CASE REPORT

Pure white cell aplasia: report of first case associated with autoimmune hepatitis

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ABSTRACT

Pure white cell aplasia (PWCA) is a rare, immune-mediated condition that causes a profound inhibition of myelopoiesis. It has been seen in association with other autoimmune conditions, thymomas, chronic lymphocytic leukaemia and as an adverse drug reaction. We report what we believe to be the first case of PWCA associated with autoimmune hepatitis. An 18-year-old woman presented with jaundice and was found to be suffering from acute hepatitis. Later she became neutropenic and lymphopenic. Liver biopsy was indicative of autoimmune hepatitis. This was later confirmed by autoantibody results. Bone marrow aspirate found an absence of all myeloid progenitor cells, highly suggestive of PWCA. The low white cell count only improved after immunosuppression with corticosteroids. Her condition remains stable 1 year later with azathioprine therapy.

CASE

An 18-year-old woman presented to the general surgeons in early May 2012. She gave a history of 2 weeks of general malaise followed by 1 week worsening jaundice associated with dark urine and pale stools, and 3 days of right upper quadrant pain. She had had no fevers, night sweats or rigours. She had no significant past medical history. She had self harmed 2 years prior by cutting herself with a knife but had no other risk factors for bloodborne viruses. There was no history of foreign travel. She was on no regular medications. She had no family history of liver disorders.

On examination she was clinically jaundiced and with epigastric tenderness on deep palpation. Examination was otherwise unremarkable.

Admission blood showed a bilirubin of 144 $\mu\text{mol/L}$ (normal range 3–17 $\mu\text{mol/L}$) alongside a markedly raised transaminase, with an alanine transaminase (ALT) of 2823 iu/L (normal range 5–35 iu/L). International normalized ratio (INR) was 1.0 (normal range 0.9–1.2) with an activated partial thromboplastin ratio (APTR) of 1.12. Coagulation was to remain normal throughout the episode. Viral serology and autoimmune liver screen were taken along with serum antibody levels and iron studies. An abdominal ultrasound scan reported mild intrahepatic duct dilatation and a dilated gall bladder. Magnetic resonance cholangiopancreatography (MRCP) was subsequently performed which showed a normal biliary tree and an oedematous gall bladder.

She was referred to our gastroenterology department and she was discharged after 3 days with a probable diagnosis of acute viral hepatitis, with a plan to perform twice weekly blood tests and regular outpatient follow-up.

For the next 4 weeks her ALT steadily declined but bilirubin continued to rise. Her symptoms remained. In early June 2012 it was noticed that her white cell count (WCC) had fallen to a level of 1.9×10^9 (normal range $4.0\text{--}11.0 \times 10^9$). Blood test in the next week showed that her WCC was 0.9×10^9 , with a neutrophil count of 0.00×10^9 (normal range $2.0\text{--}7.5 \times 10^9$) and lymphocyte count of 0.7×10^9 (normal range $1.3\text{--}3.5 \times 10^9$). Bilirubin at this time had risen to 322 $\mu\text{mol/L}$ and ALT had declined to 487 iu/L. See table 1. She was therefore immediately admitted and placed in isolation.

By this time some of the initial investigations had returned. Hepatitis and HIV

CrossMark

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Table 1 Summary of haematological and biochemical results on day 1 of both admissions

Date	12/5/2012 Initial presentation	12/6/2012 On second admission
Hb (12.5–16.5)	14.2	12.8
WCC (4.0–11.0)	5.4	0.9
Neutrophils (2–7.5)	3.4	0.00
Lymphocytes (1.5–4.0)		0.9
Platelets (150–450)	283	445
INR (0.9–1.2)	1.0	1.0
Bilirubin (3–22)	144	322
ALP (30–126)	134	77
ALT (9–52)	2823	497

ALT, alanine transaminase; ALP, alkaline phosphatase; Hb, haemoglobin; INR, international normalized ratio; WCC, white cell count.

viral serology was negative. Iron studies were unremarkable. Serum immunoglobulin levels found a raised IgG level of 19.8 g/L (normal range 6.0–16 g/L) and a raised IgA level of 3.6 g/L (normal range 0.8–2.8 g/L). The autoimmune screen was still pending at that time. A bone marrow aspirate was taken on the next day of admission. On microscopy a near total absence of myelocyte progenitor cells was discovered but plentiful megakaryocyte and erythrocyte precursors were seen, indicating pure white cell aplasia (PWCA) (see figure 1). Subsequent analysis of the patient's serum revealed no granulocyte specific IgG or antilymphocyte antibodies indicating that humoral autoimmune processes were not responsible for the patient's neutropenia. The patient was started on granulocyte colony stimulating factor (G-CSF) at a dose of 300 mg on day 3 with no effect on the WCC. On day 4 of this admission she became pyrexial, so antibiotic therapy of piperacillin-tazobactam and gentamicin was started to good clinical effect. No organisms grew from blood and urine cultures taken at this time.

A liver biopsy was arranged and performed on day 7. The biopsy was reported to show a plasma cell

Figure 1 Bone marrow aspirate: Normal erythrocyte and megakaryocyte progenitors but an absence of myelocyte precursors.

infiltration of the periportal areas with no copper, iron or fat deposition. There was some evidence of previous inflammation but no fibrosis was seen. The overall histological picture was of drug induced or autoimmune hepatitis (AIH) (see figure 2) but as stated before the patient had taken no drugs prior to admission so the former differential was discounted.

Intravenous methylprednisolone at a dose of 250 mg was not started until after the biopsy so as to not obscure the histological diagnosis. This resulted in an immediate rise in the WCC (see figure 3). G-CSF was stopped on day 7. After 3 days intravenous methylprednisolone was converted to 30 mg oral prednisolone.

Steroid therapy, aside from causing some hallucinatory side effects, resulted in a resolution of symptoms. She was discharged in early July 2012 on prednisolone 10 mg once daily and azathioprine 100 mg once daily. In mid-July 2012 she was reported to be anti-smooth muscle antibodies (SMA) positive (1:320) and antinuclear antibodies (ANA) and anti-liver/anti-kidney microsome antibody negative. Perinuclear anti-nuclear cytoplasmic antibodies (p-ANCA) taken at the same time was positive (1:640). Repeat ANA test was done in late November 2012 and found to be positive. (1:640) giving an aggregate diagnostic score of 22, and therefore a definite diagnosis of AIH type 1.

Due to persistent headaches an magnetic resonance imaging (MRI) was performed on 28 June 2012 which showed a small area of demyelination in the pons. Lumbar puncture was performed on 26 February 2012 which had a mildly elevated opening pressure of 27 mmH₂O and normal cell counts, biochemistry and was negative for oligoclonal bands.

The patient became briefly neutropenic on 20 July 2012 after regular prednisolone was weaned completely. The neutropenia resolved with the reinitiation of corticosteroids. No G-CSF was administered. The dose of azathioprine was also increased given after levels were 6-thioguanine nucleotide levels were found to be low (see figure 4). She remains stable on regular azathioprine alone 1 year later with no evidence of ongoing hepatitis or leucopenia.

DISCUSSION

AIH is an idiopathic chronic hepatitis that predominantly affects women. It is diagnosed by history characteristic findings in liver function tests (LFTs) raised immunoglobulins (especially IgG), a variety of auto-antibodies (particularly ANA and anti-SMA) and via liver histology. A well-validated scoring system produced by the AIH group is used in its diagnosis. Our patient scored 22, well over the 15 required for a definite pretreatment diagnosis.¹ Type 1 AIH differs from type 2 AIH that it typically affects women in early adulthood, is positive for anti-ANA and anti-SMA but not antiliver/antikidney microsome antibody type 1 which is specific for AIH type 2.¹ The principle

Figure 2 Liver biopsy: Left: Portal tract showing infiltrate of inflammatory cells with some periportal extension. Right: High power view of portal tract showing that the inflammatory cells were predominantly plasma cells.

treatment is immunosuppression typically using corticosteroids in the acute phase and then longer-term agents such as azathioprine or mercaptopurine. Considerable overlap exists between AIH and other putative autoimmune hepatobiliary conditions such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis.²

PWCA is a rare immune-mediated inhibition of granulopoiesis with normal maturation of erythrocyte and megakaryocyte cell lineages.³ The exact pathological mechanism of pure white cell aplasia unclear. Evidence from a limited number of cases has suggested that specific auto-antibody inhibition of receptors involved in myelocyte maturation play a key role.³ However complement⁴ and T-cell⁵ mediated inhibition have also been demonstrated. It has occurred in isolation;^{4, 7} as an adverse drug

reaction;^{5, 8–10} in association with thymomas^{11, 12} and chronic lymphocytic leukaemia,⁶ and other autoimmune conditions.¹³ As in this case, it commonly follows a relapsing and remitting course^{6, 13–15} and death from sepsis is frequently reported.^{4, 14} It should be noted, unlike our case, that the condition is largely been seen in older patients.^{4, 5, 6, 11, 14, 16} There has been one documented case of PBC and PWCA.¹⁶ This is to our knowledge the first documented case of AIH and PWCA.

Management of PWCA has been centred around the removal of offending agents such as medications or thymic masses and immunosuppression usually with steroids, but immunoglobulins,¹³ plasmapheresis,⁶ monoclonal antibodies⁵ and even bone marrow transplant¹⁴ have also been used. Interestingly G-CSF alone has been shown to be ineffective in its management. Only after immunosuppression, as in this case, do granulocyte populations recover.¹⁵ It should be noted that PWCA has a different pathological process to autoimmune neutropenia, which has also been seen in PBC, whereby mature neutrophils are destroyed by direct autoantibody attack.¹⁷

Figure 3 Clinical course of the patient from admission: G-CSF indicates period of granulocyte colony stimulating factor course, mPSL indicates when methylprednisolone was commenced. WCC, white cell count.

Figure 4 Clinical course of the patient showing steroid dependent relapsing and remitting leucopenia. mPSL indicates when methylprednisolone was commenced; WCC, white cell count.

PWCA is a rare condition but has now been seen in PBC and AIH. There has been a suggestion that AIH and PBC exist in spectrum with some overlap between the conditions. We suggest that in a patient presenting with either condition and an unexplained neutropenia, a diagnosis of PWCA should be considered.

Contributors TK: wrote and drafted the case report and discussion; DW: drafted the case report and discussion; PM: drafted the case report and offered guidance on gastroenterological content; RG: drafted the case report, reported bone marrow aspirate and offered guidance on haematological content; SM: reported liver biopsy.

Competing interests None.

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