Hepatic Dysfunction in a Child Post Bone Marrow Transplantation

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A 10-year-old female child, a known case of Beta-Thalassemia major with superimposed chronic Hepatitis C Viral (HCV) infection, underwent bone marrow transplantation and presented, 7 months later, with worsening hepatic functions and skin rash. Considering the wide variety of possible etiologies, she was evaluated and later confirmed as a case of hepatic dysfunction secondary to HCV related hepatic injury with concomitant chronic graft versus host disease (dermatological involvement only). (J CLIN EXP HEPATOL 2018;8:327–331)

CASE REPORT

Hepatic dysfunction after pediatric bone marrow transplantation is a common but serious occurrence faced by treating hematology and hepato-biliary units. It can be attributed to a multitude of causes, and in some cases, concomitant insults can exist (Figure 1).^{1–3} High degree of suspicion and good clinical acumen for careful differentiation based on historical, laboratory and histological clues is required to delineate such cases at an early stage where effective treatment strategies can be applied.

A 10-year-old female child, who was a known case of Beta-Thalassemia major since infancy, was detected to have Hepatitis C positive status at 5 years of age (but no treatment was given). She underwent HLA-matched Bone Marrow Transplantation (BMT) at 9 years of age, for increasing blood transfusion requirements and secondary iron overload, following conditioning with anti-thymocyte globulin. She then presented with chief complaints of abnormal hepatic transaminases (detected on regular screening) for last 6 months (i.e. onset 7 months post-BMT) and generalized skin rash for last 4 months. She was on regular chelation (tablet Deferasirox since early childhood); was switched to subcutaneous Desferrioxamine 2 months prior to BMT. Post-BMT, she received valganciclovir, fluconazole and trimethoprim-sulphamethoxazole

prophylaxis for 6 months, and cyclosporine was continued till 10 months post-BMT (discontinued 2 months prior to admission).

On examination, there were multiple ill defined violaceous plaque with fine whitish scale present over the nape of neck, lower back, arms, forearm, legs and feet (Figure 2). Also, there were hyperpigmented plaques over the legs, with hyperpigmentation over perioral and peritibial regions. Per-abdomen examination showed a palpable liver 5 cm below right costal margin (soft, smooth surface, rounded margins, span of 10 cm, non-tender without any bruit). Rest examination was within normal limits.

Her investigation trend is summarized in Table 1. Her basic evaluation, at admission, had shown mild anemia, moderate transaminitis, preserved hepatic synthetic functions, hepatitis C viral profile positivity, negative other viral markers and presence of iron overload (high serum ferritin). Abdominal Magnetic Resonance Imaging (MRI) showed diffuse hypointensity of liver, spleen, vertebrae and pancreas suggestive of hemosiderosis with signal drop in phase images. She was admitted for evaluation of liver dysfunction with Hepatitis C positive and post-BMT status. In view of clinical symptoms and examination, possibilities considered were: hepatitis related to Hepatitis C Virus (HCV) infection; Graft Versus Host Disease (GVHD; with skin and hepatic involvement); and Drug Induced Liver Injury (DILI; intake of chelation therapy prior to BMT, and intake of fluconazole, trimethoprim-sulphamethoxazole and cyclosporine after BMT). Other rarer possibilities kept were superimposed viral infections (post immunosuppression) and autoimmune liver disease. Her HCV profile showed decreasing trends of HCV Ribonucleic Acid (RNA) levels from 2.2×10^7 (done outside previously) to 8.15×10^2 IU/ml (at admission), along with decreasing transaminitis (aspartate aminotransferase or AST/alanine aminotransferase or ALT decreased from 1887/1976 to 316/660 IU/L). Her liver biopsy (Figure 3 (a–f)) was done to look for evidence of GVHD, viral activity and DILI; it showed chronic hepatitis with mild activity

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Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMT: Bone Marrow Transplantation; DAA: Direct-Acting Antiviral; DILI: Drug Induced Liver Injury; GVHD: Graft Versus Host Disease; HAI: Hepatic Activity Index; HCV: Hepatitis C Virus; MRI: Magnetic Resonance Imaging; RNA: Ribonucleic Acid

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Figure 1 Timeline of common etiologies of hepatic dysfunction after bone marrow transplantation.

Figure 2 Skin involvement: multiple ill defined violaceous plaques with fine whitish scales (arrows) over nape of neck, lower back, arms and forearm.

(HCV related) with periportal fibrosis and secondary hemosiderosis (Ishak's hepatic activity index/HAI Score-6 and Fibrosis stage-F2), without any cholestatic or autoimmune features. As per dermatology opinion, skin biopsy (Figure 4(a-c)) was done which showed findings suggestive of chronic GVHD.

In view of likely possibility of hepatitis C related injury with high AST/ALT, F2 fibrosis on liver biopsy and it being a treatable etiology with risk of long term risk of further hepatic damage, it was decided to treat the hepatitis C infection with anti-virals. Choice of anti-virals (Interferon/Ribavirin combination versus oral direct acting

Table 1 Laboratory Parameters at Various Time Points During Disease Course.

Baseline parameters (normal range)	Before BMT	7 months → 1 year post BMT	At admission (1.5 years post BMT)
Hemoglobin (g/dL) (12–15)	8.5	10.9	11.3
Total leukocyte count (cells/mm ³) (4000–11,000)	4300 (N52 L39)	4300 (N42 L56)	4100 (N33 L53)
Platelets (cells × 1000/mm ³) (180–400)	339	168	150
Bilirubin (T/D) (mg/dL) (0.3–1.2/0–0.2)	1.0/0.35	1.2/0.3	1.3/0.4
AST/ALT (IU/L) (5–40)	41/88	255/546 → 1887/1976	316/660
SAP/GGTP (IU/L) (32–92/7–64)	216/–	345/238	259/105
Albumin (gm/dl) (3.8–5.4)	7.1/4.6	7.2/3.6	7.1/3.5
INR (1–1.2)	–	–	1.04
HBsAg	Negative	–	Negative
Anti HCV	Reactive	Reactive	Reactive
HIV-ELISA	Negative	–	Negative
HCV RNA (IU/ml)	1.1×10^4	2.2×10^5	8.15×10^2
HCV genotype		3	3
Other viral profile			
• CMV-DNA and EBV-DNA PCR	–	–	Negative
• IgM HAV/HEV/HSV/VZV	–	–	Negative
• Total Anti-HBc (IgG)	–	–	Negative
Autoimmune profile			
• IgG (gm/l) (<13.5)	–	–	20.7
• ANA/ASMA/Anti-LKM 1/Anti-SLA	–	–	Negative
Ferritin (microgram/L)	2078	–	4910

Abbreviations: AST – Aspartate Aminotransferase, ALT – Alanine Aminotransferase, BMT – Bone Marrow Transplant, SAP – Serum Alkaline Phosphatase, GGTP – Gamma Glutamyl Transpeptidase, INR – International Normalized Ratio, HbsAg – Hepatitis B Surface Antigen, HCV – Hepatitis C Virus, HIV – Human Immunodeficiency Virus, RNA – Ribonucleic Acid, HAV – Hepatitis A Virus, HEV – Hepatitis E Virus, HSV – Herpes Simplex Virus, VZV – Varicella Zoster Virus, DNA – Deoxyribonucleic Acid, ANA – Anti-Nuclear Antibody, ASMA – Anti Smooth Muscle Antibody, LKM – Liver-Kidney-Microsome, SLA – Soluble Liver Antigen.

drugs) was also deliberated. Interferon was not considered in view of suboptimal, need of prolonged therapy, risk of hematological side-effects and evidence of GVHD in skin. Since there was no previous literature on oral direct antivirals use in pediatric population, parental written and informed consent was obtained after explaining the possible success chances and side effect profile based on adult literature. Child was thus initiated on 12 weeks course of oral Sofusbuvir (400 mg)/Daclatasvir (60 mg) half tablet once a day, as per available world literature at that time point. Also, chelation therapy in form of oral Deferasirox was re-started for secondary hemosiderosis, as per haematologist's advice. At the end of 12 weeks treatment, hepatic transaminitis resolved completely and HCV RNA levels decreased to 12 IU/ml. Considering underlying concomitant iron-related injury, persistent low grade viremia, and F2 fibrosis on liver biopsy, after parental consent, it was decided to extend therapy to total 24 weeks. At the end of treatment, HCV RNA was not detectable which was subsequently confirmed 6 months after treatment, and serum ferritin also decreased to 1583 µg/L. Skin lesions were managed using topical medications including Tacrolimus

ointment (0.1%), Pimecrolimus cream (1%) and Halobetasol propionate ointment (0.05%) as per dermatologist's advice.

DISCUSSION

Since, she was already a known case of HCV infection and was on immunosuppressive therapy (after BMT), acute hepatitis secondary to HCV infection was the foremost differential diagnosis. This was confirmed on the basis of increasing HCV viral titers, in tandem with increasing hepatic transaminases after institution of immunosuppressive therapy post-BMT. Also, decrease in viral titers and transaminases after stoppage of cyclosporine based immunosuppression pointed toward viral cause of hepatic injury. Post-BMT, HCV infection is a slowly progressive disease with little short term liver-related morbidity though long term studies have shown higher risk of cirrhosis occurrence (as high as one-fourth of patients within two decades) compared to those without BMT.^{1,4,5} Thus, treatment of any HCV infection is mandatory. The treatment options for pediatric chronic HCV infection are still limited. Only recently, Food and Drug

Figure 3 Liver biopsy findings: (a) acinar disarray with expanded portal area (100 $\times$, Hematoxylin and Eosin/HE stain); (b) Portal/Periportal fibrosis (200 $\times$, Masson's trichrome/MT stain); (c) unremarkable ducts (arrow) in all the portal areas (200 $\times$, HE); (d) secondary iron overload seen in the Kupfer cells (200 $\times$, Perl's stain); and negative immunohistochemical (IHC) staining for Epstein Barr virus (e) and cytomegalovirus (f) (200 $\times$).

Figure 4 Skin biopsy findings: (a) melanin incontinence (100 $\times$, Hematoxylin and Eosin/HE stain); (b) apoptosis of basal layer and lymphocytic infiltrate (200 $\times$, HE stain); and (c) dermal appendages highlighting periappendageal lymphoid infiltration (arrow) (200 $\times$; HE stain).

Administration approved two direct-acting antiviral (DAA) based regimens for treatment of children with chronic HCV infection >12 years of age.^{6,7} Only approved treatment option for the younger (<12 years) age group is still pegylated interferon and ribavirin, though multiple trials are currently underway in this population. Thus, individual patient-specific therapeutic decisions are needed in this younger group of patients till DAAs are officially approved for use.

Chronic GVHD (cGVHD, i.e. occurring >100 days after BMT) was also a close differential considering the dermatological manifestations and hepatic injury. Though there was lack of evidence of other typical multisystem involvement including diarrhea (gastrointestinal disease) etc., histopathology (liver and skin both) was required to allow clear differentiation between viral

hepatitis and cGVHD. This was important for therapeutic decision making since they have diametrically opposite lines of management (antivirals for HCV versus steroids for cGVHD). The iron overload in post-BMT patients is usually multifactorial; most commonly being secondary to blood transfusions and abnormal iron transport by the intestine due to bone marrow dysfunction.³ Also, it may also be precipitated by concurrent HCV infection, mainly due to decreased hepcidin levels and altered expression of other iron-metabolism-related genes.⁹ This iron overload may then influence HCV replication.⁹ Pre-BMT iron overload has been found to be associated with increased risk of early mortality after BMT, while it is also associated with infectious complications, acute GVHD and hepatic veno-occlusive disease in the early post-BMT period.^{8,10}

Hepatic injury secondary to iron overload was also considered in the present case view of evidence of iron overload on abdominal MRI, skin hyperpigmentation and significantly elevated serum ferritin levels. But considering the fact that iron overload post-BMT is rarely the sole cause of severe hepatic insult, its role as a superimposed insult over an underlying primary cause was more likely.⁸

DILI was considered less likely in view of the following: the liver injury continued to worsen even after stoppage of suspected drugs, i.e. chelation therapy, fluconazole and trimethoprim-sulphamethoxazole; Cyclosporine is known to cause elevation of bilirubin, without effect on transaminases or cholestatic enzymes.¹ Since, cyclosporine itself is a potent immunosuppressant, flare of autoimmune disease process while on drug therapy was a distant possibility.

In conclusion, hepatic dysfunction after BMT can be attributed to variety of causes which needs careful differentiation based on historical, laboratory and histological clues.

CONFLICTS OF INTEREST

The authors have none to declare.

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