripheral vascular disease, atheroembolisation, septic embolism, warfarin sodium necrosis, connective tissue diseases and other vasculitides, necrotising fasciitis, deep fungal infections, deep venous thrombosis, disseminated intravascular coagulation, cellulitis, dermatomyositis, pyoderma gangrenosum, necrobiosis lipoidica, autoimmune bullous dermatoses, necrotising araneism, the antiphospholipid syndrome, protein

C and S deficiencies, cryofibrinogenaemia, oxalosis, and the glucagonoma syndrome. There is no diagnostic laboratory test for calciophylaxis. Calciophylaxis is not associated with immunoglobulin deposition or autoimmune antibodies. While high plasma levels of PTH, phosphate, and calcium are consistent with the diagnosis, all of these abnormalities are not always present. Skin biopsies incorporating subcutaneous tissue offer an important means of establishing the diagnosis. Large biopsies are desirable because histological findings are segmental and may be missed. The diagnosis can sometimes be suggested radiologically by vessel and/or soft tissue calcification.

Given the high mortality and morbidity associated with calciophylaxis early recognition and treatment of this entity are essential. Treatment is primarily supportive with emphasis on eliminating the sensitiser and challenger. This includes rigorous control of phosphate and calcium balance, avoiding challenging agents, including the possible withdrawal of immunosuppression in the renal transplant patient. Wound care, debridement of necrotic tissue, and the administration of antibiotics for infected tissue is also imperative. Treatment with low calcium dialysate and phosphate binding antacids is indicated. Parathyroidectomy in patients with evidence of hyperparathyroidism has proved successful. The efficacy of calcium channel blockers and other vasodilators, anticoagulants, and hyperbaric oxygen therapy has not been refined. Despite therapy, the prognosis remains poor.

In this case, the patient recovered after withdrawal of warfarin sodium, meticulous wound care, administration of broad spectrum antibiotics, repeated surgical debridement of necrotic tissue, and haemodialysis three times per week.

Final diagnosis

Calciophylaxis occurring in the setting of chronic renal failure.

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- 3 Janigan DT, Hirsch DJ, Klassen GA, et al. Calcified subcutaneous arterioles with infarcts of the subcutis and skin ("calciophylaxis") in chronic renal failure. *Am J Kidney Dis* 2000;35:588–97.
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- 5 Kajander EO, Cifcioglu N. Nanobacteria: an alternative mechanism for pathogenic intra- and extracellular calcification and stone formation. *Proc Natl Acad Sci U S A* 1998;95:8274–9.