A complicated case of von Hippel-Lindau disease

G Thomas, R Hillson

A 17 year old female shop assistant presented with a three week history of generalised headache, associated with nausea, vomiting, and vertigo. She had no past medical history, and was taking no regular medication. Her mother was currently receiving radiotherapy for anaplastic carcinoma of the thyroid gland. On examination she had an ataxic gait, bilateral papilloedema, and horizontal nystagmus to right lateral gaze. Left sided dysdiadokinesis and hyper-reflexia were demonstrated. Power and sensation were preserved. Computed tomography of the brain revealed a cystic lesion within the left cerebellum. Subsequent magnetic resonance imaging (MRI) revealed a second, non-cystic lesion within the region of the right vermis (fig 1). Both images were consistent with cerebellar haemangioblastomata. A posterior fossa craniotomy was performed, with successful excision of both tumours. She made an uneventful recovery, with complete resolution of all symptoms, and was subsequently discharged.

During a follow up outpatient appointment six months later, she complained of frequent panic attacks, associated with sweating and palpitation that had begun two months earlier. These episodes were precipitated by exercise or excitement. She gave no history of heat intolerance, weight loss, or diarrhoea. Examination was entirely normal. Abdominal computed tomography (fig 2), and subsequent I$^{131}$ meta-iodobenzylguanidine (MIBG) isotope uptake scan (fig 3) are shown here.

Questions
(1) What family history should be explored in a 17 year old girl with multiple cerebellar haemangioblastomas and why?
(2) What is the nature of the current problem and unifying diagnosis?
(3) What other complications occur in this disease?
(4) What is the significance of thyroid cancer in the mother?
An unusual cause of paraplegia

S A M Saeed, D Francis, R Brooks

A 56 year old machine operator presented with mild weakness and sensory disturbance in his lower limbs after he woke up from an arthroscopy operation. At the time he did not seek medical attention. His symptoms progressed over the next four months to the degree that he was unable to stand and he developed back pain radiating to the legs, urinary frequency, hesitancy, and incontinence of urine. There was no history of claudication in the legs. He was a heavy smoker and suffered from ischaemic heart disease and type 2 diabetes mellitus.

On examination he was overweight. Straight leg raising test was within normal limits. Neurological examination showed normal cranial nerves and normal upper limbs. Lower limb examination revealed grade 3/4 proximal limb weakness with absent ankle jerks and equivocal plantar responses. Light touch and pinprick sensation was impaired in L1–S3 distribution bilaterally with impaired vibration. Coordination was normal. The remaining physical examination was otherwise unremarkable.

Laboratory examination showed high inflammatory parameters with an erythrocyte sedimentation rate of 33 mm in the first hour and a C reactive protein of 68 mg/l. The following tests were either normal or negative: full blood count, biochemistry profile, immunoglobulins, serum vitamin B12, serum and red blood cell folate, vasculitis, thrombophilia, and paraneoplastic screens, angiotensin converting enzyme level, and Treponema pallidum haemagglutination test.

Lumbar puncture showed a cerebrospinal fluid (CSF) opening pressure of 260 mm with high CSF protein at 1.9 g/l (normal 0.1–0.4) with no evidence of oligoclonal band. CSF glucose 5.7 mmol/l (blood glucose 10.4 mmol/l), 73 red cells/high power field and no leucocytes or abnormal cells on cytospin. There was no evidence of xanthochromia.

Computed tomography and magnetic resonance imaging (MRI) scans of the brain were normal; however, an MRI scan of the spinal cord was abnormal (fig 1).

After he was given specific medical treatment he became paraplegic (leg power 0/4) and lost bladder sensation. An urgent spinal angiogram confirmed the diagnosis (fig 2).

He had specific interventional treatment after which he had some improvement in sensation in the lower limbs, only to be replaced by unpleasant dysthesia, but he started passing urine normally. Lower limb strength improved to grade 2–3/4, although he was not weight bearing.

Eight months after the initial presentation he continued to improve, although he required a wheelchair for mobility.

Questions

(1) What differential clinical diagnoses would you consider?
(2) What do the spinal MRI scans show?
(3) What was the first treatment given which was followed by paraplegia?
(4) What is the pathological abnormality suggested by the spinal angiogram?
(5) What specific treatment did the patient receive?
Palpable breast mass in a lactating woman

M Goyal, T B Poulton, O Konez

A 35 year old woman noted a painless lump in her right breast during self examination. She was three months postpartum and had been breast feeding her daughter since birth. Her past medical history included three previous uneventful pregnancies, each followed by an uncomplicated period of breast feeding. She had no other significant illnesses in the past. Her mother had died of postmenopausal breast cancer. She had never been on oral contraceptives.

On examination, there was a mobile, non-tender, firm palpable mass of about 3 cm in the upper outer quadrant of the right breast, close to the nipple. There was no swelling or erythema of the overlying skin. Although the clinical impression favoured a benign breast mass, breast cancer was also considered.

High resolution ultrasound of the right breast revealed a solid, predominantly hypoechoic mass with somewhat heterogeneous echotexture. Some of the margins of the mass were indistinct causing it to blend with the surrounding breast parenchyma. The mass was ovoid, width greater than height, and there was considerable posterior acoustic enhancement. There was no evidence of calcifications and the overlying skin and subcutaneous fat were sonographically normal. Transverse and longitudinal ultrasound images of the mass are shown in fig 1.

Questions
(1) What is the differential diagnosis of a solid mass in a pregnant or lactating woman?
(2) What further work-up is needed to confirm the diagnosis in this case?
(3) What is the most likely diagnosis of this patient’s palpable breast mass?

A patient with severe hyperphosphataemia

K M Chow, P K T Li

A 67 year old Chinese woman presented to her general practitioner with abdominal pain. She had an unremarkable history except for bronchiectasis diagnosed a decade before. Colonoscopy was arranged in view of positive faecal occult blood. Preliminary investigation revealed underlying renal insufficiency with a serum creatinine concentration of 700 µmol/l (table 1). There was no abnormality except several small tubular adenomatous polyps in the colon.

She developed symptomatic hypocalcaemia shortly after colonoscopy, and subsequent investigation revealed significant hyperphosphataemia, as shown in table 1. Further evaluation confirmed chronic renal failure secondary to polycystic kidney disease.

Questions
(1) What is the cause of the hyperphosphataemia?
(2) What action would you take?
(3) How should this be avoided?
Abnormal behaviour in a man with massive, generalised, peripheral lymphadenopathy

B L Samaga, M V Nagaraj

A 33 year old Indian man, a truck driver in Mumbai, who was seropositive for human HIV and not on antiretroviral therapy, presented with a one month history of intermittent fever with sweating, gradually progressive headache, vomiting, and watery diarrhoea. He had lost 9 kg of weight in the past one month. He had smoked cigarettes for 15 years and had multiple unprotected sexual exposure in the past. He denied having had any significant illness.

On physical examination, he was emaciated, febrile, and behaving abnormally. He was irritable and restless. He was unkempt and appeared withdrawn socially with a general loss of interest. Sometimes he would answer relevantly and at other times he would become silent with a vacant stare as if unaware of his surroundings. Waxing and waning of alertness and attention deficits progressed to deeper levels of drowsiness during the hospital stay. He was anaemic with mobile, non-tender enlarged lymph nodes (3–5 cm) in the cervical, axillary, and inguinal areas. There was oropharyngeal candidiasis. His liver was enlarged 3 cm below the right costal margin; his spleen was just palpable. There were no signs of meningial irritation and no focal neurological deficits.

His haemoglobin concentration was 80 g/l, leucocyte count $2.3 \times 10^9/l$ with 28% lymphocytes, CD4 count absent, and erythrocyte sedimentation rate 8 mm in the first hour. Serum glucose, renal function, electrolytes, calcium, and phosphate were within normal limits. Liver function was abnormal with a threefold rise of alanine aminotransferase (130 U/l) and aspartate aminotransferase (146 U/l). Alkaline phosphatase was two times the normal level. Serum albumin was 28 g/l. Induced spumt was negative for acid fast bacilli and Pneumocystis carinii, and for bacterial and fungal growth. Stool was positive for cryptosporidial oocysts. Hepatitis B surface antigen, the Venereal Disease Research Laboratory test, Treponema pallidum haemagglutination, and purified protein derivative test were negative. Electrocardiography, chest radiography, and computed tomography of the brain were normal. Abdominal sonography revealed mild hepatosplenomegaly without focal lesions. Cerebrospinal fluid (CSF) was under normal pressure without pleocytosis and glucose and protein concentrations in the CSF were normal. Fine needle aspiration cytology (FNAC) of the cervical lymph node showed abnormal findings. Microscopic pictures of stained CSF and FNAC samples are shown in fig 1.

Questions

(1) What are the diagnoses?
(2) What is unusual and atypical in the case illustrated?
Oligoarthritis in an elderly woman with diarrhoea and weight loss

A L Hepburn, S A Kaye

An 80 year old woman was referred in 1995 to the haematology outpatient department with a normocytic anaemia and weight loss. She was found to be deficient in iron, folic acid, and vitamin B12 and was started on replacement treatment. A barium meal and enema were normal and antiparietal cell antibodies negative. In 1997 she fell, fracturing her right proximal ulna and distal humerus. In April 1999 she developed intermittent diarrhoea and lost further weight. There was no rectal bleeding. A sigmoidoscopy, rectal biopsy, and computed tomography pneumocolon were all normal. In September she was referred to the rheumatology outpatient department with a three month history of painful swollen ankles, chest pains, and generalised weakness. Her bowel habit had returned to normal. She continued on folic acid 5 mg/day, hydroxycobalamin 1 mg/month, and ferrous sulphate 375 mg/day, and was taking diclofenac 25 mg twice a day for her pain.

On examination she was cachectic. She was not clinically anaemic and there was no lymphadenopathy. There was a 2 cm tender liver edge but the remainder of the abdominal examination was normal. Both ankles were swollen and tender (fig 1). There was a fixed flexion deformity and the right elbow and mild weakness of the proximal musculature. There was tenderness of the chest wall, but no muscle tenderness.

Initial investigations showed a haemoglobin of 124 g/l, mean corpuscular volume 92 fl, white cell count 10.4 × 10⁹/l, and platelets 558 × 10⁹/l. The erythrocyte sedimentation rate was 30 mm/hour and C reactive protein 1 mg/l. The red cell folate was low at 92 µg/l (normal range 150–700) with a normal vitamin B12 of 254 ng/l (160–800). Iron studies were normal, as were the serum electrolytes. The adjusted calcium was 1.51 mmol/l (2.15–2.65) with an albumin of 34 g/l (33–47), phosphate 1.2 mmol/l (0.8–1.4) and alkaline phosphatase of 323 U/l (30–130). Her liver function tests, immunoglobulins, and creatine kinase were all normal. Radiographs of both ankles are shown in fig 2. An ultrasound revealed a liver normal in appearance, extending below the costal margin. Dual energy x ray absorptiometry confirmed severe osteoporosis with a T score at the hip of −3.74 and at the lumbar spine of −5.64.

Questions
(1) What is the most likely diagnosis?
(2) What would be the most useful diagnostic test to confirm this?
(3) What is the likely cause of the ankle arthropathy?
(4) Which other arthritides particularly affect the ankle joint?
Answers

Q1: What is the most likely diagnosis?
The most likely diagnosis is coeliac disease leading to osteomalacia and osteoporosis. This patient had a serum vitamin D of 7 nmol/l (15–100). There was secondary hyperparathyroidism with a serum intact parathyroid hormone of 25.69 pmol/l (1.05–5.26). She was treated with a single dose of calciferol 300 000U intramuscularly, together with calcium carbonate 1 g/day and oral cholecalciferol 800 U/day. Her chest wall pain settled rapidly and marked improvement in objective proximal muscle power was seen.

Q2: What would be the most useful diagnostic test to confirm this?
The most useful diagnostic test would be duodenal or jejunal biopsy. The biopsy showed total villous atrophy, crypt hyperplasia, and an intraepithelial infiltrate of lymphocytes (fig 3). Her antigliadin antibodies were strongly positive (IgA 81 reference units (RU)/l, normal <25; IgG 200 RU/l, normal <25), although her antienteromysial antibodies were negative.

Q3: What is the likely cause of the ankle arthropathy?
The most likely cause is coeliac associated oligoarthritis. Ankle radiographs showed osteopenia only. The patient was started on a gluten-free diet and her ankle pain and swelling settled after two months. Her serum calcium, vitamin D, and red cell folate are all now within the normal range and the titres of the antigliadin antibodies have fallen, suggesting compliance with the diet. She has gained some weight. No other joints have become painful.

Q4: Which other arthritides particularly affect the ankle joint?
Arthritides with a predilection for the ankle include sarcoidosis, rheumatoid arthritis, juvenile chronic arthritis (both pauciarticular onset and systemic onset disease), and gout (box 1).

Box 1: Arthritides commonly affecting the ankle
- Erythema nodosum.
- Sarcoidosis.
- Gout.
- Rheumatoid arthritis.
- Juvenile chronic arthritis.
- Arthritis associated with inflammatory bowel disease.
- Septic arthritis.
- Secondary osteoarthritis.

Discussion
Coeliac disease has an incidence in England of about 1:1500.1 This appears to be increasing with a shift toward an older age at diagnosis. In adults women are affected twice as frequently as men and tend to present a decade earlier, with a peak incidence in the fourth and fifth decades. Presentation beyond the age of 70 is rare. Gastrointestinal symptoms usually dominate the clinical picture, but up to 50% of adults have a normal bowel habit at diagnosis. As many as 20% of adults with coeliac disease may present with one of its musculoskeletal complications (box 2), the most common being metabolic bone disease.2 Generalised arthralgia is another common feature, and this may be present for several years before the diagnosis is made.3 Fatigue and muscle weakness may be profound, due in part to hypokalaemia seen in patients with chronic diarrhoea. Clubbing is seen in 15% of untreated patients, but it is not usually associated with the underlying risk of T cell lymphoma.

A metabolic osteopathy may be the only feature in some patients with coeliac disease. Bony pain and tenderness (particularly of the ribs, lumbar spine and pelvis) is the most common clinical manifestation.4 A proximal myopathy typical of osteomalacia may also be seen, but pathological fracture is uncommon. In a study of 17 adult patients with untreated coeliac disease, 16 had a bone mineral density in the osteoporotic range.5 The osteopathy is thought to develop as a result of defective calcium transport by the diseased small intestine and impaired vitamin D absorption. Binding of intraluminal calcium and magnesium to unsub sorbed dietary fatty acids may also contribute and as a result of these processes secondary hyperparathyroidism may develop, leading to...
Self assessment questions

The arthritis of coeliac disease is usually non-erosive and self-limiting, but progressive erosive disease can occur. In a case similar to ours, a 42 year old woman presented with a one year history of ankle pain and was found to be anaemic with a low serum iron, vitamin B12, and folate. Osteopenia and soft tissue swelling were seen on the initial radiographs but she later developed erosions in the tarsus that progressed despite a gluten-free diet. In a larger case-controlled study of 200 patients with established coeliac disease, arthritis was found in 26%. Of these 36% had a recurrent asymmetrical oligoarthritis affecting mainly the shoulders, elbows, knees and ankles, while sacroiliitis was found in 29% (80% unilateral), demonstrating some similarity to other enteropathies. Some autoimmune rheumatic conditions also appear to be associated with coeliac disease, the most common being primary Sjogren’s syndrome.

Learning points

- Coeliac disease in adults may present with a musculoskeletal complication in up to 20% of cases.
- Coeliac disease may rarely cause an oligoarthritis affecting larger joints that usually responds to a gluten-free diet.
- Adult patients with coeliac disease may have a normal bowel habit.
- Though rare, coeliac disease can present in the elderly, an underlying malignancy being the most likely differential diagnosis.
- Coeliac disease is a cause of an unexplained anaemia with multiple deficiencies. The serum folate is a sensitive screening test.

Final diagnosis

Coeliac disease complicated by osteomalacia, osteoporosis, and oligoarthritis.


www.postgradmedj.com
A reversible cause of acute renal failure

S Mehandru, A Goel

A 63 year old homeless man presented to the Bellevue Hospital Center in New York with a one month history of cough with expectoration, fever, and weight loss. One week before presentation, the patient had also developed haemoptysis. Chest radiography demonstrated extensive right upper lobe cavitation and near total destruction of the left upper lobe parenchyma. The patient’s sputum was teeming with acid fast bacilli (AFB). He was started on rifampicin 450 mg each day, isoniazid 300 mg each day, pyrizinamide 750 mg twice a day, and ethambutol 800 mg each day in consistence with the diagnosis of extensive pulmonary tuberculosis. He tested HIV negative. The laboratory results were significant for a haemoglobin of 98 g/l and an erythrocyte sedimentation rate (ESR) of 58 mm/hour. All the other results including the liver and kidney function tests were normal on admission.

The patient was kept in respiratory isolation in hospital for about four weeks as he remained AFB positive. About three weeks after admission, he began to develop a progressive deterioration of his renal function. His serum creatinine rose from 61.88 µmol/l on admission to 362.44 µmol/l and the blood urea nitrogen rose from 2.85 mmol/l to 15.31 mmol/l. The patient remained non-oliguric. His urine examination was significant for 0.3 g/l of protein with a total excretion of 1g of protein/day, there were 10–15 red blood cells/HPF and 50–60 white blood cells/HPF with 8–10 white blood cell casts. Other laboratory values were significant for an ESR of 80 mm/hour and 14% eosinophils in the peripheral blood. The antitubercular medications were discontinued, however, the deterioration in renal function continued and the creatinine concentrations reached 795.6 µmol/l. The patient was dialysed at this point.

With no further improvement in the renal function, a kidney biopsy was performed. Based on the results, the patient was started on prednisone 60 mg each day. Modified antitubercular treatment was reinstated in the form of isoniazid 300 mg each day, ciprofloxacin 750 mg twice a day, and pyrizinamide 750 mg twice a day. Within the next two weeks, the renal function started improving. Over the next three weeks, prednisone was tapered. The renal function continued to improve and returned to baseline subsequently.

Questions

(1) What are the findings on the kidney biopsy?
(2) What is the diagnosis?
(3) What are the common aetiological factors responsible for this condition?

Answers

Q1: What are the findings on the kidney biopsy?

The given biopsy slides show an interstitial, predominantly mononuclear inflammatory infiltrate comprised mainly of lymphocytes and plasma cells and areas of tubular invasion by the lymphocytes denoting tubulitis (fig 1). A few eosinophilic leucocytes are also present in the interstitium (fig 2). Of significance is the marked interstitial oedema (fig 3). In addition, there were areas of tubular invasion by the lymphocytes denoting tubulitis (fig 1). The glomerulus appears to be normal (fig 4).
Q2: What is the diagnosis?
The diagnosis is acute interstitial nephritis (AIN). The likely aetiological factor is the antitubercular drug therapy, the most probable cause being rifampicin.

Q3: What are the common aetiological factors responsible for this condition?
The causes of AIN can be classified into five general categories: drug hypersensitivity reactions, infections, immune mediated diseases, glomerular diseases, and idiopathic. Drug hypersensitivity has become the most common aetiological factor responsible for the condition. Other classes include non-steroidal anti-inflammatory agents (NSAIDs); antibiotics such as β-lactams, sulphonamides, tetracycline, vancomycin, indinavir, interferon α, and rifampicin. Rifampicin has been implicated as a cause particularly when it is taken discontinuously. Some of the many other drugs implicated in causing AIN are diuretics, phenytoin, cimetidine, allopurinol, and aspirin. Infections are becoming less common a cause of AIN, particularly in areas where there is ready access to antibiotics. The reported causative agents include bacteria such as streptococci and staphylococci; viruses such as cytomegalovirus, Epstein-Barr virus and HIV; toxoplasma, mycoplasma; rickettsiae; leishmaniae and spirochaetes such as leptospira and Treponema pallidum. AIN can also occur with the autoimmune diseases such as systemic lupus erythematosus, Sjogren’s syndrome, essential cryoglobulinemia, and primary biliary cirrhosis. The various glomerulonephrites can have interstitial nephritis as the accompanying component. AIN can also be idiopathic, for example, as a defining entity of the tubulointerstitial nephritis-uveitis syndrome.

Discussion
AIN is becoming an important cause of acute but reversible renal failure. Drug hypersensitivity, as discussed above, has become the most common aetiological factor responsible for the condition. The typical presentation of AIN is that of abrupt onset of renal dysfunction in a hospitalised patient with progressive rise of the serum creatinine. The triad of a rash, fever and eosinophyluria, though classical, may be found in only about 30% of the cases, more commonly so with the drug hypersensitivity reactions. Renal biopsy remains the “gold standard” for establishing the diagnosis. It should be considered if the serum creatinine continues to rise even after discontinuation of the offending drugs and immunosuppressive therapy is contemplated, or if a drug critical to the patient’s treatment is suspected to be the cause of AIN. The urine analysis in AIN typically displays leukocytes, leucocyte casts, and occasionally red blood cells. Red blood cell casts are found very rarely. Eosinophiluria detectable by the Wright’s stain or Hansel’s stain was considered to be diagnostic for AIN, but it is increasingly falling out of favour in establishing the diagnosis not only because the stains may not be readily available but also because the finding may have a sensitivity of about 40% and a specificity of about 72% only. Proteinuria in AIN is typically less than 1 g/day, the urine output is usually maintained and there may be isosthenuria. Light microscopy usually shows an inflammatory cell infiltrate along with interstitial oedema. Plasma cells or eosinophils may be seen in the interstitium. Among the lymphocytes, the CD4+ cells predominante. Granulomas can be seen, particularly with the drug hypersensitivity reactions. In NSAID induced AIN, the changes may resemble those seen in minimal change disease with the effacement of the epithelial foot processes on electron microscopy. The mainstay of treatment is supportive and withdrawal of the offending drug. Early diagnosis and discontinuation of the drug are critical in the recovery of the renal function. In cases where the drug withdrawal does not lead to a recovery of the renal function, pharmacotherapy must be considered. Prednisolone is the most commonly prescribed drug, in a dose of 1 mg/kg/day, given orally. Adjunct therapy with cyclophosphamide has been considered if trials of steroid therapy yield a poor response; there is however, little clinical
evidence to support the efficacy of cyclophosphamide in this disorder and the drug is probably required only very rarely. Plasmapheresis may be considered in addition to prednisolone and cyclophosphamide in the very rare patient in whom the interstitial nephritis is demonstrated to be due to antitubular basement antibodies, as suggested by the linear deposition of IgG along the tubular basement membranes on immunofluorescent microscopy. However, again there is no proof that this modality is effective in the treatment of acute interstitial nephritis. Immunosuppressive therapy is unlikely to be effective in patients who have pre-existing advanced chronic renal disease on their renal biopsy and little evidence of acute inflammation and should be withheld in these cases.

AIN thus remains an important cause of potentially reversible renal failure that needs a high index of suspicion for the diagnosis and an early withdrawal of the offending drug for recovery of renal function.

Final diagnosis
Acute interstitial nephritis.