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Autoimmune Like Hepatitis Post Allogeneic Hematopoietic Stem Cell Transplant: A Case Report

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Abstract

Hematopoietic stem cell transplant is the standard of care in the management of multiple hematological malignancies. Infections, graft-versus-host disease and primary disease relapse are known complications of hematopoietic stem cell transplant which contribute to morbidity and mortality. Immune mediated complications post hematopoietic stem cell transplant is an under recognized phenomena due to its heterogeneous presentation which can have clinical overlap with graft-versus-host disease. We present a case of autoimmune like hepatitis in a patient status post allogeneic hematopoietic stem cell transplant. The patient initially presented with mildly elevated liver enzymes followed by progression to bilirubinemia, acholic stools, unintentional weight loss, and increasing fatigue. Furthermore, we discuss the diagnostic challenge, suspected pathogenesis and management of autoimmune like hepatitis.

Keywords: Hematopoietic stem cell transplant; Graft-versus-host disease; Autoimmune like hepatitis; Autoimmune hepatitis; Myelofibrosis.

Abbreviations: HSCT: Hematopoietic Stem Cell Transplant; GVHD: Graft-Versus-Host Disease; MRD: Matched Related Donor; RIC: Reduced Intensity Conditioning; BU: Busulfan; FU: Fludarabine; LAEs: Liver Associated Enzymes; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; MRI: Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction; APCs: Antigen-Presenting Cells.

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Background

Hematopoietic stem cell transplant (HSCT) is a rapidly evolving field of oncology that plays an integral role in the management of hematological malignancies, non-hematological malignancies, and non-malignant disease such as severe autoimmune disease [1]. HSCT can largely be divided into either autologous or allogeneic transplant. Autologous transplantation involves administration of the patient's own hematopoietic stem cells. Allogeneic transplantation relies on donor-derived hematopoietic stem cells to provide alloimmunity to enable graft-versus-tumor effect in order to eliminate cancer cells and prevent relapse [2]. In allogeneic HSCT, donor cells can be from either a matched related sibling or a haploidentical (partially matched) family member. Additionally, cryopreserved cord blood unit stem cells can also be utilized in allogeneic transplantation [2]. However, HSCT is not without risks and is marked by elevated marked morbidity, mortality, and high cost [2].

Complications associated with HSCT include infections, graft-versus-host disease (GVHD), chemotherapy and radiation related toxicities as well as primary disease relapse [1]. GVHD remains the most serious and common immune mediated complication following allogeneic transplant. Acute GVHD is mediated by antigen presenting cell activation, donor T-cell activation, and target tissue destruction [3]. The mechanism of chronic GVHD is not as well understood as acute GVHD and appears to involve immune dysfunction, immunodeficiency and impaired organ function [3].

Immune mediated complications post transplantation have not been commonly reported. Immune mediated diseases post HSCT is likely underdiagnosed due to diagnostic challenges, as clinical features of immune mediated diseases may overlap with other common transplant related complications. There are case reports describing non-GVHD immune diseases, such as autoimmune thrombocytopenia in a patient following one antigen mismatched unrelated donor bone marrow transplantation, as well as a case series documenting autoimmune thyroid dysfunction in 10 patients following HSCT (seven allogeneic and three autologous HSCT) [4, 5]. We present a case of biopsy proven autoimmune like hepatitis (AILH) in a patient status post matched related donor (MRD) allogeneic transplant for post-polycythemia myelofibrosis.

Case presentation

A 69 year old female with post-polycythemia myelofibrosis received MRD allogeneic transplant with reduced intensity conditioning (RIC) with busulfan (BU) and fludarabine (Fu). She presented for a routine clinic visit and was found to have elevated liver associated enzymes (LAEs) in a mixed injury pattern 14 months post-transplant. Labs on post-transplant day +422 showed aspartate aminotransferase (AST) of 79 U/L, alanine aminotransferase (ALT) of 61 U/L and alkaline phosphate (ALP) of 182 U/L with a normal bilirubin. LAEs for this patient 2 months prior were normal. Review of systems was negative for right upper quadrant pain, jaundice, diarrhea, constipation, early satiety, or changes in weight. The patient denied alcohol consumption, new medications, or herbal supplements. Repeat labs 1 month later showed increasing LAEs with an AST of 278 U/L, ALT of 318 U/L, ALP of 424 U/L and a normal bilirubin. The patient's synthetic function remained intact with normal albumin and normal coagulation indices. The patient remained asymptomatic. Right upper quadrant ultrasound with doppler was significant for cholelithiasis without signs of cholecystitis,

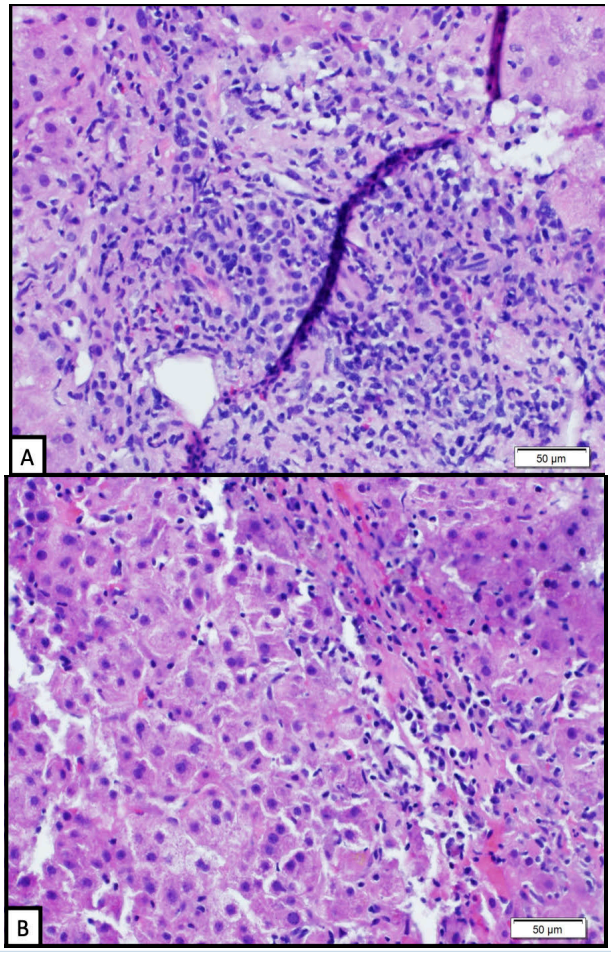

Figure 1: A, B H&E stained Histology sections of liver at 200x magnification. **(A)** Demonstrates a portal track with bile duct injury, lymphoplasmacytic inflammation, and interface hepatitis. **(B)** Demonstrates hepatic parenchyma with severe lobular necroinflammatory activity including parenchymal collapse, bridging necrosis, and focal cholestasis (brown pigment in hepatocyte prominent in bottom center of photomicrograph). Copious plasma cells are present.

and patent hepatic vasculature. Magnetic resonance imaging (MRI) of the liver confirmed cholelithiasis and was negative for any concerning lesions. A complete serological evaluation revealed a normal iron panel, negative anti-smooth muscle antibodies, negative anti-mitochondrial antibodies, and negative hepatitis B and C infection. Immunoglobulin G was elevated at 2722 mg/dL. The patient was directly admitted to the hospital for an expedited liver biopsy to determine the etiology of her elevated LAEs.

At time of hospital admission, the patient reported increasing orange discoloration of her urine, acholic stools, unintentional weight loss, and increasing fatigue. Labs on admission were significant for AST of 1052 U/L, ALT of 691 U/L, ALP of 427 U/L, direct bilirubin of 4.7 mg/dL and total bilirubin of 5.5 mg/dL. Ursodiol and replacement pancreatic enzymes were initiated for concern of chronic GVHD in the setting of gradual weight loss. Additional labs including anti-nuclear antibodies, anti-liver kidney microsomal antibodies, cytomegalovirus polymerase chain reaction (PCR), and Epstein-Bar-Virus PCR were negative. Ultrasound guided liver biopsy was performed without any complications. Liver tissue pathology (Figure 1) demonstrated severe lobular necroinflammatory activity including parenchymal collapse, focal bridging necrosis, centrilobular injury with scattered bile duct injury, and copious plasma cells present. These findings were consistent with acute hepatitis concerning for auto-

immune hepatitis or autoimmune like hepatitis in the setting of allogeneic transplant. The patient was started on prednisone 60mg daily with rapid improvement in her LAEs within 24 hours of initiation, consistent with autoimmune hepatitis. The patient was later started on azathioprine and prednisone was slowly tapered over 12 weeks. The patient's LAEs decreased to her baseline levels after 2 weeks of steroid use and have remained normal on azathioprine monotherapy.

Discussion

HSCT continues to remain the mainstay therapy for several hematological malignancies and other nonmalignant diseases. Early recognition and treatment of complications such as infection, primary disease relapse and GVHD is key to decreasing morbidity and mortality of HSCT patients. Though not as well understood or recognized as GVHD, immune mediated disease after HSCT is becoming an increasingly described phenomenon in the literature. A review by Li et al demonstrated that immune mediated complications post HSCT can manifest as hematological complications, thyroid disease, neurological disease, vitiligo, rheumatic diseases, and autoimmune like hepatitis [6]. The diagnosis of immune mediated disease post HSCT remains difficult due to its heterogeneous entity with varying organ involvement and clinical features which may overlap with GVHD.

Our patient's clinical presentation, histology, and clinical improvement with corticosteroids suggest an autoimmune like hepatitis (AILH) post-transplant. The term autoimmune like hepatitis is used to describe this hepatic entity as the disorder is not considered autoimmune in the setting of allogeneic HSCT [7]. AILH post HSCT is a rare phenomenon that has been reported in case reports as well as a recent cohort study by Koyama et al [7-9]. Clinical features of AILH and hepatic GVHD overlap as intermittent chronic liver enzyme elevations is a frequent problem in allogeneic HSCT patients. Koyama et al investigated 66 out of 635 allogeneic HSCT patients between 1991 and 2010 who underwent liver biopsies for elevated LAEs five times the upper limit of normal. Based on histology, 5 patients were diagnosed with AILH, 23 patients with hepatic GVHD and the remaining were diagnosed with ischemic cholangiopathy, veno-occlusive disease, steatohepatitis, drug-induced hepatitis, viral hepatitis, hemosiderosis and other nonspecific lesions [7]. Koyama et al utilized the International Autoimmune Hepatitis scoring system to histologically diagnose AILH [7]. Histopathology of AILH like that of autoimmune hepatitis will demonstrate portal mononuclear cell inflammatory infiltrate extending into the lobule known as interface hepatitis [10, 11]. Other histological characteristics of AILH and autoimmune hepatitis include rosette formation, ballooning of hepatocytes, necroinflammatory foci, bridging necrosis and emperipolesis [10, 11]. Conversely, the diagnostic hallmark of GVHD is bile duct injury and destruction [7,11,12]. Damaged bile ducts in hepatic GVHD histologically show nuclear enlargement, pleomorphism, cytoplasmic vacuolization, and loss of nuclear polarity as well as varying degree of centrilobular cholestasis [11]. Though the AILH group within Koyama et al study did not show any bile duct injury on histopathology, bile duct destruction has been reported in 12% of autoimmune hepatitis biopsies with an additional 12-29% of autoimmune hepatitis cases with lymphocytic infiltration of the bile duct epithelium (lymphocyte cholangitis) [9,13]. Though our patient's liver biopsy did demonstrate evidence of scattered bile duct injury, it was unusual that the degree of bile duct injury was not greater given that her LAEs were elevated for approximately 50 days prior to biopsy. AILH remains an entity with clinical features which may overlap with hepatic GVHD. However, our patient had features of interface hepatitis with scattered biliary duct injury suggesting that AILH may also have shared histopathological characteristics of GVHD. More sampling data of AILH histology is needed to further elucidate specific findings to help clinicians differentiate between AILH and hepatic GVHD in allogeneic HSCT patients.

The pathogenesis of autoimmune disease post HSCT is not well understood. The immune system is a complex system of regulatory mechanisms which differentiate between self and non-self [1, 6]. Tolerance against self is maintained within lymphoid tissue such as bone marrow and thymus [1]. The majority of T-cells die within the thymus due to ineffective interaction with self-major histocompatibility complex molecules on dendritic cells or reactivity against self-components [1,6]. Suppression of autoreactive T-cells that reach maturity and migrate to the periphery are achieved by regulatory T-cells, however the detailed mechanism in humans still remains unclear [1,6]. The underlying mechanisms for autoimmune disease post HSCT are even less understood. Proposed mechanisms include dysfunctional reconstitution of the immune system after transplantation due to prior chemotherapy, long-term complications of transplantation such as infection and GVHD, as well as transfer of antibodies resulting in aberrant lymphogenesis [6]. Additionally, autoimmunity may also be affected by the type of transplantation. Autoimmune predisposition in allogeneic HSCT is likely due to allogeneic lymphocytes generating auto-antibodies to donor while in autologous HSCT, T-cells are likely to target self-due to tolerance imbalance [6]. Furthermore, homeostatic expansion following severe acquired lymphopenia from either infection, stress or lymphoablative conditioning may play a role in autoimmune disease [1,6]. Homeostatic expansion is the process of robust T-cell proliferation after a state of lymphopenia. It is possible that during homeostatic expansion, dysregulation and loss of self-tolerance results in the proliferation of auto active lymphocytes resulting in autoimmunity [6]. Conversely, acute GVHD is also T-cell mediated. However acute GVHD is due to activation of antigen-presenting cells (APCs) from underlying disease and HSCT conditioning regimens [14]. Primed APCs results in donor T-cell activation, proliferation, differentiation and migration. Activated T-cells migrate to target organs and damage organs through a complex cascade of cellular and inflammatory mediators [14]. Compared to acute GVHD, the pathophysiology of chronic GVHD is more obscure. The current proposed mechanism of action of chronic GVHD is a 3 phase model involving (1) early inflammation and tissue injury, (2) chronic inflammation and immunity dysregulation followed by (3) aberrant tissue repair with fibrosis [15,16]. Koyama et al demonstrated in the AILH samples CD8 positive T-cells infiltration which are the main effectors of GVHD with distinct CD20 positive B-cell and CD138 positive plasma cells. Koyama et al suggests pathogenesis of AILH may be a humoral type of hepatic GVHD with the involvement of CD20 positive B-cells and CD138 positive plasma cells [7]. Until more data is available to illuminate the pathogenesis of autoimmune disease in post HSCT, early recognition and treatment of immune mediated complications is imperative in the reduction of morbidity and mortality.

First line therapy for AILH or autoimmune hepatitis is high dose corticosteroids in combination with azathioprine for induction. Azathioprine can be started at the same time as corticosteroids or started a few weeks later to confirm steroid responsiveness and to evaluate for thiopurine S-methyltransferase status. The goal for induction is biochemical remission. Once that is

achieved, prednisone should be slowly tapered (2.5-5mg every 2 weeks) with close monitoring to ensure the patient remains in laboratory remission. Patients may be maintained on azathioprine monotherapy or alternative steroid sparing agent such as mycophenolate mofetil or tacrolimus [17]. During the maintenance phase, fixed doses of prednisone or prednisolone and azathioprine are continued until normalization of serum AST, ALT, and bilirubin [18]. The exact mechanism of action of azathioprine is unclear but may be related to suppression of nucleic acid synthesis [19]. Corticosteroid monotherapy also is divided into a 4 week induction phase followed by a maintenance phase. During the induction phase, prednisone or prednisolone is administered at 60mg daily for 1 week followed by 40mg daily for 1 week and 30mg daily for 2 weeks. In the maintenance phase of corticosteroid monotherapy, prednisone or prednisolone is continued at 20 mg daily until resolution of clinical, laboratory or histological findings [18]. For individuals who either cannot tolerate or have treatment failure from combination corticosteroid/azathioprine therapy, or corticosteroid monotherapy, alternative drug regimens have been investigated. Budesonide remains the alternative frontline therapy whereas mycophenolate mofetil and calcineurin inhibitors have been used primarily as salvage therapy [18,19].

Conclusion

Recognition of post HSCT immune mediated complications are critical in reducing morbidity and mortality of this treatment paradigm. Immune mediated phenomenon post HSCT present a diagnostic challenge because of its overlap with other post transplantation complications. However, immune mediated complications post HSCT have been increasingly reported in literature with significant sequela. Our case demonstrates the clinical challenge of differentiating AILH from other hepatic pathology such as GVHD post HSCT. As clinician awareness of immune mediated complications post HSCT such as AILH increases, hopefully more information can be obtained to distinguish hepatic GVHD from AILH on a histopathological level. In the meantime, clinical suspicion of AILH in HSCT patients with elevated liver enzymes is critical for early recognition and treatment of AILH to reduce morbidity and mortality.

Conflicts of interest

The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the Department of Defense, the U.S. Air Force, the U.S. Army, the U.S. Air Force Medical Department, the U.S. Army Medical Department, the United States Air Force Office of the Surgeon General, the United States Army Office of the Surgeon General or the U.S. Government.

There are no conflicts of interest for any authors.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/ relative of the patient.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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