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CASE REPORT

Liver transplantation for acute liver failure caused by macrophage activation syndrome

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Abstract

Macrophage activation syndrome (MAS) is a rare, potentially fatal condition, which most frequently complicates rheumatological conditions and is often associated with liver dysfunction. In this case report of a patient with MAS, acute liver failure developed despite conventional immunosuppressive therapy. Liver transplantation resulted in rapid recovery and the patient has remained well for six years. A recent diagnosis of Adult Onset Still's Disease (AOSD) provides additional supporting evidence that the initial presentation was caused by MAS. While transplantation in the context of systemic disease remains controversial, this first reported case of successful adult liver transplantation for acute liver failure caused by MAS raises an interesting clinical dilemma.

Introduction

Macrophage activation syndrome (MAS) is a rare, but potentially fatal acquired form of haemophagocytic lymphohistiocytosis (HLH). It can occur as a result of a variety of triggers, including autoimmunity, infection, drugs or malignancy and often results in hepatic dysfunction [1]. The mainstay of treatment is immunosuppression, but despite this it can be fatal with mortality rates estimated at 8–22% [2]. Here, we report the first adult case report of successful liver transplantation for acute liver failure caused by MAS.

Case report

A 26-year-old Asian male was admitted with pyrexia of unknown origin (PUO). He reported a 2-week history of malaise and a 5-day history of febrile illness. His past medical and family history were unremarkable and he was on no regular medication. Physical examination revealed jaundice and a rash. Routine laboratory investigations showed bilirubin 245 μmol/l, alanine aminotransferase (ALT) 1795 U/l, alkaline phosphatase (Alk P) 256 U/l, albumin 34 g/l, INR 1.7 and sodium 131 mmol/l. Full blood count (FBC) revealed neutrophilia (WBC 13.3 × 10^9/l, Neut 9.9 × 10^9/l, Lymph 1.4 × 10^9/l) with normal haemoglobin (140 g/l) and platelet count (200 × 10^9/l). C-reactive protein was elevated at 29 mg/l but erythrocyte sedimentation rate was normal at 6 mm/h. Ferritin was markedly elevated at 20 772 ng/ml but other iron studies were normal, including a transferrin saturation of 45%.

Repeated blood, urine and sputum samples were culture negative. Testing for malaria was negative and serology for HIV, herpes simplex, parvovirus B19, hepatitis A, B, C and

E, CMV, EBV and Toxoplasma were all negative. Immunoglobulins showed a polyclonal increase in IgA and IgM (4.84 and 2.32 g/l, respectively) with normal IgG (14.5 g/l). An extensive autoantibody screen was negative. Chest X-ray was clear and CT abdomen showed a thickened gallbladder wall, oedema around the hepatic and portal veins and lymphadenopathy at the portahepatis measuring up to 14 mm.

Initial management comprised empirical intravenous gentamicin, but despite this the patient had a nonremitting fever. His liver function continued to deteriorate (INR 2.0, albumin 24 g/l), he became cytopenic (Hb 70 g/l, Plts 41×10^9/l, WBC 3.9×10^9/l, Neut 3.1×10^9/l) and fibrinogen fell from 2.0 to 0.8 g/l. Bone marrow biopsy revealed enlargement of individual stromal macrophages containing phagocytosed debris within the cytoplasm, with no evidence of lymphoma. Transjugular liver biopsy showed an acute hepatitic process with confluent necrosis and marked lobular hepatocyte apoptosis. The combination of fever, cytopenia, hypofibrinogenaemia, marked hyperferritinaemia (peaking at 122 560 ng/ml) and bone marrow haemophagocytosis raised the clinical suspicion of MAS. Treatment with IV methylprednisolone was commenced 6 days after admission with intravenous pooled immunoglobulin G (IgG) added on day 10.

Despite treatment for a diagnosis of possible MAS, his liver function continued to deteriorate (Bil 420 μmol/l, INR 3.9, albumin 22g/l). On day 13, acute liver failure developed with grade 3 hepatic encephalopathy. At this point, the patient was registered for super-urgent liver transplantation. The following day, he underwent orthotopic liver transplantation, receiving a liver from a 44-year-old brain-stem dead donor. Explant liver histology showed areas of panacinar necrosis with accumulation of macrophages and increased numbers of lymphocytes in the parenchyma. There was distension of liver sinusoids by macrophages, which showed very strong membranous and cytoplasmic expression of CD163 (Fig. 1) on immunohistochemistry. CD68 expression was moderately strong in the activated macrophages.

Postoperatively he received cyclosporine, mycophenolate mofetil (MMF) and a reducing course of prednisolone for immunosuppression and was discharged home on day 28. Figure 2 illustrates the clinical course and shows that ferritin levels normalized by 50 days after transplantation.

During outpatient follow-up, he was maintained on cyclosporine and MMF immunosuppression and returned to full-time employment remaining well for six years. At this point, he was admitted with a week long history of headache and fevers following recent otitis media. A CT head was normal, multiple blood and urine cultures grew no pathogens and chest X-ray was normal. PCR testing of a throat swab for respiratory viruses was negative.

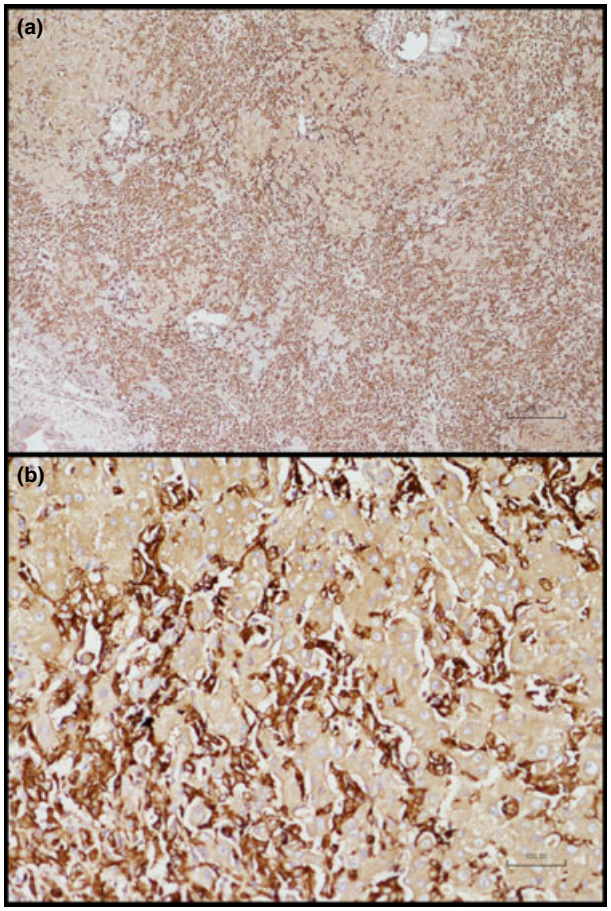

Figure 1 Immunohistochemical analysis of explant liver using the monoclonal antibody against CD163, a marker of macrophage activation. (a) Low power view (original magnification 40×) shows darker staining macrophages with loss of liver cells and confluent and panacinar necrosis. (b) High power view (original magnification 400×) shows intense membranous and cytoplasmic staining of macrophages within the sinusoidal spaces between preserved liver cell plates.

Graft function was normal on admission (Bil 18 μmol/l, ALT 26 U/l, Alk P 69 U/l, Alb 50 g/l, INR 1.0) but subsequently deteriorated (ALT peaked at 470 U/l) although synthetic function remained normal. He developed a pink transient fleeting rash, joint swelling and tenderness, and ferritin became markedly elevated at >16 500 ng/ml. Adult onset Still's disease (AOSD) was diagnosed following a rheumatology consultation. A percutaneous liver biopsy showed apoptotic liver cell loss and reactive Kupffer cells, interpreted as not representative of recurrent MAS. He was commenced on oral prednisolone and the interleukin-1 antagonist anakinra 11 days after admission resulting in an improvement of his rash and graft function. On outpatient follow-up, his symptoms resolved, and graft function and serum ferritin normalized. He remains well seven months later.

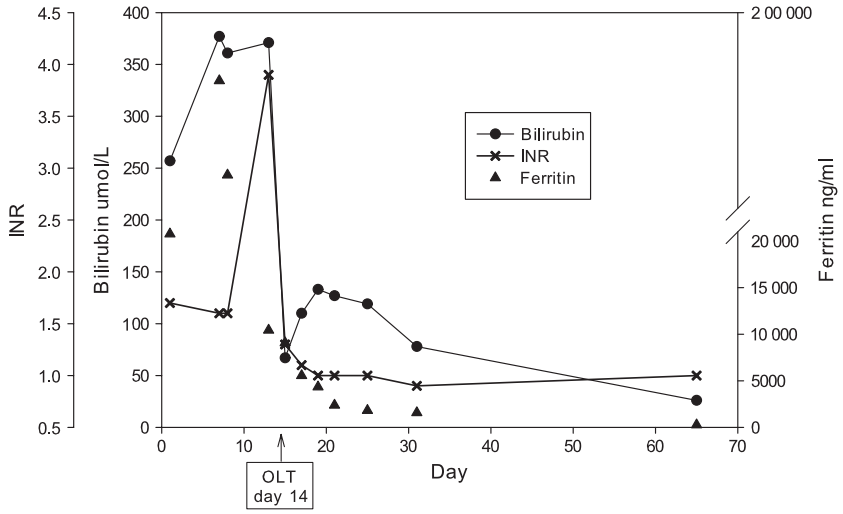

Figure 2 Clinical course of the initial presentation. Serum bilirubin (μmol/l, circles), ferritin (ng/ml, triangles) and INR (crosses) demonstrate progressive impairment of synthetic hepatic function and markedly elevated ferritin over the first 13 days of admission. Liver transplantation was performed on day 14 following which bilirubin, INR and ferritin normalized.

Discussion

To our knowledge, this is the first adult case report of successful liver transplantation to treat acute liver failure caused by MAS. As in our case, MAS is most commonly associated with autoimmune disease, particularly systemic juvenile idiopathic arthritis (sJIA) [3] and its adult equivalent, AOSD. The pathogenesis of MAS is incompletely understood, but it is thought that decreased natural killer (NK) cell and cytotoxic T-cell function results in increased proliferation and activation of macrophages and T cells leading to phagocytosis of haemopoietic cells within the reticuloendothelial tissues [4]. Our case highlights challenges in diagnosing and managing MAS.

Many of the reported typical features of MAS, including persistent fever, lymphadenopathy and hyperferritinaemia were present in our case. However, the diagnostic criteria for HLH [1] were initially unhelpful, as thrombocytopenia and hypofibrinogenaemia developed late, likely because of the underlying pro-inflammatory condition. Although bone marrow examination revealed haemophagocytosis, consistent with MAS [3], the absence of previous autoimmunity or other trigger meant that a definite diagnosis was not made until after transplantation. Subsequent immunohistochemical evaluation of CD163 expression, a marker of macrophage activity [5], was strongly reactive (see Fig. 1) providing supportive evidence for the diagnosis.

The mainstay of treatment for MAS is immunosuppression, typically with high dose corticosteroids [6], although cyclosporine [4] and anakinra [7,8] are also gaining acceptance. Had the diagnosis been clearer, earlier treatment may have prevented further deterioration. However, despite immunosuppression our patient developed acute liver failure with encephalopathy and coagulopathy, achieving UK criteria for registration for super-urgent liver transplantation [9]. Given the diagnostic uncertainty, sero-negative hepatitis was considered as an alternative cause and he was listed for transplantation. However, his presentation six years later with arthralgia, fever and rash provides evidence for an underlying diagnosis of AOSD and it is now most likely that MAS was the cause of his acute liver failure.

From the literature, it is clear that MAS is a serious condition, which can be fatal. In one case series of 9 children with MAS, mostly on the background of sJIA, 2 died [3]. A series of 14 patients with AOSD included 2 whose disease was complicated by MAS of which 1 patient died [10]. With specific reference to liver involvement, there have been other cases describing liver dysfunction as the first presenting feature of MAS [11,12]. In the largest published case series of hepatic involvement in MAS, 12 of the 30 patients (40%) died, mostly of multiorgan failure or sepsis [13]. Furthermore, all the factors found to be significantly linked to higher mortality (higher bilirubin, low albumin, low fibrinogen and higher alkaline phosphatase) were present in our patient. It is therefore highly likely that our patient's prognosis was poor with a high risk of mortality without liver transplant.

There is one other published case report of successful liver transplantation in the context of MAS, although this 14-year old also had Wilson's disease with biopsy evidence of cirrhosis [14]. As in our case, acute liver failure developed despite immunosuppression. Following liver transplantation, MAS resolved and supported by normalization

of the serum ferritin. However, liver transplantation in the context of a multi-system disease is controversial because of concerns that the pathological process may recur in the transplanted liver. Indeed, there is one published case where progressive HLH resulted in death after liver transplantation [15]. In this case, a neonate with acute liver failure and hyperferritinaemia was transplanted for presumed neonatal haemochromatosis, but the explant histology showed haemophagocytosis and the child died 44 days later.

In conclusion, this is the first reported case of successful adult liver transplantation for acute liver failure caused by MAS. Had the underlying diagnosis of a multi-system disease been clearer at the time, it is probable that the patient may have been deemed ineligible for liver transplantation. However, it is clear that his prognosis without transplantation was very poor and he has performed extremely well since transplantation, providing an interesting clinical dilemma for the future management of similar patients.

Authorship

JO: wrote the manuscript. YB: provided histology description and images, reviewed manuscript. MH: reviewed manuscript. SM: last author and reviewed manuscript

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