Short reports

Spontaneous necrosis of parathyroid adenoma: biochemical and imaging follow-up for two years

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Summary

We report a patient with a biochemically and radiologically confirmed parathyroid adenoma, which underwent spontaneous resolution by necrosis. The patient was followed-up over the subsequent two years during which time the tumour and hypercalcaemia recurred. Sequential radiological and biochemical changes at the time of diagnosis, spontaneous necrosis and recurrence are documented fully.

Keywords: hyperparathyroidism; hypocalcaemia; apoplexy

Primary hyperparathyroidism is one of the commonest endocrine disorders. However, spontaneous resolution by necrosis of a parathyroid adenoma is rare. Although there have been approximately 10 reported cases since the condition was first described in 1946,¹ in most cases the infarcted gland was removed soon after diagnosis. Therefore, the natural history, biochemical and hormonal changes following spontaneous infarction are not well known. We report a patient who had spontaneous infarction of her parathyroid adenoma, while awaiting surgery, with detailed documentation of the above-mentioned features.

Case report

A 78-year-old woman was referred to our clinic for further management of Type 2 diabetes. She gave a history of renal stone, with right nephrectomy, 8 years before. She was put on oral hypoglycaemic therapy. She was found incidentally to have hypercalcaemia with a calcium concentration of 3.43 mmol/l (normal range 2.20–2.62 mmol/l) together with a reduced phosphate concentration of 0.55 mmol/l (0.82–1.40 mmol/l). Alkaline phosphatase was normal at 85 IU/l (45–145 IU/l). There was renal impairment with a plasma creatinine concentration of 160 µmol/l (44–107 µmol/l), but she had stable glycaemic control as indicated by a HbA_{1c} concentration of 7.4%. Physical examination revealed mild peripheral neuropathy and the nephrectomy scar, but no obvious neck mass. Further investigations confirmed primary hyperparathyroidism. Her parathyroid hormone (PTH) was 44 pmol/l (1.16–5.67 pmol/l, intact PTH assay; coefficient of variation 7%) with concomitant plasma calcium of 3.40 mmol/l and ionized calcium of 1.61 mmol/l (1.13–1.32 mmol/l).

Ultrasound of the abdomen confirmed the previous right nephrectomy but showed no other abnormality. Her hypercalcaemia improved to approximately 2.8 mmol/l with adequate hydration, a low calcium diet and oral phosphate solution. She was referred for parathyroidectomy and was on the waiting list for surgery. During subsequent follow-up, her alkaline phosphatase gradually increased to 1465 IU/l, indicating development of parathyroid bone disease. Her glycaemic control was stable on oral hypoglycaemic therapy and there was no further deterioration of diabetic complications.

She was put on the waiting list for surgery, which was very long in our hospital. Two years later, she underwent pre-operative imaging to localise the parathyroid adenoma. Computed tomography (CT) showed a 2.5 × 1.5 cm well-defined parathyroid adenoma posterior to the upper pole of the left lobe of the thyroid. The adenoma was of homogenous soft tissue attenuation and revealed diffuse enhancement after contrast (figure 1). However, 4 months later, before surgery could be performed, she was admitted to our hospital having sustained a fracture of the right neck of femur after a fall. On admission, she was found to be hypocalcaemic (plasma calcium concentration 1.37 mmol/l (albumin adjusted)). Plasma phosphate was 0.89 mmol/l, magnesium was 0.55 mmol/l (0.67–1.01 mmol/l) and alkaline phosphatase was 1730 IU/l. Trousseau's sign was positive and the electrocardiogram showed a prolonged QT interval. She was treated with intravenous calcium gluconate followed by oral calcium supplementation and calcitriol. Magnesium was replaced with oral magnesium chloride. Two days later, the PTH concentration was 32.5 pmol/l and the calcium concentration 1.84 mmol/l. Serum 25-OH vitamin D3 concentration was 34 nmol/l (10–50 nmol/l). A CT scan of the neck showed no change in the size of the parathyroid adenoma but now there was evidence of central necrosis with a low attenuation centre which failed to enhance after contrast (figure 2). Plasma calcium was maintained within the normal range with calcitriol and oral calcium, and a right hip replacement was performed uneventfully.

On subsequent follow-up, her calcium level was maintained within the normal range and calcium and calcitriol doses were gradually reduced over a period of 8 months. The parathyroid hormone concentration dropped gradually to 5.4 pmol/l one month after admission and then showed a gradual rise during

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Figure 1 Contrast CT scan of the neck showing a parathyroid adenoma posterior to the left lobe of the thyroid at diagnosis

Figure 2 Contrast CT scan of the neck at the time of spontaneous necrosis

Figure 3 Contrast CT scan of the neck at the time of involution

further follow-up. A further CT scan of the neck 3 months later showed involution of the parathyroid adenoma which had almost disappeared, leaving a residual 5 mm soft tissue mass (figure 3). Her calcium concentration rose beyond the normal range one month after calcium and calcitriol were stopped. Recurrence of primary hyperparathyroidism was confirmed with concomitant measurements of PTH (24.2 pmol/l) and plasma calcium (2.68 mmol/l). Details of the biochemical changes and clinical events are summarised in figure 4.

Discussion

Parathyroid apoplexy, as described by Eric Nylen to signify parathyroid spontaneous

Figure 4 Biochemical profile over 2 years

necrosis or haemorrhage, is a rare complication of primary hyperparathyroidism.² So far, only around 10 cases have been reported in the literature. Its presentation can be quite variable, including pressure symptoms due to haemorrhage,³⁻⁶ neck pain,⁷⁻⁹ hypercalcaemia due to acute release of stored PTH,¹⁰ hypocalcaemia due to autopharyroidectomy,^{1,2,8,11} or normalisation of plasma calcium.^{9,12,13} The biochemical changes can be drastic if there is significant necrosis, and death has been reported due to severe hypercalcaemia.¹⁰ Most reported cases were treated by parathyroidectomy after the event and therefore the long-term consequences and clinical course remain unclear.

As our patient was already 77 years old at the time of parathyroid apoplexy, and was reluctant to undergo any further surgical intervention, it provided us with an opportunity to examine the subsequent course of this condition. She was relatively asymptomatic, despite severe hypocalcaemia. We did not observe a phase of transient worsening of hypercalcaemia. This may be due to delayed presentation, but agrees with some case reports of patients with normal or low calcium concentration at the time of presentation.^{1,2,8,11} Of those cases in whom PTH concentration had been measured at the time of presentation, most showed a decrease in PTH soon after the episode of necrosis.^{2,9} However, our patient had a persistently raised PTH level at presentation and subsequently showed a further rise to 49.4 pmol/l. Although the PTH level remained above the normal range, it stayed well below the initial level. We postulate that the abrupt drop in PTH due to parathyroid necrosis resulted in hypocalcaemia and hungry bone syndrome. The situation closely simulates that of surgical parathyroidectomy. This may have further triggered a secondary or compensatory response. This is supported by the observation that the PTH concentration gradually returned to near normal as the hypocalcaemia resolved with treatment. The other possibility was osteomalacia due to vitamin D deficiency. There has been a reported case of osteomalacia associated with primary hyperparathyroidism¹⁴; however, the normal vitamin D3 level excluded this diagnosis.

Although the necrotic parathyroid adenoma was not excised and hence there was no histo-

logical confirmation, the characteristic CT and clinical features appear confirmatory. In addition, the CT scan several months later showed continuous involution of the initial necrotic adenoma. This further confirmed the initial diagnosis of parathyroid adenoma necrosis. There have been reports of primary hyperparathyroidism entering remission after parathyroid gland necrosis.^{2 9 13 15} However, in most reported cases, the necrotic parathyroid adenoma were excised.^{9 13 15} A recent report by Nylen *et al* showed that the primary hyperparathyroidism could enter remission even without surgical excision.² By contrast, our patient exhibited recurrence of the disease 9 months after the acute event and the repeated CT 3 months after the event still showed a 5-mm soft tissue mass suggesting a remnant adenoma. Thus, such patients need to be followed closely as recurrence with a need for treatment is possible.

The cause of necrosis in our patient remains uncertain. There was no evidence to suggest previous hypotension, angiography¹⁶ or thyroid surgery,⁵ as suggested by previous reports, although hypotension related to fracture is still a possible cause. However, one common feature shared by all reported cases is that the adenomas exceed 1 cm in diameter, most

Learning points

- primary hyperparathyroid patients with parathyroid adenoma greater than 1 cm diameter need early surgical excision in order to avoid potential crisis of apoplexy
- surgical removal of adenoma is still indicated after apoplexy due to the possibility of recurrence

exceeding 2 cm. Relatively large size may increase the risk of ischaemia and necrosis, and this may be an additional indication for early surgical intervention in subjects with parathyroid adenomas exceeding 1 cm in size.

Conclusion

In summary, we present a case of parathyroid apoplexy complicated initially by hypocalcaemia, but with later recurrence of hypercalcaemia. The later recurrence of disease weighs in favour of surgical intervention in these patients. Review of the literature indicates that this complication occurs primarily in subjects with large parathyroid adenomas (>1 cm diameter).

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Acute myoedema: an unusual presenting manifestation of hypothyroid myopathy

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Summary

We describe a patient with primary hypothyroidism due to autoimmune thyroiditis, presenting with acute myoedema and spontaneous rhabdomyolysis. During his hospital stay, he developed altered sensorium due to hypo-osmolal hyponatraemia and later developed bilateral foot drop that responded to appropriate treatment.

Keywords: hypothyroidism; myoedema; rhabdomyolysis

Muscle weakness, aches and cramps, stiffness and delayed tendon jerk relaxation are usual features of hypothyroid myopathy (30–80%), while muscle hypertrophy, myoedema and wasting are occasionally seen.^{1,2} They evolve gradually over a long period of time. We report a patient with primary hypothyroidism, who presented with acute generalised myoedema, stiffness and spontaneous rhabdomyolysis.

Case report

A 41-year-old man presented with generalised body swelling and increasing stiffness for 2 weeks. He had experienced severe aches and pains, lower limb weakness and oliguria, for 3 days prior to his admission. He denied any form of strenuous muscle exercise. He had been a diagnosed hypertensive for 8 years with poor drug compliance. He was diagnosed to have autoimmune thyroiditis with primary hypothyroidism 6 years ago, requiring thyroxine for 6 months only. He remained euthyroid (serum thyroid-stimulating hormone (TSH) 2.5 μ IU/ml) thereafter until about a month prior to admission.

On examination, he was pale, afebrile but tachypnoeic, had peri-orbital puffiness and no goitre. His pulse was 78 beats/min regular, blood pressure 170/110 mmHg and voice was hoarse. All his limb muscles were swollen, firm, nonpitting, severely stiff and hypertonic but distinctly nontender, characteristically described as myoedema. He had proximal muscle weakness in both shoulder (4/5) and pelvic girdles (3/5) and had pseudomyotonia. Relaxation of deep tendon reflexes was grossly delayed. He had a few coarse crepitations in the left infra-scapular region. Other systemic examinations were normal.

Investigations revealed: haemoglobin 10.7 g/dl, total leucocyte count 10×10^9 /l with 90% polymorphs, serum Na^+ 125 mEq/l, K^+ 3.6 mEq/l, urea 14.2 mmol/l, creatinine 133

μ mol/l, random blood glucose 6 mmol/l, serum aspartate transaminase 19 IU/l, alanine transaminase 77 IU/l, creatine kinase-MM (CK-MM) 80 730 IU/l (normal up to 20 IU/l) and aldolase 35 IU/l (1–7.6 at 37° C) and serum myoglobin > 85 ng/ml. The centrifuged plasma was normal in colour. Arterial blood gas analysis showed PaO_2 83, PaCO_2 30, pH 7.5, HCO_3^- 23.9. His serum T3 was 0.2 ng/ml (0.6–1.2), T4 9 ng/ml (60–130), TSH 58.9 μ IU/ml (0.3–5), cortisol at 08.00 h 500 nmol/l (400–600) and at 16.00 420 nmol/l (200–400). Antimicrosomal antibody titre was abnormally elevated. Electromyogram (EMG) revealed polyphasic action potentials consistent with myopathy.

He received intravenous dextrose-saline, rapidly increasing doses of L-thyroxine from a starting dose of 25 μ g to 150 μ g in one week, cefotaxime and amikacin. On day 3 of admission, he became drowsy and disoriented, when his serum Na^+ was 110 mEq/l, serum osmolality 232 mOsmol/kg and urine osmolality 345 mOsmol/kg, indicating hypo-osmolal hyponatraemia. In addition to intravenous saline, he received oral salt supplementation and intravenous hydrocortisone. His sensorium gradually improved over the following 10–12 h with an increase in serum Na^+ to 124 mEq/l and serum osmolality to 258 mOsmol/kg. Urine spot Na^+ dropped from 61 mEq/l to 30 mEq/l. On day 5, he developed bilateral foot drop with sensory loss in L4–5/S1 dermatomes. Nerve conduction velocity showed impaired conduction through the common peroneal nerve. After 3 months of thyroxine replacement, his muscle rigidity and stiffness were markedly reduced and power in foot dorsiflexors improved to 3/5. At 6 months of follow-up serum CK-MM had decreased to 432 IU/l and serum myoglobin was undetectable.

Discussion

The clinical spectrum of hypothyroid myopathy is varied. Delayed relaxation of tendon jerks and proximal muscle weakness correlate with biochemical severity of hypothyroidism (serum T4 <20 ng/ml).³ Acute myoedema and rhabdomyolysis are, however, distinctly rare.^{2,4} Raised serum CK-MM and myoglobin, typical myopathic EMG, low T4 and high TSH, and their reversibility with L-thyroxine treatment supported the diagnosis of hypothyroid myopathy with rhabdomyolysis.

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Transient hypothyroidism many years earlier followed by complete clinical and biochemical recovery suggested autoimmune thyroiditis, which eventually led to atrophy of the thyroid and hypothyroidism. The muscle involvement in hypothyroidism is caused by changes in muscle fibres from fast twitching type II to slow twitching type I fibres, deposition of glycosaminoglycans, poor contractility of actin-myosin units, low myosin ATPase activity and low ATP turnover in skeletal muscle.⁵

Hypo-osmolal hyponatraemia is occasionally encountered in primary hypothyroidism. It is accompanied by a decrease in glomerular filtration rate, inappropriately elevated circulating antidiuretic hormone, because of its slow catabolism, and concomitant cortisol deficiency.⁶ Bilateral symmetrical foot drop in

Learning points

- myoedema, muscle hypertrophy, and wasting are uncommon features of hypothyroid myopathy
- CK-MM can be used as a marker of hypothyroid myopathy
- hypothyroid myopathy responds to L-thyroxine therapy
- hypo-osmolal hyponatraemia can be an important cause of altered sensorium in long-standing untreated hypothyroidism

this patient was possibly caused by peroneal neuropathy due to decubitus pressure or glycosaminoglycans deposition in the perineural sheath.⁷

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Hepatocellular adenomatosis associated with hereditary haemochromatosis

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Summary

A young healthy man presented with abdominal pain following an accidental fall. Imaging studies and laparoscopy revealed multiple yellowish well-defined hepatic lesions. Liver biopsies showed hepatic adenomas and iron overload. Laboratory investigation confirmed a diagnosis of hereditary haemochromatosis. To our knowledge this represents the first report of an association of hepatic adenomatosis and primary haemochromatosis.

Keywords: liver, adenomatosis, haemochromatosis

Hepatocellular adenomatosis is a rare disease characterised by the presence of more than four adenomas. It represents an entity which is distinct from hepatocellular adenoma and its pathogenesis continues to be unknown.^{1,2} Isolated cases of hepatic adenoma and secondary iron overload have been described.^{3,4} Hereditary haemochromatosis is known to be complicated by hepatic cirrhosis and carcinoma but not adenomas.

Case report

A 26-year-old man presented to the emergency room 7 years ago with abdominal pain following an accidental fall. On examination, he was found to have tenderness throughout the right upper quadrant and a palpable lower liver edge. A presumptive diagnosis of liver injury was made and the patient was admitted for observation. A computed tomography (CT) scan at the time demonstrated multiple intra-hepatic lesions of variable sizes ranging from less than 1 cm to 5 cm, with no suggestion of intra-abdominal haemorrhage or injury (figure 1). The differential diagnosis based on the CT scan included multiple haemangiomas and the possibility of metastatic disease. In view of the liver function tests, carcinoembryonic antigen and alpha-feto protein markers were assayed and were within normal range. A liver biopsy was performed and revealed hepatic adenoma with parenchymal iron overload.

The patient's condition stabilised and he was discharged to annual follow-up by clinical and radiological examination. He presented again in 1995 with abdominal discomfort. Labora-

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Figure 1 Enhanced CT scan taken at the level of the splenic artery shows multiple low attenuation lesions. The largest lesion anteriorly measures 5.0 cm and shows inhomogeneity

tory tests showed the following results: haemoglobin 151 g/l; haematocrit 0.424; red blood cell count $4.72 \times 10^{12}/l$; white blood cell $8.8 \times 10^9/l$; bilirubin 6 mmol/l; aspartate transaminase 30 IU/l (normal range 0–18 IU/l); alanine transaminase 26 IU/l (0–22 IU/l); serum iron 36 mmol/l (13–33 mmol/l); total iron-binding capacity 81 mmol (41–63 mmol); saturation 47% (25–56%); ferritin 437 $\mu g/l$ (24–250 $\mu g/l$). There was no history of transfusions, intramuscular injection of iron, haemolysis, chronic illness or alcoholism. Laparoscopy showed multiple well-defined hepatic lesions. Biopsies were taken from three lesions and hepatic parenchyma. HLA typing was performed and revealed HLA Type A3 B7. Blood work performed on family members showed a sibling with the same HLA type, high serum iron, ferritin and saturation index. However, ultrasound of the parents and four siblings revealed no hepatic lesions.

Figure 2 (A) Hepatic adenoma with fatty changes and evident vascularity; (B) adjacent parenchyma shows iron overload

Both the initial and the most current liver biopsy samples showed similar changes. There were lesions clearly distinguishable from the adjacent liver parenchyma. They were composed of three or more cell thick cords of benign appearing hepatocytes with uniform nuclei and pale, vacuolar cytoplasm due to marked fatty changes (figure 2A). Portal tracts were absent, but several medium sized vessels were present within the lesions.

The adjacent normal appearing parenchyma revealed massive deposition of haemosiderin pigments in hepatocytes (grade 3 & 4 by the modified Scheuer histologic grading method for iron),⁵ and bile duct cells with mild portal fibrosis and no evidence of cirrhosis (figure 2B). The adenomas were completely devoid of haemosiderin pigments. Hepatic iron assayed on paraffin-fixed tissue was 115.7 $\mu mol/l$ and hepatic iron index was 4.45.

Discussion

Hepatocellular adenomatosis is a very uncommon disease, is characterised by the presence of numerous adenomas (more than four) within an otherwise normal parenchyma.¹ Since the description of the disease in 1985, 16 cases have been reported in the literature, excluding those present in association with glycogen storage disease, oral contraceptives or androgenic steroids.^{1,2} It is recognised as an entity distinct from hepatocellular adenoma.⁶ Hepatocellular adenomas are usually single or occasionally multiple, arise in women of child-bearing age, with strong relation to prolonged use of oral contraceptive, anabolic/androgenic steroids, non-contraceptive oestrogen, danazol, virilising and feminising ovarian tumours, type I glycogen disease and diabetes mellitus.¹ The prevalence of hepatic adenomatosis is equal in men and women. In men, the tumour has been associated with anabolic corticosteroids.⁷ The patient under discussion was asymptomatic until his accident with the diagnosis becoming apparent after a CT scan and a needle liver biopsy, followed by thorough clinical and biochemical examination.

The pathogenesis of hepatocellular adenomatosis remains unknown. This is the first case report of hepatic adenomatosis with primary haemochromatosis, and it is possible that this may be an incidental finding. However, adenomas have been described with iron overload. Review of the world literature reveals two case reports of single hepatic adenomas described in patients with secondary haemochromatosis, complicating thalassaemia.^{3,4} Genetic haemochromatosis is an autosomal recessive disorder that is associated with HLA-A3, B7 and B14 MHC antigens, and a putative defect on the short arm of chromosome 6.⁸ The precise cytopathological mechanisms by which iron induces neoplastic transformation is unknown, but may be due in part to induction of hepatic damage with resultant hepatocyte regeneration. Iron has been demonstrated to be directly mutagenic, possibly by peroxidative damage to DNA.⁹ The pathogenesis of hepatic adenomatosis in iron overload is not clear. The lack of

Summary points

- hepatic adenomatosis is defined by the presence of multiple adenomas of an uncertain aetiology
- the natural history and treatment of liver adenomatosis are not yet well defined hence clinical and radiological follow-up is mandatory, as the risk of malignant changes is not known
- a conservative surgical approach is advocated for symptomatic large lesions
- this entity is rare but should be considered in the differential of multiple hepatic lesions

iron in these lesions is an indication that these adenomas function independently from the rest of the liver and suggest that a neoplastic process is involved in their formation.

This case presents a dilemma as to future management. There is a potential risk of devel-

oping cirrhosis and hepatocellular carcinoma in a patient with haemochromatosis. Intratumoural bleeding causing abdominal pain and haemoperitoneum has been reported in adenomatosis.¹ Therapeutic manoeuvres include removal of iron, monitoring of liver function tests and radiological follow-up to determine if the lesions change. The patient is young and otherwise healthy and needs to be considered for hepatic transplantation should cirrhosis or malignant transformation occur. However, the outcome of liver transplantation in patients with haemochromatosis is rather poor. Survival of patients with haemochromatosis after transplantation is decreased compared to other recipients, due to cardiac, infectious and malignant complications which account for excess morbidity and mortality in these patients.⁹ A conservative surgical approach with resection of large or symptomatic lesions and observation of smaller lesions has been advocated.¹⁰

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An aggressive intrasinusoidal lymphoma presenting with marked systemic disturbance but normal imaging studies

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Summary

A patient with an aggressive intrasinusoidal non-Hodgkins lymphoma, presenting with marked systemic disturbance but only a mildly raised alkaline phosphatase as a localising sign is described. All imaging studies of the liver were normal and the diagnosis was delayed until a percutaneous liver biopsy was performed. Once diagnosed, the patient responded extremely well to conventional anti-lymphoma chemotherapy.

Keywords: lymphoma; fever of unknown origin

Mildly abnormal liver function tests detected during the investigation of a pyrexia of unknown origin (PUO) are often disregarded in the presence of normal imaging studies of the liver. However, such results are not always epiphenomena. Similarly, the finding of a normal appearing hepatic parenchyma on ultrasound or computed tomography (CT) scanning does not necessarily exclude significant pathology. Here we report the case of an aggressive intrasinusoidal lymphoma of the liver, presenting as a PUO, with only a mildly raised alkaline phosphatase as an initial localising feature.

Case report

A previously well 62-year-old Caucasian man was referred to the Infectious Diseases Unit, Newcastle General Hospital, with a PUO. He reported 3 months of general malaise, recurrent drenching sweats, rigors and 15 kg weight loss. Apart from evidence of recent weight loss and temperatures spiking up to 39°C several times a day, there were no other abnormalities on physical examination.

Autoimmune and extensive microbiological investigations including serology for HIV, hepatitis A, B and C were negative. A bone marrow biopsy showed only reactive plasma cells. Cerebrospinal fluid analysis including cytology was unremarkable. A bone scan, an abdominal ultrasound scan and a CT scan of the thorax and abdomen all appeared normal.

Inflammatory markers on admission revealed a normal white cell count of $4.9 \times 10^9/l$ (normal differential) but an erythrocyte sedimentation rate of 137 mm/h and a C-reactive protein of 347 mg/l (normal < 10). Immuno-

globulin levels and clotting times were unremarkable. Liver function tests showed a low albumin at 25 g/l (normal 34–50) with normal levels of bilirubin, alanine transaminase and gamma-glutamyl transferase. A mildly raised alkaline phosphatase at 169 U/l (normal 65–100) was felt to be 'reactive'.

The patient deteriorated rapidly, losing weight, becoming extremely weak and intermittently confused. He developed oral ulceration, a normochromic, normocytic anaemia (haemoglobin 8.1 g/dl) and thrombocytopenia ($26 \times 10^9/l$). By the third week of his hospital admission the patient had become moribund. His alkaline phosphatase had risen to 293 U/l and his lactate dehydrogenase to 1025 U/l (normal < 430).

Following platelet infusion pre-procedure, a percutaneous liver biopsy revealed an intrasinusoidal high-grade centroblastic B-cell non-Hodgkins lymphoma (figure 1). With the already available imaging information this was designated stage 1E non-Hodgkins lymphoma with B symptoms.

Initial therapy with high-dose intravenous (iv) dexamethasone (4 mg qid) produced a dramatic fall in temperature (figure 2). Urgent combination chemotherapy was then commenced using 3-week cycles of CHOP (cyclophosphamide 750 mg/m² iv, adriamycin 50 mg/m² iv, vincristine 2 mg iv, with oral prednisolone 40 mg daily for 5 days). A reduced dose (75%) was used in the first course and full doses thereafter. By the sixth

Figure 1 Liver biopsy (periodic acid-Schiff stain). Note presence of abundant large pleomorphic lymphoid cells in the hepatic sinusoids. Immunostaining showed the cells to be CD20 and CD45 positive. A 25-µm scale marker is shown

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Figure 2 Temperature chart showing lysis of patient's pyrexia following commencement of high dose dexamethasone (arrow). Intervals of 24 hours (at midnight) are marked

and final course he was afebrile, had gained 18 kg in weight and his liver function tests had normalised. A repeat liver biopsy performed one month after his last course of chemotherapy showed no evidence of persistent lymphoma. Six months later he remains clinically and biochemically disease-free. A CT scan of the abdomen, pelvis and thorax performed during follow-up appeared normal, as had all previous imaging modalities.

Discussion

Primary non-Hodgkins lymphoma of the liver (stage 1E) is rare.¹ A 4:1 male to female preponderance with a mean age of onset in the 5th decade has been described.² In 50% of cases B symptoms, particularly weight loss, appear prominent. Biochemically, 80% of cases show an elevated alkaline phosphatase, and 100% show an elevated lactate dehydrogenase.^{3,4} The majority are diffuse

Learning points

- primary lymphoma of the liver can present with severe systemic disturbance but few localising signs
- normal ultrasound or CT imaging studies of the liver do not exclude significant hepatic pathology
- mild elevation of alkaline phosphatase levels occurring during PUO is not always nonspecific

large cell lymphomas of B-cell lineage.³ The prognosis with treatment appears variable, ranging from 14% to 56% survival 4 years after diagnosis.^{1,2} In the present case, thrombocytopenia was a prominent feature, previously noted commonly only in Chinese patients.¹ The lack of hepatomegaly was unusual, being present in the majority (63–100%) of previously reported cases.^{1–5} The unique feature in this patient was the normal appearance of the liver on ultrasound and CT scanning. In all other recorded cases, imaging studies of the liver have shown either a diffuse abnormality or a uni-/multi-nodular pattern,^{1–5} directly precipitating biopsy.

This case demonstrates that mildly abnormal liver function tests in a patient with a PUO should not necessarily be dismissed as non-specific findings. The case also demonstrates that a normal liver ultrasound or CT scan in this situation does not exclude relevant hepatic pathology. Percutaneous liver biopsy proved to be diagnostic. We recommend a low threshold for liver biopsy in the investigation of PUOs in a similar clinical setting, having ensured an adequate platelet count and clotting beforehand.

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Aspergillus niger endocarditis in an immunocompetent patient: an unusual course

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Summary

Aspergillus is an opportunistic nosocomial fungus generally associated with a high mortality rate. *A. niger* has been rarely associated with infection, and most cases have occurred in patients who have recently undergone heart surgery or in immunocompromised patients. We present a case of an immunocompetent patient with *A. niger* endocarditis which illustrates the difficulties in diagnosis and the possible insidious course of fungal endocarditis.

Keywords: endocarditis; *Aspergillus niger*; transoesophageal echocardiography

Aspergillus is an opportunistic nosocomial fungus generally associated with a high mortality rate.¹ While *A. fumigatus* has been reported to be the most frequent cause of aspergillosis, *A. niger* has been rarely associated with infection, and most cases have occurred in patients who have recently undergone heart surgery for valvular replacement and pacemaker implantation, as well as in patients with neoplastic diseases, intravenous treatment or drug addiction, long-term parental feeding and immunosuppression.²

The optimal therapy for *Aspergillus* endocarditis has not been established, but it usually requires combined aggressive medical and surgical treatment,³ as high-dose amphotericin alone is ineffective because of the resistance of many *Aspergillus* species and poor penetration into tissues, while surgical treatment alone may be insufficient, as most patients have disseminated disease at the time of diagnosis.³ The length of therapy, the efficacy of alternative modalities, such as liposomal amphotericin or new imidazole derivatives, are of unproved value as yet.⁴

We present a case of an immunocompetent patient with *A. niger* endocarditis which illustrates the difficulties in diagnosis and the important role of repeated transoesophageal echocardiography (TOE) in proper management of infective endocarditis.

Case report

A 57-year-old man was admitted for malaise and fever of 5 days duration, 2 months after mitral valve repair for severe mitral valve prolapse and regurgitation. Apart from fever (38.5°C) and an apical systolic murmur, his

physical examination was unremarkable. His blood pressure was 110/70 mmHg, the pulse rate 96 beats/min, and there were no signs of petechiae, splenomegaly, clubbing, or other signs of endocarditis. The chest X-ray and electrocardiogram were within normal limits. Laboratory results showed accelerated erythrocyte sedimentation rate (ESR 120 mm/h, Westergren) and mild normocytic, normochromic anaemia (haematocrit ratio 0.33). The urinalysis was normal, without haematuria, as were the results of serum biochemical profile. Seven blood culture sets were negative, as were serology for rickettsia and Q fever. At that time we performed TOE, which revealed a 4 mm mobile lesion on the mitral valve, suggestive of vegetation, but without evidence for valvular damage. With the diagnosis of culture-negative prosthetic valve endocarditis, vancomycin and gentamycin were administered and the fever subsided. After 2 weeks, low-grade fever reappeared, and the treatment was changed to vancomycin, ciprofloxacin and rifampin. After 6 weeks of parenteral antibiotic treatment the patient's general condition improved markedly, the fever and anaemia resolved and the elevated ESR decreased, and the patient, who was apparently cured, was ready to be discharged. However, to our surprise, a routine pre-discharge TOE demonstrated a marked increase in the vegetation to 11 mm, with a highly mobile appearance (figure 1). The patient was then referred for surgery, and a large friable vegetation on the mitral valve was found and excised.

Direct microscopy of the vegetation stained with 10% KOH-Quink revealed septate hyphae and culture grew *A. niger* (figure 2). The patient had been treated with amphotericin for two

Figure 1 TOE after 6 weeks of antibiotic treatment showing the 11 mm vegetation (arrow). At that time the patient was afebrile, ready to be discharged

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Figure 2 KOH-Quink stain of the vegetation showing septate hyphae typical of *Aspergillus* sp later defined as *A niger*. Orig $\times 40$

months and subsequently with itraconazole for a year. A repeat TOE 6 months after surgery revealed only mild mitral regurgitation. At present, 16 months after surgery, the patient is doing well, without evidence of recurrence.

Discussion

The present case illustrates the difficulties in diagnosis and the possible insidious course of fungal endocarditis. The only predisposing factor for *A niger* infection in this patient was the open heart surgery. Only one previous report of a surviving case of *A niger* endocarditis has recently been reported.⁵ As in the

present case, the patient was immunocompetent. However, the present case is distinct for the 'benign' course and the apparent 'clinical cure' after 6 weeks of antibacterial treatment. The TOE findings were fundamental both in diagnosis and in our decision to refer the patient to immediate surgery. Indeed, TOE, as demonstrated in the present case, is a powerful diagnostic method, with an established accuracy for vegetations of over 90%.⁶ Although stratification of patients into groups that are at high risk for systemic emboli and death according to vegetation size is still controversial, data from echocardiographic studies suggest that patients with vegetations > 10 mm in diameter are at increased risk of embolic complications, particularly when it involves the mitral valve or when it has a high grade of mobility.⁶ Moreover, serial TOE examinations should increase the specificity and diagnostic accuracy of the findings and provide stronger instrument for decision making. In our patient, the vegetation size, its mobility and the involvement of the mitral valve, were all criteria which led us to refer the patient for surgery despite his excellent clinical condition.

In conclusion, we presented a case of *A niger* endocarditis who had had an insidious course and a favourable outcome of surgery combined with prolonged antifungal treatment. The case emphasizes the role of serial TOE in the diagnosis and management of patients with infective endocarditis, particularly in patients with culture-negative endocarditis.

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