Hemophagocytic syndrome occurring in an adult liver transplant recipient having Still's disease

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Abstract Hemophagocytic syndrome is a potentially fatal complication that rarely occurs after liver transplantation. We present a 25-year-old man with a history of Still's disease who presented with fever, arthralgia, and elevated serum ferritin levels 6 months after undergoing liver transplantation for fulminant hepatic failure due to autoimmune hepatitis potentially triggered by infliximab therapy. Liver biopsy demonstrated features consistent with hemophagocytic syndrome. The patient was successfully treated with a course of high dose steroids and had complete resolution of his symptoms and normalization of liver chemistry test abnormalities. Patients with Still's disease may rarely complicate with fulminant hepatic failure with infliximab therapy. Hemophagocytic syndrome a rare potentially life threatening condition may occur in such patients following liver transplantation.

Keywords Rheumatoid arthritis · Macrophage activation syndrome · Liver transplantation

Introduction

Hemophagocytic syndrome (HPS) is a potentially fatal complication that rarely occurs after liver transplantation (LT) and has been more commonly reported in the pediatric population [1–5]. HPS can be difficult to diagnose both clinically and histologically, with delays in the

diagnosis leading to significant morbidity and mortality [6, 7]. We report a case of fulminant hepatic failure (FHF) occurring secondary to autoimmune hepatitis in a 25-year old man with Still's disease that was potentially triggered by infliximab therapy, who went on to develop HPS post-LT. The HPS was managed with high dose corticosteroids and anakinra leading to complete resolution of his symptoms and abnormalities.

Case report

A 25-year-old man with history of Still's disease for 5 years was transferred to our institution for evaluation regarding abnormal liver chemistry tests. One week prior to hospitalization he developed significant loss of appetite, nausea and upper abdominal discomfort for which he visited the emergency department and was noted to have AST 3316 IU/mL, ALT 4773 IU/mL, and alkaline phosphatase 121 IU/mL along with serum bilirubin of 19.3 mg/dL. His INR on admission was 4.2. The patient had no history of prior known liver disease, exposure to hepatotoxic drugs, illicit drug use, or alcohol abuse.

He was receiving infliximab infusion at a dose of 5 mg/kg of weight every 8 weeks for almost 3 years as treatment of Still's disease. From the time he had been diagnosed with Still's disease 5 years prior, he had been treated with a variety of regimens. He was initially taking prednisone monotherapy with poor control of symptoms and was subsequently treated with etanercept for 2 years. He was then switched to methotrexate and infliximab, which he took for 1 year. The methotrexate was then discontinued after the development of abnormal AST and ALT up to 100 IU/mL with normalization of his liver tests on follow-up. He was continued on infliximab infusion at a dose of

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5 mg/kg of weight every 8 weeks. He received his last infliximab infusion 2 weeks prior to his hospitalization.

Multiple laboratory tests and serologic tests were performed including IgM/IgG anti-HAV, HBsAg, anti-HBs, anti-HBc, HBV-DNA, anti-HCV and HCV PCR, IgG HEV, hepatitis G PCR, CMV PCR, IgG HSV-1, EBV PCR, varicella zoster (IgG) and all were negative. Additional laboratory test results were serum iron (161 $\mu\text{g/dL}$), TIBC (171 $\mu\text{g/dL}$), Transferrin sat (94%), Ferritin (5,436 ng/mL) alpha-1-antitrypsin (171 mg/dl), and AFP (20.9 ng/mL). Serum protein electrophoresis showed a polyclonal increase in the gamma region. ANA was positive with a titer of 1:320 (no prior ANA was available for comparison). He was also positive for ASMA (1:160) and ds-DNA. Tests for anti-LKM, SLA (soluble liver antigen autoantibodies), anti-liver cytosol, AMA, c-ANCA, p-ANCA, S.cerevisiae (IgG and IgA) were negative and ceruloplasmin was within the normal range. His rheumatoid factor level was 122 IU/mL.

CT scan of the abdomen showed a heterogeneous appearing shrunken liver with an estimated liver volume of 900 cc. The patient was treated with oral prednisone 60 mg/day and intravenous fluids. On day 4 of the hospital admission he became confused and developed slurred and incoherent speech, asterixis and was listed for LT. On day 5 of the hospital stay he underwent successful LT. The donor was a 59-year-old female who died of stroke.

The liver explant specimen weighed 731 g and the surface of the liver was slightly wrinkled (Fig. 1). The hepatic outflow veins, hepatic artery, portal veins and common hepatic ducts were patent. Serial sectioning and microscopic

examination of the liver showed diffuse congestion and areas of parenchymal collapse consistent with massive hepatic necrosis (Fig. 2). Upon microscopic examination of representative areas of the liver, only very rare foci of residual hepatic parenchyma were noted along with formation of ductular hepatocytes. The collapsed areas were infiltrated with sheets of mononuclear cells, prominent of which were plasma cells consistent with autoimmune hepatitis and numerous ceroid macrophages. Trichrome stain showed patchy fibrosis and reticulin stain confirmed the extensive collapse of the reticulin framework.

The patient received corticosteroids intra-operatively and induction with basiliximab. Post-LT he was kept on a standard immunosuppression regimen of prednisone (tapered off after 3 months), mycophenolate and tacrolimus. He never had an episode of acute cellular rejection and overall had an uncomplicated post-operative course. The patient continued to do well for 6 months until he developed low-grade fever, fatigue, joint pain and abnormal liver chemistry tests (AST 157 IU/mL, ALT 183 IU/mL, alkaline phosphatase 64 IU/mL, GGTP 54 IU/mL, total bilirubin 2.2 mg/dL and INR 1.2). Tests for anti-nuclear antibody, anti-smooth muscle antibody, liver-kidney microsomal antibody, p-ANCA, c-ANCA, liver cytosol antibodies, anti-cardiolipin antibodies and rheumatoid factor were all negative. Serologies for CMV and EBV were also negative. Serum ferritin level (1181 ng/mL) and C-reactive protein level (14.1 mg/L) were extremely elevated. Measurement of serum cytokine levels revealed normal TNF-alpha level (8.8 IU/mL), and IL1 beta levels (<3.9 IU/mL). Serum levels of $\beta 2$ -microglobulin were elevated (3.92 mg/L). Besides, hypertriglyceridemia, leucopenia and thrombocytopenia were other notable findings. A liver biopsy of the allograft was performed showing centrilobular sinusoidal congestion with hepatocyte drop out with red blood cells and red blood cell fragments found in the Disse spaces (Fig. 3a). Occasional red blood cells are noted to be engulfed by histiocyte (Fig. 3b). No fibrosis was noted on trichrome stain. These findings on liver biopsy were consistent with HPS. The patient received high dose oral corticosteroids with complete remission of the hepatocellular dysfunction over the next 3 months. He had ongoing problems with glucose intolerance, hypertension and anxiety. Thus he was started on anakinra 100 mg subcutaneously in an effort to taper off his steroids, which was accomplished over the next 4 months. At 1-year follow-up the patient is now doing well and totally is off corticosteroids.

Fig. 1 Explanted liver specimen. **a** Anterior aspect of liver showing areas of collapse, most prominent in segment four. **b** Cut surface of liver showing areas of collapse, congestion and regeneration

Discussion

This case demonstrates two rare complications occurring in the clinical course of a patient with Still's disease: FHF is

Fig. 2 **a** Microscopic appearance of 2.5 cm regenerative nodule ($\times 50$ magnification). **b** Liver parenchyma with collapse, congestion and scattered viable hepatocytes ($\times 50$ magnification). **c** Trichrome stain demonstrates increased fibrosis in collapsed areas ($\times 50$ magnification). **d** The inflammatory infiltrate consists of plasma cells and lymphocytes ($\times 400$ magnification)

Fig. 3 **a** Severe sinusoidal congestion is present in centrilobular and zone 2 areas. An arrow points to a tight aggregate of red blood cells in a widened sinusoid (H&E, original magnification $\times 400$). **b** Occasional red blood cells are noted to be engulfed by a histiocyte (hemophagocytosis) (arrow). (H&E, original magnification $\times 400$)

related to autoimmune hepatitis potentially related to infliximab use and the subsequent development of HPS in the post-LT setting. We believe the later was due to recurrent Still's disease.

Minor abnormalities in liver chemistry tests are relatively common with the use of anti-TNF- α agents [8], but severe hepatic reactions are infrequent. These may include a cholestatic hepatitis, autoimmune hepatitis (AIH), and FHF. It is noteworthy that a number of cases of adverse hepatic reactions [9–14] including a case of FHF resulting in LT have now been reported [9]. According to the manufacturer of infliximab, at least 35 patients have been reported to have had severe hepatic adverse events in the post-marketing period up to 2004 [10]. Autoimmune hepatitis is a rare but nonetheless increasingly recognized complication of treatment with infliximab [9, 11–14]. Low titer ANA may be demonstrated in subjects receiving infliximab, and their presence does not conclusively establish the diagnosis of AIH. In the present case, in addition to ANA the histopathology of the explants was conclusive. The patient in the report may have been predisposed to this as suggested by his abnormal liver tests while taking another TNF antagonist (etanercept) along with methotrexate.

Table 1 summarizes the reported cases [9, 11–14] of infliximab-related autoimmune hepatitis including a case of FHF, which led to LT [9]. Neither that patient [9] nor our patient received concurrent immunosuppressive therapy during treatment with infliximab. The development of autoimmune antibodies and complications may possibly be more significant when infliximab is used alone or in higher doses. TNF antagonists are being used more frequently post-LT, such as in the treatment of graft-versus-host disease and in the management of inflammatory bowel disease; hence clinicians need to be familiarized with its use [15, 16].

One postulated mechanism by which infliximab is thought to contribute to development of autoimmune

Table 1 Case reports of infliximab treatment and development of AIH

Patient	Gender	Age (years)	Disease	INFX infusions		MTX use		ANA titer		Anti-dsDNA development
				Dose (mg/kg)	No	Concurrent	Past	Pre-infx	Post-infx	
Tobon et al. [9]	F	39	RA	3	6	No	No	0	1:40	Yes
Tobon et al. [9]	F	54	RA	3	12	Yes	Yes	0	1:160	ND
Fairhurst et al. [11]	F	22	PsA	5	3	Yes	No	1:40	1:640	Negative
Saleem et al. [12]	F	36	RA	3	3	No	Yes	1/20	1:640	Yes
Germano et al. [13]	F	53	PsA	3	8	Yes	Yes	1/80	1:160	Yes
Ozorio et al. [14]	F	56	AS	5	6	No	No	0	1:640	Yes
Satapathy et al. ^a	M	25	RA	5	29	No	Yes	N/A	1:320	Yes

RA rheumatoid arthritis, PsA psoriatic arthritis, AS ankylosing spondylitis, INFX infliximab, MTX methotrexate, dsDNA double-stranded DNA

^a Current patient

hepatitis in predisposed patients is by triggering development of autoantibodies which include ANA and anti-dsDNA [17]. One possible explanation for this is that TNF- α blockade interferes with normal cytotoxic T lymphocyte suppression of auto (self)-reactive B cell production. A second postulated mechanism could be that anti-TNF- α agents interfere with the induced cell death of CD8 T cells. Studies in patients with rheumatoid arthritis support infliximab-related autoantibody development [17, 18] demonstrating elevations in both ANA and anti-dsDNA titers after infliximab therapy.

HPS, also known as macrophage activation syndrome (MAS) is a severe, potentially life-threatening condition that can be induced by chronic rheumatic diseases, including Still's disease [6, 7]. The term MAS has been used almost exclusively to describe this condition in association with rheumatic diseases. It is characterized by fever, hepatosplenomegaly, lymphadenopathy, skin rash, lung infiltration, and liver dysfunction. Associated laboratory findings are pancytopenia, liver chemistry tests abnormalities, low platelets, coagulopathy with low fibrinogen, hypertriglyceridemia, and elevated ferritin levels. Histological findings of phagocytosis of hematopoietic precursor cells in bone marrow, lymph node, liver and spleen provide the conclusive diagnosis [19, 20]. With respect to liver involvement hepatomegaly, cholestasis, and FHF have all been reported [6, 7, 19].

Two forms of HPS have been characterized: primary/familial hemophagocytic lymphohistiocytosis and secondary/reactive HPS. Reactive HPS can develop secondary to various diseases, such as systemic infections, as well as malignancy and collagen vascular diseases [20–22]. Reactive HPS is usually associated with viruses such as CMV and EBV as well as other infectious organisms, such as bacteria, mycobacterium tuberculosis, fungi, parasites and many other viral infections [20, 21, 23, 24]. Although systemic infection is a frequent complication after LT, reactive HPS has only been reported sporadically in adult

LT recipients [25, 26] and mostly only in the pediatric literature [1–5].

In HPS, uncontrolled T-cell proliferation is followed by overproduction of cytokines by deregulated T lymphocytes, which include interferon- γ , IL-6, tumor necrosis factor- α , macrophage colony-stimulating factor, and soluble IL-2 receptor [27–29]. These cytokines account for the activation of macrophages that are subsequently transformed to hemophagocytes and are also responsible for a variety of clinical manifestations and laboratory findings in HPS. Fever, cachexia, and a generalized inflammatory state that includes an elevated serum ferritin and lactate dehydrogenase (LDH), may be secondary to high serum interleukin-1 and tumor necrosis factor- α concentrations [30]. However, in the post LT period these levels may be normal as noted in our patient as immunosuppression might have affected the cytokine profile. Although awareness and early diagnosis of HPS are required to institute timely treatment essential to reduce fatality, clinical data are always of utility in establishing the diagnosis. Serum interferon- γ and soluble IL-2 receptor levels may be elevated but it is not practical to follow disease activity because it is time-consuming and expensive [29]. Recently, several investigators have focused on the relevance of elevated serum ferritin [31] and urine and serum β 2-microglobulin [32] levels. To avoid high morbidity and mortality rates with HPS mostly related to its underlying etiology [6, 7], it is imperative to establish the diagnosis with bone marrow or liver biopsy as early as possible. The indication criteria for bone marrow biopsy are high fever, unexplained cytopenia, hypercholesterolemia, hypertriglyceridemia, hyperferritinemia, and marked elevation of urine β 2-microglobulin [33]. A similar reasoning would be justifiable for liver biopsy as well in the setting of abnormal liver tests.

In a series of 30 cases of HPS, de Kerguenec et al. [33] found the prognosis to be related to whether or not a treatable underlying disease was present or not. Among the 21 cases in which an underlying disease was identified and

appropriately treated, complete remission of HPS was achieved in fifteen. Current treatment and recommendations for HPS are therapy of the underlying disease, increasing immunosuppression, chemotherapy, plasmapheresis, whole blood exchange, and bone marrow or stem cell transplantation [28]. The usefulness of granulocyte colony-stimulating factor in HPS has also been reported [34]. IL-1 receptor antagonist (IL-1Ra) is a naturally occurring IL-1RI-binding molecule that blocks the biologic effects of the proinflammatory cytokine IL-1. The recombinant form of human IL-1Ra, anakinra, has been approved for use in rheumatoid arthritis (RA) patients that is refractory to more conventional forms of treatment [35]. Over the last few years, it has become increasingly evident that anakinra is highly effective and safe in patients with Still's disease [36]. Given the known side effects associated with prolonged steroid use, our institutional protocol is not to continue steroids beyond 3 months after LT. In the current case, although high dose corticosteroids was useful in achieving clinical remission of Still's disease relapse, we were successful in tapering off the steroids and still able to maintain the clinical remission.

In summary, we report a case of fulminant autoimmune hepatitis requiring LT that was potentially induced by infliximab therapy of underlying Still's disease. Potential hepatotoxicity should be taken into consideration when using infliximab even after multiple well-tolerated infusions, and close monitoring of clinical and laboratory data is warranted. We believe that HPS was triggered by the Still's disease post LT [37]. Since HPS may be triggered in the post LT period by certain infections such as CMV and EBV, etc., as well as post transplant lymphoproliferative disease that themselves produce symptoms similar to those of HPS (such as fever, constitutional symptoms and cytopenias as well as lymphadenopathy), the diagnosis of HPS may be easily overlooked and thus should be included in the differential diagnosis of such conditions. Elevated ferritin and triglyceride levels should prompt the treating physician to make a tissue diagnosis so that timely treatment of HPS or its underlying etiology can be initiated.

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