Self-assessment questions

Massive splenomegaly in tropical West Africa

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We describe two cases of massive splenomegaly from an area of Ghana endemic for malaria.

Case 1

A 32-year-old woman presented with lethargy and an abdominal mass which had been present for 3 years. On examination she had moderately pale conjunctivae but no jaundice or lymphadenopathy and there were no stigmata of chronic liver disease. A non-tender, massively enlarged, firm spleen was palpable 24 cm below the costal margin and there was hepatomegaly of 2 cm with no detectable ascites. Stool and urine microscopy were unremarkable. Haematological investigations revealed a normochromic, normocytic anaemia 7.5 g/dl, total lymphocyte count $12.4 \times 10^9/l$ and platelet count $100 \times 10^9/l$. There were no malaria parasites in her peripheral blood and haemoglobin electrophoresis showed genotype AS. Her total IgM was 7.9 g/l, which was markedly raised compared to the local, normal mean of 3.5 g/l (+2 SD). She was treated with proguanil 100 mg daily and both her spleen size and leucocyte counts reduced. However, despite continuous antimalarial therapy, her spleen enlarged again after 3 years. Further investigations including protein electrophoresis (figure 1) were undertaken.

Case 2

A 46-year-old man with a 4-year history of abdominal swelling, weight loss and night sweats was found to have generalised lymphadenopathy and splenomegaly of 17 cm. His haemoglobin was 11.4 g/dl, total leucocyte count $93.4 \times 10^9/l$ and platelet count $150 \times 10^9/l$. Bone marrow aspirate showed marked infiltration with mature lymphocytes. There were no malaria parasites on the blood film and haemoglobin electrophoresis showed genotype AA. Immunoglobulin studies revealed IgG 7.6 g/l, IgA 0.9 g/l and IgM 0.07 g/l. There was no paraprotein band on protein electrophoresis. Two months later the patient was re-admitted with a 3-day history of severe diarrhoea and dehydration and died 2 hours after admission.

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Figure 1 Protein electrophoresis of case 1 (lower lane). The upper lane is from a normal control

Questions

- 1 What are the common causes of massive splenomegaly in malarious areas?
- 2 Case 1: What was the initial diagnosis?
- 3 Case 1: What does the protein electrophoresis show in the gamma region (figure 1)?
- 4 Case 2: What is the likely diagnosis?
- 5 Case 2: How do you explain the results of the immunoglobulin studies?

Answers

QUESTION 1
See box 1.

Causes of massive splenomegaly in malarious areas

- chronic myeloid leukaemia
- Gaucher disease
- haemoglobin SC
- hairy cell leukaemia
- hyper-reactive malarial splenomegaly
- idiopathic and secondary myelofibrosis
- leishmaniasis (kala-azar)
- malignant lymphoma
- portal hypertension
- thalassaemia major

Box 1

QUESTION 2

Hyper-reactive malarial splenomegaly (HMS), formerly known as tropical splenomegaly syndrome.

QUESTION 3

Paraprotein band in the gamma region.

QUESTION 4

Chronic lymphocytic leukaemia.

QUESTION 5

Severe, selective IgM deficiency.

Discussion

Although both these cases presented with massive splenomegaly and lymphocytosis, the sex and age of the patients, the response to antimalarial therapy (case 1) and the associated lymphadenopathy (case 2), pointed towards different diagnoses. Diagnostic criteria for HMS include splenomegaly ≥ 10 cm, elevated IgM, response to antimalarial therapy, and exclusion of underlying lymphoma.¹ Initially, case 1 fulfilled criteria for HMS but immunofixation and immunoselection of her paraprotein demonstrated μ -heavy chain with no associated immunoglobulin light chain (figure 2) and a diagnosis of μ -heavy chain disease was made. μ -Heavy chain disease is the least common type of heavy chain disease and was first reported in 1970.² It is usually associated with massive splenic enlargement and lymphocytosis; bone lesions and transformation to large cell lymphoma have also been described.^{3,4} Several of the reported cases originated in West Africa, leading to the suggestion that a high rate of parasitic infestation and subsequent IgM response may be relevant to the aetiology.

Although chronic lymphocytic leukaemia in industrialised countries is usually associated with lymphadenopathy, splenomegaly is a common presentation in Africa (case 2).⁵ B-Lymphoproliferative disorders are often as-

Learning points

- the commonest causes of massive splenomegaly in the tropics are chronic granulocytic leukaemia, myelofibrosis, portal hypertension, leishmaniasis, haemoglobinopathies, and HMS
- multiple pathologies and late presentations with gross clinical features are common in tropical practice
- it is important to make an accurate diagnosis of massive splenomegaly even if no specific treatment is available in order to avoid the inconvenience, expense and toxicity of inappropriate therapies
- a diagnosis of HMS should be based on specific clinical and laboratory features; it is not a diagnosis 'of exclusion'
- the clinical features and a simple panel of laboratory tests is usually sufficient to diagnose the common causes of massive splenomegaly in the tropics

Box 2

sociated with reduced immunoglobulin levels. However, case 2 had severe selective IgM deficiency with normal IgG and IgA levels. This immunoglobulin profile has been described in adults in association with systemic lupus erythematosus, Hashimoto's disease, atopy, coeliac disease, meningococcal septicaemia and as a familial condition.⁶ It is not a feature of chronic lymphocytic leukaemia. In adults, selective IgM deficiency is usually detected incidentally but despite this, reports indicate a fatal outcome, usually from infection, as in this case.

Figure 2 Rocket immunoselection for the detection of heavy chain disease⁷ in case 1. Key: lane 1: IgM λ serum; lanes 2, 6, 8, 10, 12, 14 & 19: normal serum; lane 3: polyclonal IgM serum; lane 4: IgM κ serum; lanes 5 & 15: serum from case 1, 1990; lanes 7 & 16: serum from case 1, 1992; lanes 9 & 17: serum from case 1, 1994; lanes 11 & 18: serum from case 1, 1997; lane 13: neat urine from case 1, 1997. The lower part of the gel contains anti- κ and anti- λ which will trap any intact immunoglobulin but will allow heavy chain alone through the gel. The upper part of the gel contains anti- μ antiserum. Free μ chains passing through the trapping gel precipitate as a 'rocket' in the detection layer

These two patients illustrate that the classical list of causes of massive splenic enlargement should not be considered exclusive, and that if

clinical and laboratory findings do not completely support the initial diagnosis, supplementary tests should be performed.

Final diagnoses

Case 1: μ -heavy chain disease.

Case 2: chronic lymphocytic leukaemia with selective IgM deficiency.

Keywords: massive splenomegaly; malaria; heavy chain disease; IgM deficiency; Rocket immunoselection

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A young man with dry skin and nodules on elbows and buttocks

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A 32-year-old man sought consultation for dry flaky skin, painless nodules on elbows and buttocks, constipation, cold intolerance, muscle aches and diminished appetite of 4 months duration. On examination he had the features shown in his palms (figure 1), elbows (figure 2) and gluteal region (figure 3).

Figure 1

Figure 2

Figure 3

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Questions

- 1 What are the abnormalities shown in the figures?
- 2 What is the disorder which has unmasked these abnormalities?

Answers

QUESTION 1

Figure 1 shows palmar xanthomas, which are planar xanthomas in the palmar creases. They are virtually pathognomonic of type III hyperlipoproteinaemia, also known as familial dysbetalipoproteinaemia.¹ Figure 2 shows tubero-eruptive xanthomas on the elbows. Figure 3 shows tuberous xanthomas in the gluteal region. Tuberous and tubero-eruptive xanthomas are also seen in but are less specific for this disorder. Salient features of type III hyperlipoproteinaemia are listed in box 1.

Type III hyperlipoproteinaemia

- autosomal recessive (rarely dominant) inheritance; mutant gene Apo E
- lipoprotein pattern type III
- palmar and tuberous xanthomas
- no pancreatitis
- peripheral vascular disease present
- predominant elevated plasma lipoprotein remnants: beta, VLDLs
- predominant elevated plasma lipids: triglycerides and cholesterol
- plasma appears turbid after refrigeration
- coexistent metabolic conditions exacerbating phenotype of type III hyperlipoproteinaemia, eg, hypothyroidism, obesity, diabetes mellitus and alcohol consumption usually present

Box 1

QUESTION 2

Detailed clinical evaluation revealed that patient had obesity, hypothyroid facies, moderate diffuse non-tender thyromegaly, proximal myopathy, bradycardia and delayed relaxation of tendon jerks. There was no history of coronary or peripheral vascular disease.

Investigations revealed fasting cholesterol 11 mmol/l (normal range 4.3–6.18 mmol/l); fasting triglycerides 5.4 mmol/l (<1.8 mmol/l); VLDL cholesterol/ triglyceride ratio >0.3 (0.2), plasma lipoprotein electrophoresis demonstrated broad band in beta migrating lipoprotein region (type III pattern), fasting plasma glucose 4.2 mmol/l (4.2–6.1 mmol/l); thyroid-stimulating hormone 48 mU/l (0.4–5.0 mU/l); thyroxine 51 nmol/l (64–154 nmol/l); fine needle aspiration cytology of thyroid showed diffuse lymphocytic infiltration with germinal centre formation, obliteration of thyroid follicles, and fibrosis. Destruction of epithelial cells was seen, and few larger epithelial cells with oxyphilic changes in the cytoplasm (Askanazy cells) were present. Thyroid peroxidase antibodies were positive. This was consistent with primary hypothyroidism due to Hashimoto's thyroiditis. Liver enzymes, chest X-ray, electrocardiogram and serum immune electrophoresis were normal. Isoelectric focussing of plasma for apo-E2 homozygosity or apo-E genotyping of DNA obtained from leucocytes could not be done.

Learning points

- hypothyroidism is a common cause of secondary hyperlipidaemia
- all patients with significant hyperlipidaemia should be screened for hypothyroidism
- clinical expression of type III hyperlipoproteinaemia is significantly exacerbated by hypothyroidism
- type III hyperlipoproteinaemia associated with hypothyroidism responds dramatically to thyroid hormone replacement therapy

Box 2

Discussion

Alterations in thyroid functions affect plasma lipids significantly,² and hypothyroidism is a common cause of secondary hyperlipidaemia. All patients with significant hyperlipidaemia must be screened for hypothyroidism. The classic manifestation of hypothyroidism is increased levels of plasma LDL cholesterol. Another abnormality is increased plasma triglyceride levels.³ HDL cholesterol levels are normal or slightly lower in hypothyroidism. Elevated plasma cholesterol levels in hypothyroidism are associated with decreased LDL catabolism by way of the LDL receptor pathway,⁴ and with an increased risk for atherosclerosis. Subclinical hypothyroidism can also lead to hypercholesterolaemia, which regresses with thyroid hormone therapy.⁵

A predisposition to increased triglyceride levels is due to impaired lipoprotein lipase activity in hypothyroidism. This can exacerbate the hypertriglyceridaemia of an underlying genetic triglyceride disorder, and chylomicronaemia can occur. Hypothyroidism interferes with remnant metabolism by impaired lipoprotein clearance, and individuals with E2/E2 genotype may present with marked lipid elevations and tubero-eruptive xanthomas. Thus, hypothyroidism can modulate the clinical expression of type III hyperlipoproteinaemia.^{6,7} Type III hyperlipoproteinaemia associated with hypothyroidism responds dramatically to thyroid hormone replacement therapy.⁷

This patient was managed with thyroid hormone replacement therapy and institution of the National Cholesterol Education Programme step I diet. His tubero-eruptive and palmar xanthomas, features of hypothyroidism, and lipid and thyroid hormone abnormalities regressed completely over a period of 14 weeks. He is now asymptomatic and is being followed up in the thyroid clinic on thyroxine and diet therapy. There was no family history of similar disorder, or premature coronary/peripheral vascular disease. Screening of first-degree relatives for type III hyperlipoproteinaemia is planned.

Final diagnosis

Type III hyperlipoproteinaemia with phenotypic exacerbation by primary hypothyroidism.

Keywords: hypothyroidism; hyperlipidaemia; xanthomas

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An unusual cause of cardiac failure

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A 91-year-old woman, with long-standing swelling of both ankles, presented with a 2-month history of increasing swelling of both legs and lower abdomen. She was otherwise asymptomatic. She had undergone a mastectomy for carcinoma of the breast in 1981. At this time, no cardiac murmurs were documented and her electrocardiogram (ECG) showed normal sinus rhythm with a partial right bundle branch block. She remained well at follow-up. There was no history of ischaemic heart disease. Recently her general practitioner had commenced her on digoxin and diuretics for atrial fibrillation and the oedema.

On examination she was acyanotic. Her apical heart rate was irregularly irregular with a ventricular rate of 70 beats/min, blood pressure was 140/80 mmHg and carotid pulses were small volume. The right ventricular impulse was prominent and there was evidence of right ventricular failure (the jugular venous pulse was raised 10 cm above the sternal angle, a smooth, regular, non-tender, liver was palpated three finger breadths below the right costal margin and there was bilateral, non-tender, pitting oedema of both legs up to and involving the lower abdomen). There was no ascites. On auscultation there was fixed splitting of the second heart sound but no increase in the pulmonary component. There was evidence of tricuspid regurgitation (a pansystolic murmur was heard at the left sternal edge in the fourth intercostal space, loudest during inspiration, with a pulsatile hepatomegaly and a large V wave in the jugular venous pulse). There was also evidence of increased blood flow across the pulmonary valve (an ejection systolic murmur was heard at the upper left sternal edge, loudest during inspiration).

An ECG showed atrial fibrillation, right bundle branch block, right axis deviation and ventricular ectopic beats with coupling. A chest X-ray showed enlargement of both atria and the right ventricle. The pulmonary artery was dilated, with pulmonary plethora, and upper lobe venous distension. There were small bilateral basal pleural effusions.

Questions

- 1 What investigation would you perform next?
- 2 What is the diagnosis?

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Answers

QUESTION 1

The patient presented with a clinical picture suggestive of cardiac failure (predominantly right sided) secondary to an atrial septal defect. The next investigation that should be performed is a transthoracic Doppler 2D echocardiogram, to allow identification of the atrial septal defect and direction of blood flow across the defect. It will also allow for assessment of ventricular function and confirmation of the valvular lesions.

QUESTION 2

An echocardiogram was performed and confirmed the presence of an ASD secundum, 2.1 cm in length with left to right shunting. Both atria and right ventricle were enlarged. Biventricular function was vigorous (ejection fraction 71%) and there was severe tricuspid regurgitation. The patient refused cardiac catheterisation and was treated with diuretics and angiotensin-converting enzyme inhibitors. Her digoxin was temporarily stopped in view of the ventricular ectopics and coupling, but was restarted once digoxin toxicity had been excluded. At the present time she remains well.

Discussion

Atrial septal defects are thought to shorten life expectancy. With increasing age, clinical deterioration occurs with the onset of atrial fibrillation, embolic phenomena, pulmonary hypertension, cardiac failure and bronchopulmonary infections, so that by middle age most patients are symptomatic.^{1 2}

Mortality figures suggest that in patients with clinically overt disease, 75% are dead by the age of 50 years and 90% by 60 years.³ Only two previous reports of survival into the ninth decade have been recorded.^{4 5} Our patient is unusual not only for her longevity, but also for her freedom from significant symptoms for so long.

It is accepted that surgical closure of atrial septal defects in children and young adults carries a low operative mortality and should be performed to prevent future complications. The benefit of surgery in older patients remains debatable. Early studies claimed to show improvements in morbidity and mortality in adult patients treated surgically,¹ but recent studies have found similar rates of morbidity and mortality in both medically and surgically treated adult patients, with survival of up to 91% in medically treated patients.²

Clinical features of ostium secundum atrial septal defects

Symptoms

- rare in infancy
- uncommon in childhood
- usual in adults
- palpitations
- exertional dyspnoea
- ankle swelling
- chest pain
- respiratory tract infection

Signs

- small volume pulse
- atrial fibrillation
- raised jugular venous pressure
- peripheral oedema
- ascites
- prominent right ventricular impulse
- loud first heart sound
- loud P2
- fourth heart sound
- fixed splitting of second heart sound
- pulmonary / tricuspid flow murmur
- pulmonary / tricuspid regurgitant murmur

Investigations

- ECG
- right bundle branch block
- right axis deviation
- atrial fibrillation
- chest X-ray
- right ventricular dilatation
- right atrial enlargement
- bi-atrial enlargement with atrial fibrillation
- small aortic knuckle
- pulmonary artery dilatation
- pulmonary plethora

This case illustrates that not all cases of cardiac failure in the elderly are due to common aetiologies, such as hypertension or ischaemia and, therefore, thorough evaluation of such cases is important, with echocardiogram forming an important part of that evaluation. The longevity and well being of our patient and of others of such longevity,^{4 5} also indicates that surgical intervention in middle-aged and elderly patients with atrial septal defects remains of questionable value.

Final diagnosis

Cardiac failure secondary to ostium secundum atrial septal defect.

Keywords: cardiac failure; atrial septal defect

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Acute Q fever in a patient returning from the tropics

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A 40-year-old man living in Marseille was admitted to our hospital with a 3-day history of fever. The patient had returned from Senegal 3 weeks earlier. He had stayed in the eastern part of the country, near the Senegal River, the northern border with Mauritania and the eastern border with Mali. He had been there for 2 months without chemoprophylaxis against malaria. On admission his temperature was 39°C, and the pulse 110 beats/min. He complained of severe headaches, vertigo, and a dry cough. Physical findings were unremarkable. Chest X-ray showed a moderate bibasilar interstitial infiltrate. The white blood cell count was $7.6 \times 10^9/l$ with 70% band forms. The platelet count was $112 \times 10^9/l$. The haemoglobin level was within normal limits. Blood chemistry analysis showed raised enzymes (lactate dehydrogenase 635 IU/l, gamma glutamyl transpeptidase 165 IU/l, and aspartate transaminase 65 IU/l). Repeated blood smears disclosed no parasites. The cerebrospinal fluid analysis was normal. Bacteriological culture of the faeces and three blood cultures remained negative. Serum testing for antibodies to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Coxiella burnetii*, and HIV was negative. On day 4, the patient became spontaneously afebrile, and all the symptoms disappeared. He was discharged from the hospital. Ten days later, a new set of serologic studies were performed. The indirect immunofluorescence assay for antibodies reactive with phase II *Coxiella burnetii* antigens showed raised IgM (1:400) and IgG (1:25). These results confirmed the diagnosis of acute Query (Q) fever.¹

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Questions

- 1 *Coxiella burnetii*:
A is a Gram-negative bacteria
B is a strict intracellular bacteria
C may persist in the environment
D is cultivable on blood agar gelose
E has to be isolated in biosafety level 3 laboratories only
- 2 How is Q fever usually acquired?
A by mosquitoes bites
B by tick bites
C by ingestion of raw milk
D by inhalation
E by percutaneous route
- 3 Where does Q fever represent a risk for travellers?
A Asia
B Europe
C Africa
D Australia
E USA
- 4 What are the principal clinical manifestations of acute Q fever?
A isolated fever
B pneumonia
C gastroenteritis
D hepatitis
E meningitis
- 5 What is the treatment?
A aminopenicilline
B rifampicine
C doxycycline
D erythromycine
E clindamycine
- 6 Chronic Q fever:
A occurs in approximately 15% of patients infected with *C burnetii*
B may develop years after the acute phase
C may manifest as endocarditis
D is diagnosed by blood cultures
E is diagnosed by serology

Answers

QUESTION 1

A, B, C and E are true.

QUESTION 2

C and D are true. Q fever is usually acquired by the ingestion or inhalation of virulent organisms from infected mammals. Goats, sheep or cats are frequently involved. Generation of infectious aerosols often follows parturition, owing to high concentrations of the organism in the infected placenta.^{1,2} Questioning our patient revealed direct contact for 1 month with pregnant ewes and newborn sheep, some of which died after one week of life.

QUESTION 3

A, B, C, D and E are true. Q fever is endemic in every part of the world except New Zealand.^{1,2} Although the disease is distributed throughout Africa, seroprevalences vary greatly, from 1% to more than 35%.³ There is a good correlation between the seroprevalence and the development of the stock-breeding industry,³ which is significant in Senegal, particularly in the River area. No recent data

about the seroprevalence of Q fever are available from Senegal. However, a seroprevalence of 24% was recently reported among healthy adults in the eastern neighbour Mali, where the stock-breeding industry is also highly developed.³

QUESTION 4

A, B and D are the correct answers. Clinical signs are often subclinical (50%) or very mild.^{1,2} The incubation period has been estimated to be approximately 3 weeks (range 14–39 days).

QUESTION 5

C is the correct answer. The treatment of acute Q fever is based on tetracycline (doxycycline 200 mg daily) for 3 weeks. Our patient received this treatment and remained well.

QUESTION 6

B, C and E are correct. Chronic Q fever occurs in approximately 5% of patients infected with *Coxiella burnetii*. Blood culture-negative endocarditis is the principal manifestation. Elevated anti-phase I antibodies are uniformly detected.¹

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Exertional dyspnoea and nonproductive cough in a 22-year-old man

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A 22-year-old man presented with a 2-year history of nonproductive cough and exertional dyspnoea. He had never smoked. Because of a diagnosis of presumed bronchial asthma about 2 years ago, he was treated with multiple bronchodilators and inhaled corticosteroids for several months but no improvement in his symptoms resulted. One year prior to admission, he had been admitted to another hospital with same complaints and pulmonary tuberculosis had been suspected. Therapy with isoniazid (300 mg/d), rifampicin (600 mg/d), and ethambutol (25 mg/kg/d) for 9 months resulted in no improvement.

Physical examination revealed a blood pressure of 130/80 mmHg, heart rate of 100 beats/min, temperature of 37°C, and respiratory rate of 28 breaths/min. Breath sounds were normal on quiet breathing, but there were inspiratory and expiratory wheezes and coarse rales over the right upper lung on forced inspiration and expiration. Findings from the rest of the physical examination were within normal limits.

Serum electrolytes, renal function, and urinalysis results were normal. Chest X-ray showed right hilar and paratracheal lymph node enlargement with right upper lobe atelectasis (figure 1). His peak flow was 100 l/min and did not improve following the inhalation of nebulized salbutamol. His forced expiratory volume in 1 s (FEV₁) was 1.8 l at best, vital capacity was 4.2 l and flow volume loop showed flat inspiratory and expiratory phases indicative of large intrathoracic airway obstruction. The patient was anergic to skin test with purified protein derivative. Bronchoscopy revealed a regular bluish nodular lesion with slightly increased vascularity and nearly complete obliteration of the orifice of the anterior segmental bronchus of the right upper lobe. Multiple biopsies taken from this endobronchial mass lesion were reported as non-caseating infiltration of the mucosa by epithelioid cell granulomas.

Figure 1 Chest X-ray showing right hilar and paratracheal lymph node enlargement with right upper lobe atelectasis

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Questions

- 1 What is your diagnosis?
- 2 What other possible diagnoses are compatible with the patient's clinical presentation?
- 3 How would you manage this patient?

Answers

QUESTION 1

The diagnosis is sarcoidosis.

QUESTION 2

Other possible diagnoses include neoplasm (bronchogenic carcinoma or lymphoma), tuberculosis, fungal disorders (aspergillosis, nocardiosis), other granulomatous disease (syphilis), HIV, and bronchial asthma.

QUESTION 3

The patient should receive corticosteroid therapy.

Outcome

Prednisolone 40 mg daily was started and gradually tapered to 10 mg on alternate days. The patient's clinical condition improved within 2 months, and 3 months after the initiation of therapy, a control chest X-ray showed complete resolution of the previous right-upper lobe atelectasis, and also right hilar lymph node enlargement (figure 2). Control bronchoscopy revealed partial resolution of the previous nodular endobronchial lesion.

Discussion

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology, characterised histologically by epithelioid tubercles involving various organs or tissue, with symptoms dependent on the site and degree of involvement. It occurs predominantly between ages 20 and 40. The most common sites are the lungs, lymph nodes, liver, eyes, and skin.¹ The lungs are the most frequently involved organ, and pulmonary symptoms include dyspnoea on

Figure 2 Control chest X-ray showing complete resolution of the previous right-upper lobe atelectasis, and also right hilar lymph node enlargement

Classic X-ray patterns of pulmonary sarcoidosis

Grade I: lymph node enlargement without pulmonary parenchymal abnormalities
 Grade IIA: combination of lymph node and diffuse pulmonary parenchymal disease
 Grade IIB: diffuse parenchymal disease without lymph enlargement
 Grade III: pulmonary parenchymal fibrosis

Box 1

exertion, nonproductive cough, and wheezing. Because the lung is involved so commonly, the routine chest film is usually abnormal (box 1).¹

Much attention has been focused on the restrictive ventilatory defect seen in pulmonary sarcoidosis. However, a number of reports have indicated that sarcoidosis may cause varying degrees of upper and lower airway obstruction.^{2,3} Initial reports suggested that obstructive ventilatory defects occur only in the late stages of the disease, associated with pulmonary fibrosis. However, occlusion of a lobar bronchus and lobar atelectasis may occur without pulmonary fibrosis due to extrinsic compression by enlarged lymph nodes or, rarely, endobronchial disease.⁴ Moreover, isolated endobronchial lesions, which are extremely rare in pulmonary sarcoidosis,⁵ may also cause obstructive ventilatory defects, as in our patient.

Because sarcoidosis can occur in almost any part of the body, like tuberculosis or syphilis, it may be confused with other disorders. However, it is most commonly confused with neoplastic disease such as bronchogenic cancer and lymphoma or with disorders also characterised by a mononuclear cell granulomatous inflammatory process, such as the mycobacterial and fungal disorders.^{1,6} Whether or not the presentation is 'classic', biopsy evidence of a mononuclear cell granulomatous inflammatory process is mandatory in order to make a definitive diagnosis.⁶ However, the histologic findings are not sufficiently specific to make the diagnosis by themselves, since noncaseating granulomas are found in a number of other diseases, including infections and malignancy. Thus, a definitive diagnosis of sarcoidosis is based on biopsy in the context of the history, physical examination, blood tests, X-ray, lung function, and, if available, gallium 67 scan and bronchoalveolar lavage (figure 3).⁶

The therapy of choice for sarcoidosis is glucocorticoids.⁶ The major problem in treat-

Figure 3 Diagnosis of sarcoidosis (adapted from⁶)

ing sarcoidosis is in deciding when to treat. Since the disease may remit spontaneously and since steroids may cause significant side-effects, treatment is usually started only if there is an indication of interference with the function of a vital organ (lungs, kidneys, eyes, heart, or central nervous system). Because of severe dyspnoea and cough, the present case was treated with high-dose oral corticosteroids. He improved dramatically within 3 months and has been free of complications for 2 years.

Final diagnosis

Bronchial obstruction due to endobronchial sarcoidosis.

Learning points

- although obstructive ventilatory defects rarely occur in the early stage of pulmonary sarcoidosis, endobronchial sarcoidosis must be considered in a young patient presenting with clinical features of bronchial obstruction, when no evidence of other common cause of airway obstruction can be found
- corticosteroids are still an effective and safe treatment for this disorder

Box 2

Keywords: sarcoidosis; corticosteroids; pulmonary obstruction

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Masked hypercalcaemia

P M Byrne, R Freaney, M J McKenna

A 29-year-old man presented with a 6-month history of steatorrhoea and a weight loss of 5 kg over 2 months. Endoscopy showed ulcers in the descending duodenum. Fasting serum gastrin was 427 ng/l (normal range less than 100 ng/l). Basal gastric acid secretion was 42.8 mmol/h (normal less than 15 mmol/h). No abnormality was found on abdominal computed tomography (CT) scan. The patient also complained of proximal muscle weakness and rib pain. On examination he had Harrison's sulci and lower rib tenderness. Biochemical measurements are shown in the table.

Table Serum biochemistry

	At presentation	Post-vitamin D supplementation	Post- para- thyroidectomy	Reference range
Ionised Ca (mmol/l)	1.24	1.49	1.25	1.19–1.35
PTH (pmol/l)	87.3	42.1	7.64	0.2–5.5
Phosphate (mmol/l)	0.5	0.79	1.14	0.8–1.4
25(OH)D (nmol/l)	<5.0	53.2	17	<50
Osteocalcin (ng/ml)	—	152	3	8.8–14.8
Ur DPD (nmol/mmol Cr)	—	39.5	5	3.1–5.6

Ur DPD = urinary free deoxypyridinoline

Questions

- 1 What was the most likely diagnosis in this patient ?

2 Why did the patient have steatorrhoea ?

3 What other conditions did this patient have and can you explain the reasons for this?

4 What syndrome did the patient have ?

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Answers

QUESTION 1

This patient had Zollinger-Ellison syndrome (ZES), namely hypergastrinaemia from a gastrin-secreting tumour or tumours. The presence of peptic ulcers in the second part of the duodenum is almost pathognomonic of this condition. The elevated basal gastric acid secretion and circulating gastrin levels confirmed this diagnosis. Failure to demonstrate a discrete tumour in the pancreas or duodenal wall on CT scan is a common problem as many tumours are very small and some patients have multiple microtumours scattered throughout the pancreas and duodenal wall.

QUESTION 2

The excessive acid production denatures digestive enzymes in the duodenum, including pancreatic lipase. This causes fat malabsorption.

QUESTION 3

The clinical features of proximal muscle weakness and rib pain in conjunction with severe hypovitaminosis D and markedly elevated parathyroid hormone (PTH) level are consistent with severe vitamin D deficiency that has resulted in osteomalacia and secondary hyperparathyroidism.¹ Vitamin D is fat soluble. ZES causes fat malabsorption and malabsorption of fat-soluble vitamins such as vitamin D. In addition, steatorrhoea diminishes calcium absorption.

QUESTION 4

The combination of ZES and hyperparathyroidism with parathyroid gland hyperplasia suggests that the patient had multiple endocrine neoplasia type 1 (MEN type 1).

Treatment

He was treated with a proton pump inhibitor and a high dose of parenteral vitamin D (30 000 IU calciferol weekly). After one month of therapy, serum 25-hydroxyvitamin D (25(OH)D) concentration had increased to within the normal range at 53.2 nmol/l. Then hypercalcaemia was noted. Serum PTH concentration had decreased but was still elevated (table). There are two possible explanations for the hypercalcaemia. The patient could have had coexisting primary hyperparathyroidism (PHPT), either sporadic or as part of the MEN syndrome. The other possibility is that he had tertiary 'autonomous' hyperparathyroidism due to longstanding secondary hyperparathyroidism which was a consequence of chronic malabsorption.

A total parathyroidectomy was performed and part of a gland was autotransplanted to a sternomastoid muscle. Histological examination showed hyperplasia in all four glands. After surgery, serum ionised calcium concentration returned to normal and serum PTH concentration was only mildly elevated (table).

Hyperplasia of parathyroid glands in patients with MEN type 1 is a result of expansion of multiple-cell clones, whereas in sporadic

Learning points

- patients with ZES may have a coexisting primary hyperparathyroidism as part of a MEN type 1 syndrome. However, they may not have hypercalcaemia initially and the primary hyperparathyroidism will only become unmasked after the ZES-related vitamin D and calcium malabsorption and hypovitaminosis D are corrected
- the diagnosis of MEN 1 requires the presence of tumours in two or more of the three principal organs affected (parathyroid, pancreatic islet and anterior pituitary)
- patients with hypothyroidism or hypovitaminosis D from nutritional deficiency, malabsorption syndromes or drug-induced alterations in vitamin D metabolism, may also have masked autonomous primary (or tertiary) hyperparathyroidism. Frank hypercalcaemia only develops when the hypovitaminosis D or hypothyroidism is corrected

PHPT the parathyroid adenoma results from activation of a single cell clone.² The diagnosis of MEN type 1 requires the presence of tumours in two or more of the three principal organs affected (parathyroid, pancreatic islet (gastrinoma, insulinoma), and anterior pituitary (most commonly prolactinoma)). Some patients have ZES alone at diagnosis while others have both ZES and PHPT.³ PHPT is the most common manifestation, occurring in 80–100% of cases.

Discussion

This patient with MEN type 1, presented with osteomalacia. Vitamin D and calcium malabsorption were caused by steatorrhoea due to ZES. Following correction of the steatorrhoea and hypovitaminosis D, the PTH concentration fell but remained above normal. The patient developed symptomatic hypercalcaemia because an underlying hyperparathyroidism became unmasked after vitamin D replenishment. This hyperparathyroidism could have been caused by a coexisting PHPT or by tertiary hyperparathyroidism due to longstanding secondary hyperparathyroidism in response to the vitamin D deficiency. Since this patient has many features of MEN type 1, PHPT is the most likely explanation.

The following is the most probable mechanism by which ZES can mask coexisting hyperparathyroidism. Hypergastrinaemia stimulates excess gastric acid production which denatures intestinal digestive enzymes, giving rise to malabsorption of vitamin D and calcium. PTH secretion increases to restore calcium levels to the normal range. This phenomenon of hypovitaminosis D leading to secondary hyperparathyroidism in malabsorptive disorders has been well documented.⁴ Following correction of the hypovitaminosis D, hypercalcaemia developed. If the elevated serum PTH concentration had been caused by hypovitaminosis D alone, PTH would have been expected to return to normal. However,

PTH remained significantly elevated, which was consistent with coexisting primary hyperparathyroidism.

Any cause of fat malabsorption with associated hypovitaminosis D can mask primary hyperparathyroidism. Reported examples include coeliac disease⁵ and jejunoileal bypass surgery for obesity.⁶ Primary hyperparathyroidism can also be masked by hypovitaminosis D arising from nutritional deficiency.⁷⁻⁸ It can also be masked by alterations in vitamin D metabolism induced by some medications, such as isoniazid, rifampicin and phenytoin.⁹⁻¹⁰ Primary hyperparathyroidism has also been masked by hypothyroidism¹¹; the mechanism is

unclear but hypovitaminosis D is not implicated.

Final diagnosis

Multiple endocrine neoplasia type 1 consisting of Zollinger-Ellison syndrome and primary hyperparathyroidism which was initially masked by vitamin D and calcium malabsorption due to Zollinger-Ellison syndrome.

Keywords: endocrine neoplasia; hypovitaminosis D; hyperparathyroidism; Zollinger-Ellison syndrome

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