LESSON OF THE MONTH

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

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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 Initial treatment with azathioprine was withdrawn owing to thrombocytopenia and she was subsequently treated for three years with oral cyclophosphamide.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 35 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and although treatment with cyclosporin and, subsequently, tacrolimus resulted in improvement, these agents were withdrawn owing to uncontrolled hypertension.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 pneumoniae* pneumonia that responded to intravenous cefuroxime.

At presentation, clinical examination showed a small unwell woman with mild icterus. She had fever of 39°C, tachycardia, normal blood pressure but an ejection systolic murmur. Bilateral coarse crepitations were audible in the chest. Liver was palpable 4 cm below the costal margin and a splenectomy scar was notable.

Laboratory investigations disclosed haemoglobin 109 g/l, leucocyte count $11.1 \times 10^9/l$, platelets $253 \times 10^9/l$, erythrocyte sedimentation rate 26 mm/1st h, and C reactive protein 129 mg/l, renal function normal but liver function mildly deranged. There was a polyclonal increase in IgM of 8.8 g/l with normal IgA and preinfusion IgG. A chest radiograph suggested mild bronchiectasis. Gram negative *Morganella mor-*

ganni was grown in one of six blood culture bottles. A transthoracic echocardiogram was normal. Abdominal ultrasound showed mild thickening of the gall bladder wall, with tiny stones, an enlarged liver, and minimal pelvic ascites.

Initial treatment with broad spectrum antibiotics was changed to ciprofloxacin after the growth of *Morganella morganii*. Her fevers and rigors, however, persisted with increasing jaundice and the emergence of right upper quadrant pain. Liver function tests deteriorated with bilirubin 44 $\mu\text{mol/l}$, 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).¹ 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.² Other rare cases have been reported of diagnosis of PAN by cholecystectomy. These

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

Figure 1 Cystic artery showing fibrinoid necrosis.

Figure 2 Coeliac arteriogram demonstrating multiple small aneurysms.

include suspected diagnoses of cholelithiasis and an eight year old girl with familial Mediterranean fever and right upper quadrant pain.^{2,3} Other unusual gastrointestinal manifestations of PAN include spontaneous intracholecystic haemorrhage and pancreatitis.^{4,5}

The aetiology of PAN is unclear, although streptococcal infections, as in this case, may precede disease onset or relapse.^{6,7} The timing of onset of PAN in this case is difficult to establish. In view of the history of diarrhoea in response to steroids, immunosuppressant treatment might have partially suppressed PAN before this presentation.

Untreated PAN has a poor prognosis with five year survival of <12%.^{8,9} Our patient appears to have responded clinically to cyclophosphamide as shown by the resolution of fevers and biliary disease. Dramatic regression of aneurysms with cyclophosphamide has been reported, and partial improvement was seen in this case.^{10,11}

This patient also has evidence of a humoral immunodeficiency as illustrated by IgG and IgG2 levels and failure to respond to certain vaccines. Primary antibody deficiency encompasses clinical and immunological heterogeneity and is characterised by recurrent bacterial infections, particularly of the respiratory and gastrointestinal tract. Treatment with intravenous immunoglobulin prevents long term complications—for example, bronchiectasis.¹² Our patient

shows many typical features of primary antibody deficiency, including age at diagnosis (mean 33 years for women), associated autoimmune features preceding onset of recurrent infection, and clinical presentation with pneumonia.¹³ ITP and haemolytic anaemia have been reported in 6% and 5% of patients, respectively, with common variable immunodeficiency.¹³ The diagnosis of primary antibody deficiency, however, requires exclusion of secondary causes, which in this case include gastrointestinal protein loss and drugs. Patients with gastrointestinal protein loss would typically have intact vaccine specific responses. There are no records available of immunoglobulin levels during the initial course of cyclophosphamide or azathioprine treatment, making exclusion of cytotoxic induced hypogammaglobulinaemia problematic. The coexistence of antibody deficiency and PAN appears to be previously unrecognised.

In summary we have described an unusual presentation of classical PAN where the diagnosis became apparent after cholecystectomy. Hypogammaglobulinaemic patients are both susceptible to streptococcal infections and to inadvertent transmission of viruses by immunoglobulin infusion. However, coexistence of antibody deficiency and PAN appears not to have been recognised previously.

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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