LEsson of the month

Recurrent fevers in the presence of multiple autoimmune diseases and antibody deficiency

E Drewe, A P Huissoon, M J Thomas, P C Lanyon, R J Powell

CASE HISTORY

A 37 year old white South African woman presented with a two week history of fevers, rigors, and watery diarrhoea up to six times a day.

She had a complex past medical history, developing insulin dependent diabetes mellitus aged 2 years and hypothyroidism aged 11 years. At 13 years she was diagnosed with idiopathic thrombocytopenic purpura (ITP) and two years later underwent splenectomy, with a partial response. At 25 years, she developed haemolytic anaemia. Initial treatment with azathioprine was withdrawn owing to thrombocytopenia and she was subsequently treated for three years with oral cyclophosphamide. On moving to the United Kingdom, treatment was changed to a combination of danazol, hydroxychloroquine, and 10–30 mg oral prednisolone a day.

At the age of 33 she was diagnosed with primary antibody deficiency on the basis of recurrent pneumonia, autoimmune disease, borderline low and falling total IgG, low IgG2 subclass, and failure to produce a specific IgG response to tetanus and pneumovax immunisations. Intravenous immunoglobulin replacement treatment was started.

In the six years before the above presentation she had also described intermittent watery diarrhoea, controlled with loperamide and on several occasions remitted when the steroid dose for ITP was increased. Stool culture and parasitology, abdominal ultrasound scan, gastroscopy and duodenal biopsy, flexible sigmoidoscopy, barium meal and follow through, and barium enema were all normal. Biopsies of the rectum and sigmoid colon showed a chronic inflammatory cell infiltrate compatible with immunodeficiency.

Other problems included hypoadrenalism attributed to either prolonged steroid use or autoimmune disease, and premature ovarian failure. She also had an autonomic neuropathy presumed to be secondary to her diabetes. At age 33 her ITP became more problematic and although treatment with cyclosporin and, subsequently, tacrolimus resulted in improvement, these agents were withdrawn owing to uncontrolled hypertension.

Shortly before her above presentation she had visited South Africa and returned with a penicillin resistant Streptococcus pneumonia, controlled with ciprofloxacin after the growth of Morganella morgani. Her fevers and rigors, however, persisted with increasing jaundice and the emergence of right upper quadrant pain. Liver function tests deteriorated with bilirubin 44 μmol/l, alkaline phosphatase 983 U/l, alanine aminotransferase 144 U/l, γ-glutamyltransferase 868 U/l. Treatment with gentamicin and metronidazole was started for presumed intra-abdominal sepsis. A subsequent abdominal computed tomography scan showed free focal fluid and a shrunken gall bladder compatible with cholecystitis. Endoscopic retrograde cholangiopancreatography was normal except for gall bladder stones.

One month after presentation her condition settled while receiving ciprofloxacin, and her liver function tests improved. Several months later elective cholecystectomy with open liver and lymph node biopsy were performed without complication. Biliary histology showed an inflammatory infiltrate and necrosis of the cystic artery suggestive of polyarteritis nodosa (PAN) (fig 1). A coeliac arteriogram subsequently confirmed microaneurysms of the liver, pancreas, and kidney (fig 2). Granulomatous hepatitis was present on liver biopsy with no specific changes in the lymph nodes. Microbiology tests of lymph node, bile, and gall bladder were all negative, including studies for tuberculosis and cryptosporidium.

The patient was treated with 500–1000 mg pulses of intravenous cyclophosphamide for one year with methylprednisolone initially. Complications included co-trimoxazole hypersensitivity rash (PCP prophylaxis) and one episode of pneumonia. No fevers or jaundice have recurred, and liver function tests remain improved, with IgM in the normal range. A repeat angiogram has shown some disease regression, although tiny microaneurysms persist in the liver and kidney. The condition of the patient is now maintained with azathioprine.

DISCUSSION

The patient has a diagnosis of classical PAN demonstrated by the presence of fibrinoid necrosis of the cystic artery and the absence of glomerulonephritis or vasculitis in arterioles, capillaries, and venules (Chapel Hill Consensus Conference definition). Healing of damaged elastic lamina may produce aneurysms giving rise to “nodosa” as seen by angiography in this case. Although gastrointestinal symptoms—for example, abdominal pain, are common in PAN, cholecystitis represents a rare but recognised presentation. Other rare cases have been reported of diagnosis of PAN by cholecystectomy. These

Abbreviations: ITP, idiopathic thrombocytopenic purpura; PAN, polyarteritis nodosa

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primary antibody deficiency requires careful exclusion of secondary causes, and a definite answer may not result.

THE LESSONS
- Further evaluation of the history of steroid responsive diarrhoea might have led to an earlier diagnosis.
- The presence of multiple conditions does not exclude additional further significant diseases.
- A diagnosis of primary antibody deficiency requires careful exclusion of secondary causes, but a definite answer may not result.

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