CASE REPORT

Granulomatosis with polyangiitis: an unusual cause of acute liver injury

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SUMMARY

Granulomatosis with polyangiitis (GPA) causing liver injury is rare. Where liver biopsies have been taken findings are not always typical and diagnosis can be challenging. Here, we present a case of a 58-year-old male who on admission to hospital was found to have acute liver injury. Diagnosis of liver involvement in GPA is supported by liver histology and the resolution of hepatitis after commencement of immunosuppressive treatment.

BACKGROUND

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA are small vessel vasculitic syndromes collectively known as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV).¹ AAVs are considered rare diseases with a reported incidence of 10–20 cases per million per year.² GPA (formerly known as Wegener's granulomatosis) is characterised by necrotising granulomatosis of the upper and lower respiratory tract and by glomerulonephritis; however, it can, in principle, affect any organ. Over the last two decades, improvement in the mortality of GPA has been seen with increasing physician awareness and improvements in management.^{3–4} In addition to the use of corticosteroids and cyclophosphamide, rituximab, both in inducing remission and as a maintenance treatment, has become a promising therapeutic agent for GPA.⁵ Despite this, mortality from GPA is four times higher than the background population, and early death is associated with active disease and infection.⁶

The importance of making an accurate, early diagnosis is crucial in GPA. The gastrointestinal tract has been reported to be involved in 5%–11% of cases,⁷ with the spectrum of symptoms wide from asymptomatic acute liver injury to bowel infarction. In such cases, where the disease presents atypically, GPA can be a diagnostic challenge.

CASE PRESENTATION

A 58-year-old Caucasian male presented to hospital with several weeks' history of increasing breathlessness. The patient had been under follow-up for the previous 18 months in the rheumatology clinic following a diagnosis of seronegative polyarthritis (rheumatoid factor negative, extractable nuclear antibody ELISA screen negative and antinuclear antibody positive to titre 1:160 speckled pattern) and treated with hydroxychloroquine and

methotrexate. During this period, he developed microscopic haematuria and was investigated with a cystoscopy that showed no pathology. He was found to have normocytic normochromic anaemia; a gastroscopy was undertaken and was normal. Three months prior to admission, the patient developed rhinitis, epistaxis and hearing loss.

On admission to hospital, the patient was found to have digital infarcts bilaterally; his examination was otherwise unremarkable with a normal respiratory examination. Investigations revealed acute liver injury (alkaline phosphatase (ALP): 531 U/L, alanine aminotransferase (ALT): 39 U/L, bilirubin: 8 µmol/L) and renal impairment (138 µmol/L) (figure 1), with further blood results documented in table 1. A chest X-ray was initially performed that showed no nodules, infiltrates or cavities, followed by a CT thorax, abdomen and pelvis that showed no focal lung lesion or lymphadenopathy. An ultrasound scan showed a normal liver and spleen.

A viral and autoimmune liver screen was negative (table 1), and a liver biopsy was performed. On H&E staining, the biopsy showed mild and patchy lymphocytic infiltration into the portal tract, no interface hepatitis, clusters of neutrophils within the sinusoids forming microabscesses (figure 2A), plasma cells and occasional blast like cells suggesting a degree of extramedullary haematopoiesis and possible haemophagocytosis (figure 2B). Interestingly, on admission the patient was found to have thrombocytopaenia ($75 \times 10^9/L$) and elevated ferritin (606 µg/L), supporting the finding of haemophagocytosis.

During the first week of admission, the patient's renal function continued to deteriorate, the creatinine reaching a peak of 204 µmol/L from a baseline of 80 µmol/L. ANCA was measure and was strongly proteinase 3 (PR3)-ANCA positive with an anti-PR3 titre of 152 U/mL, together with epistaxis, an abnormal urinary sediment of blood and protein and worsening acute kidney injury; the diagnosis of GPA was strongly suspected. A kidney biopsy was performed to confirm the diagnosis. On H&E staining, the biopsy showed 40% of glomeruli to have sharply defined segmental lesions, fibrinoid necrosis and extracapillary proliferation consistent with active segmental vasculitic lesions (figure 3). Immunoperoxidase showed no significant deposition for IgG, IgA, IgM or C9 in glomeruli. The features were consistent with acute vasculitic glomerulonephritis.

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Figure 1 Liver function tests over time. Day 0 is the day of admission, and day 12 is the day patient was given the first dose of methylprednisolone. ALP, alkaline phosphatase; CRP, C reactive protein.

OUTCOME AND FOLLOW-UP

The patient was pulsed with three doses of methylprednisolone from day 12 of admission and commenced on oral prednisolone. Due to the patient's significant liver impairment on initiation of treatment (ALP 1334 U/L, ALT 81 U/L, bilirubin 50 μmol/L), cyclophosphamide was avoided, and the patient was treated with rituximab. As seen on figure 1 following immunosuppression, the patient's liver function tests returned to normal, and creatinine improved to 117 μmol/L. The thrombocytopaenia also resolved, with platelets returning to $198 \times 10^9/L$, and ferritin returned to the normal range. Sustained resolution of the acute liver injury on immunosuppression supported secondary liver involvement from vasculitis. A primary liver inflammatory disease was very unlikely. The serology was negative for autoimmune hepatitis and primary biliary cholangitis, and the liver biopsy did not show evidence for these diseases. Ultrasound scan of the biliary tree showed no evidence of primary sclerosing cholangitis and again no evidence was seen on biopsy. The patient was discharged 20 days after admission, and he remains well and under active outpatient follow-up.

Table 1 Blood results on admission

White cell count	$4.8 \times 10^9/L$	Anti-PR3	152.0 U/mL (normal, 0.0–0.2 U/mL)
Haemoglobin	96 g/L	Anti-MPO	<0.2 U/mL (normal, 0.0–3.6 U/mL)
Platelet count	$75 \times 10^9/L$	Anti-GBM	1.7 U/mL (normal, 0.0–7.0 U/mL)
Creatinine	138 μmol/L	ANA	1:160
Ferritin	606 μg/L	HIV	Negative
Protein:creatinine ratio	116 mg/mmol	Hepatitis B antigen	Negative
Total protein	69 g/L	Hepatitis C antigen	Negative
Albumin	33 g/L	Antimitochondrial antibodies	Negative
APTT	46.5 s	Anti-LKM antibodies	Negative
Fibrinogen	5.6 g/L	Antismooth muscle antibodies	Negative
Prothrombin time	11.2 s	Antiparietal antibodies	Negative
Plasma viscosity	1.93 mPa		

APTT, activated partial thromboplastin time; PR3, proteinase 3; MPO, myeloperoxidase; GBM, glomerular basement membrane; ANA, antinuclear antibody; LKM, anti-liver-kidney microsomal antibody

Figure 2 (A) Liver biopsy showing hepatic sinusoids with neutrophilic infiltration and microabscess formation (arrows), H&E staining, 200× magnification. (B) Liver biopsy showing possible haemophagocytosis (arrow), H&E staining, 400× magnification.

DISCUSSION

In principle, GPA can affect any organ in the body; however, systematic review of the literature reveals liver involvement to be a rare finding.⁸ A systemic analysis by Willeke *et al*⁹ was conducted to explore the prevalence of liver involvement in AAV. Thirty-one per cent of a cohort of 67 patients with GPA presented with a rise in alkaline phosphatase (ALP), with a significant decrease ($P < 0.001$) seen on remission of the disease. By comparison, in a study by Pavone *et al*³ of 23 patients included with GPA, ALP was elevated in only 3% of patients at the time of diagnosis. This is in keeping with liver involvement in large vessel vasculitis where the biochemical picture is reported as a cholestatic pattern.^{8,9} However, it is not possible to determine whether either study truly reflect GPA manifesting itself in the liver, as the systemic inflammatory process caused by vasculitis could explain elevated ALP, a well-recognised acute phase reactant. Definitive evidence of GPA affecting the liver is made from histological analysis, the hallmark of which is microabscesses, granulomas and necrotising vasculitis.¹⁰ In the study by Pavone *et al*, no liver biopsies were reported; in the study by Willeke *et al*, liver biopsies were performed on eight patients, and granuloma like lesions were seen in only one patient; in the other biopsies, non-alcoholic steatohepatitis, drug toxicity and non-specific change were reported. Both Willeke and Pavone

Figure 3 Renal biopsy showing glomeruli with acute vasculitic changes (arrows), H&E staining, 400× magnification.

showed an increase in mortality in patients with liver injury at time of presentation.

In our case, the features on liver histology in keeping with vasculitis were microabscesses and possible haemophagocytosis. Haemophagocytosis is characterised as the activation of macrophages with phagocytosis within the reticuloendothelial system¹¹ and has been described in conditions where the immunity has been altered, such as in vasculitis.^{11 12} The focal nature of GPA, where active disease could be missed on biopsy, can make diagnosis difficult.^{13 14} More typically, as found by Willeke *et al*, liver histology is non-specific. In a case described by Goritsas *et al*¹⁵ of a 58-year-old man presenting with acute liver injury following a 9-month history of acute hearing loss, worsening cough and rhinitis, the liver biopsy revealed mild non-specific lobular hepatitis, and a pulmonary biopsy showed neutrophilic microabscesses and granulomas. As in our case, the diagnosis of GPA was made after a second organ was biopsied.

Drug therapy has been described as a cause of liver injury in vasculitis, either by the drug-inducing AAV, as with propylthiouracil,¹⁶ or through drug hepatotoxicity.¹⁷ Drug reaction was unlikely in our patient; he had taken methotrexate and hydroxychloroquine for more than 12 months prior to developing abnormal liver function tests, and initiation of treatment for vasculitis reversed hepatic injury.

Primary liver pathologies have also been reported in patients with vasculitis. Tovoli *et al*¹⁸ describe a patient diagnosed simultaneously with GPA and primary biliary sclerosis. Although it is difficult to completely exclude autoimmune liver disease once our patient had been treated for vasculitis, liver function tests have continued to remain normal over 1 year later on surveillance in outpatient clinic.

Learning points

- ▶ Liver involvement is a relatively late sign of untreated granulomatosis with polyangiitis (GPA) and as such a poor prognostic indicator.
- ▶ It is important to consider rarer, multisystem diseases when presented with a patient with non-drug and non-viral induced acute liver injury.
- ▶ Although microabscesses and haemophagocytosis on liver biopsy were suggestive of a vasculitic process, the diagnosis of GPA was confirmed by positive proteinase 3-antineutrophil cytoplasmic antibody and renal histology.

Contributors DOR conducted literature review and wrote case report. AG interpreted slides and provided images of slides. DAG supervised and edited case report.

Competing interests None declared.

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