



## Case Report

# Anti-LKM1 Autoimmune Hepatitis as a Mimicker to Hepatitic Variant of Liver Graft-Versus-Host-Disease Following HLA-Identical Stem Cell Transplantation-A Case Report and Literature Review

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### Abstract

Recommendations have been established for both autologous and allogeneic stem cell transplantation in a diverse range of malignant and non-malignant hematologic disorders. Despite the manifold advantages, it is imperative to carefully consider certain issues. Graft-versus-host disease (GvHD), a frequently encountered complication subsequent to allogeneic hematopoietic cell transplantation, typically manifests as mucositis, diarrhea, or hepatitis. In the context of chronic GvHD, this complication can occur in up to 50% of transplantation cases. Chronic liver GvHD is typified by a progressive onset of cholestatic jaundice accompanied by a significant elevation in alkaline phosphatase levels. However, it is noteworthy that the hepatitic variant of liver GvHD demonstrates notable distinctions from its classical counterpart. In the hepatitic variant, discernible hepatocellular injury and a remarkable surge in transaminase levels are often observed, particularly during the tapering phase of immunosuppressant. Recently, there has been an increased recognition of autoimmune hepatitic features within the liver biopsy findings of the hepatitic variant of liver GvHD, underscoring its significance as a plausible differential cause of acute hepatitis. To further elucidate this matter, we hereby present a compelling case study involving a 31-year-old male diagnosed with myelodysplastic syndrome, who developed jaundice 153 days following hematopoietic stem cell transplantation. Liver histology unequivocally confirmed the presence of autoimmune hepatitis, as evidenced by positive serum anti-LKM1 results.

## Introduction

Graft-versus-host disease (GvHD) has historically been categorized as either acute or chronic, based on the temporal pattern of manifestations. Acute GvHD is operationally defined as the manifestation of the disease within 100 days following transplantation, whereas chronic GvHD is characterized by its onset occurring 100 days after the commencement of the intervention. In the context of chronic GvHD, prominent involvement is often observed in vital organs such as the liver, gastrointestinal tract, skin, mucosal surfaces, lungs, and bone marrow, although their manifestations may not invariably co-occur. Among the diverse array of GvHD subtypes, chronic liver GvHD has been the subject of extensive investigation and has gained recognition for its characteristic presentation of a gradual or sudden onset of jaundice accompanied by an elevation in alkaline phosphatase (ALP) levels [1,2].

Hepatic GvHD, classified based on clinical features, can manifest in three distinct ways. The first presentation, referred to as typical acute GvHD, is characterized by elevated levels of alkaline phosphatase (ALP) and total bilirubin, along with mild increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). This type typically occurs within the initial two weeks following stem cell transplantation and is frequently accompanied by symptoms such as skin rash and diarrhea. The second presentation, known as the hepatitis variant, is defined by a notable elevation in AST and ALT levels, with a minimal rise in ALP. This variant typically arises during the period of immunosuppression tapering. Unlike typical acute GvHD, the simultaneous occurrence of skin and gastrointestinal symptoms is infrequent in this variant. The final presentation, identified as chronic GvHD, is characterized by a progressive escalation in ALP levels, followed by the onset of jaundice [2]. However, the distinct histopathological findings in hepatitis variant GvHD can occasionally resemble those observed in autoimmune hepatitis. In this report, we present a case of chronic liver GvHD that presented as acute hepatitis and exhibited a favourable response to an autoimmune hepatitis treatment regimen. This unfamiliar diagnosis presents a significant clinical challenge.

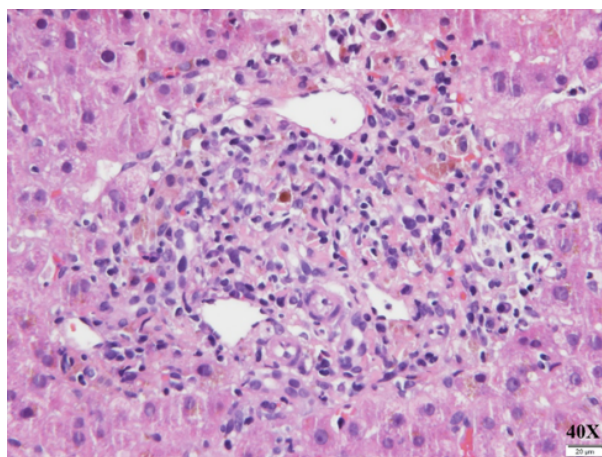
## Case Report

A 31-year-old Thai male patient was diagnosed with myelodysplastic syndrome (MDS) classified as intermediate risk according to the International Prognostic Scoring System (IPSS). Initially, treatment with decitabine, a nucleic acid synthesis inhibitor, was administered but resulted in severe febrile neutropenia and bleeding as complications. Subsequently, the patient underwent peripheral hematopoietic stem cell transplantation (HSCT) with a sibling who matched in terms of human leukocyte antigen (HLA) compatibility. The allogeneic HLA-identical HSCT took place in February 2021, preceded

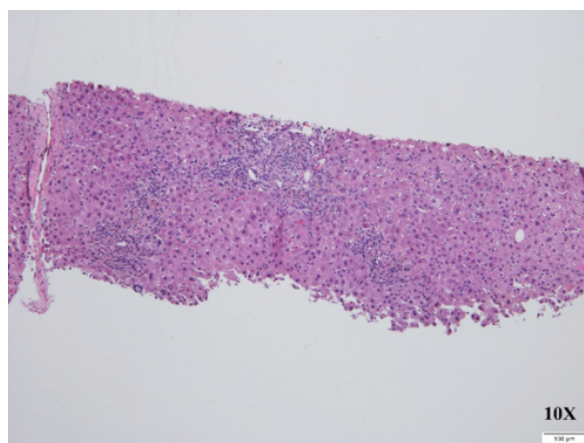
by pre-transplant chemotherapy consisting of busulfan and cyclophosphamide. The transplantation procedure proceeded without noteworthy incidents. Both the patient and the donor tested negative for hepatitis B/C and cytomegalovirus, and their liver function tests yielded normal results. There was no family history of autoimmune disease. The initial post-transplant period was uneventful, with successful neutrophil engraftment occurring on day 20 and platelet engraftment on day 31. No infections or complications related to acute GvHD were observed. To prevent GvHD, the patient received cyclosporin A (CsA) along with a short course of methotrexate. The duration of CsA treatment spanned approximately 2 months, during which liver function tests were carefully monitored while gradually tapering off the medication. In July 2021, precisely 153 days after the HLA-identical HSCT, the patient, who was currently receiving a daily dose of 25 mg of CsA, presented with symptoms of fatigue and jaundice. The blood chemistry analysis revealed significant elevations in ALT (1,022 U/L), AST (606 U/L), ALP (198 U/L), total bilirubin (2.06 mg/dL), direct bilirubin (1.47 mg/dL), albumin (4.2 g/dL), and globulin (3.9 g/dL). There were no indications of other chronic GvHD manifestations, such as skin rash or diarrhea. The differential diagnosis for the acute hepatocellular injury, which occurred nearly 6 months after the engraftment of the bone marrow, encompassed CsA-induced hepatotoxicity, acute viral hepatitis (HAV/HBV/HEV), reactivation of other viruses (cytomegalovirus, herpes virus, or Epstein-Barr virus), or a distinct presentation of GvHD, particularly the hepatitis variant of liver GvHD, which raised concerns. However, it appeared unlikely that CsA was the causative agent, given that the drug level fell within the normal range (168 ng/mL, range 100-450), and adverse toxicity typically presents as cholestatic hepatic injury. Serological tests, as well as tests for viral DNA and RNA (which yielded negative results for Anti-HBc IgM, Anti-HEV IgM, Anti-HAV IgM, HSV-1&2 IgM, EBV - Capsid IgM, HBV DNA, HCV RNA, and CMV RNA), ruled out viral hepatitis. An abdominal ultrasound suggested the presence of liver parenchymal disease without a definitive space-occupying lesion. Following inconclusive laboratory results, a liver biopsy was conducted, revealing histopathological findings indicative of moderate portal infiltration characterized by a significant presence of lymphocytes, plasma cells, and eosinophils. These cellular infiltrations were accompanied by moderate interface hepatitis and lobular inflammation, further supported by evidence of bile duct injury and endothelitis (refer to Figure 1&2). Immunostaining analysis targeting inflammatory cells exhibited positive results for CD4 and CD8 T cells, CD138 plasma cells, and a few CD20 B cells specifically localized in periportal areas (refer to Figure 1,2). These notable pathological findings led the suspicion of autoimmune hepatitis as the underlying etiology of the patient's condition. Consequently, serum tests were performed to detect autoantibodies, yielding the following results: a positive

antinuclear antibody (ANA) titer of 1:160 with a fine speckled pattern, a negative anti-smooth muscle antibody (SMA), and a positive anti-liver kidney microsomal-1 antibody (LKM-1). Furthermore, the patient's serum immunoglobulin G (IgG) level was measured at 2,060 mg/dL, surpassing the normal range of 700-1,600 mg/dL. The histopathological findings, along with the presence of autoantibody markers, provided compelling evidence supporting a diagnosis of autoimmune hepatitis as opposed to hepatic variant liver graft-versus-host disease (GvHD). The patient's International Autoimmune Hepatitis Group (IAIHG) simplified score of 8, which corresponds to a classification of "definite" autoimmune hepatitis, guided the initiation of treatment

with prednisolone at a dosage of 0.5 mg/kg/day. Remarkably, following a two-week course of corticosteroid therapy, there was a profound normalization observed in the levels of ALT/AST and bilirubin. Consequently, a gradual tapering of the prednisolone dosage to 10 mg/day was implemented, accompanied by the maintenance administration of azathioprine at a daily dose of 100 mg (equivalent to 1 mg/kg/day). Throughout an ensuing 6-month follow-up period, the patient's clinical condition remained stable without any notable exacerbations or complications.



**Figure 1:** Histopathological Findings



**Figure 2:** Immunostaining Analysis

Gender	Age	Underlying disease	Day of symptoms	Laboratory results	Autoantibody	Pathological findings	Treatment	Reference
Male	44	Stage IV follicular lymphoma	1 month	ALT - 16*ULN AST - 15*ULN ALP - 3*ULN TB - 3 mg/dL IgG 32 g/L	ANA -, SMA -, AMA -, anti-LKM1 +	Interface hepatitis with predominantly lymphoplasmacytic infiltrate, bridging fibrosis, and nodular regeneration	Death due to decompensated cirrhosis and pulmonary sepsis, unresponsive to corticosteroid	3
Female	43	Chronic myelogenous leukemia	27 months	ALT 965 IU/L AST 723 IU/L ALP 96 IU/L TB 0.6 mg/dL	ANA + (1:160) nucleolar, homogeneous pattern, SMA -, anti-LKM1 -, AMA -	Chronic active hepatitis with numerous plasma cells localized to portal regions, and mild piecemeal necrosis, mild centrilobular plasmacytosis	Prednisolone 20 mg/day, azathioprine 50 mg/day with normalization of transaminases level	4
Female	30	Lymphoblastic leukemia	356 days	ALT 1,980 IU/L AST 812 IU/L ALP & TB - normal	Negative autoimmune markers	Interface hepatitis with predominantly lymphoplasmacytic infiltrate and piecemeal necrosis	Liver transplantation due to fulminant hepatitis and methylprednisolone failure	5
Male	7	Lymphoblastic leukemia	180 days	ALT 811 IU/L AST 862 IU/L ALP 2,081 IU/L TB 2.2 mg/dL IgG 3,500 mg/dL	ANA + (1:160), AMA + (1:80)	Chronic portal inflammation with interface hepatitis infiltrated by lymphocytes and plasma cells without interlobular bile ducts damage	Prednisolone 1 mg/kg/day	6
Female	1	Myeloid leukemia	135 days	ALT 748 IU/L AST 495 IU/L IgG 1,878 mg/dL	Negative autoimmune markers	Interface hepatitis with lymphoplasmacytic infiltrate in portal areas with modest lobular inflammation and marked hepatocyte swelling	Rituximab due to unresponsive to prednisolone with mycophenolate mofetil	7
Male	31	Myelodysplastic syndrome	153 days	ALT 1,022 IU/L AST 606 IU/L ALP 198 IU/L TB 2.06 mg/dL IgG 2,060 mg/dL	ANA + (1:160) fine speckled pattern, anti-LKM1 +, SMA -	Moderate interface and lobular hepatitis, Bile duct injury and endothelitis	Prednisolone 0.5 mg/kg/day Azathioprine 1 mg/kg/day	This case

**Table 1:** Summary of case reports; clinical details, laboratory results, and treatment.



## Discussion and Conclusion

Allogeneic hematopoietic stem cell transplantation (HSCT) is a widely recommended therapeutic intervention for various hematologic disorders. While the primary objective of HSCT is curative in nature, it is essential to acknowledge the potential occurrence of complications. Among these complications, graft-versus-host disease (GvHD) stands out as one of the most frequently encountered adverse events subsequent to HSCT. GvHD manifests as damage to the skin, gastrointestinal mucosa, and liver. Extensive research studies have reported an incidence rate of up to 50% for GvHD in transplanted cases. Given the substantial morbidity and mortality associated with GvHD, the prompt recognition and timely intervention in cases of its manifestation assume utmost importance. Liver GvHD, a commonly observed manifestation of GvHD, presents itself in three distinct clinical categories. The first category is characterized by notable increases in ALP and total bilirubin levels, accompanied by mild elevations in AST and ALT levels, which serve as indicators of acute GvHD. The second category exhibits a significant elevation in transaminase levels, with or without the concurrent presence of jaundice. The third category demonstrates a gradual onset of cholestasis or chronic GvHD. The hepatic variant of liver GvHD, also known as type two hepatic GvHD, is predominantly associated with the reduction of immunosuppression or the infusion of donor lymphocytes. Notably, this specific variant may manifest without evident skin and gastrointestinal lesions. In addition to pronounced transaminase elevations, the pathological findings of the hepatic variant of GvHD predominantly reveal lobular hepatitis, accompanied by mild damage to the epithelial cells of the bile duct. Conversely, typical chronic GvHD is characterized by injury to the bile duct epithelium, accompanied by sparse infiltration of lymphocytes in the lobular and portal regions. To date, several case reports have documented distinct features of autoimmune-like hepatitis subsequent to HSCT. These features display clinical and laboratory resemblances to the hepatic variant of liver GvHD. In contrast, autoimmune hepatitis (AIH) represents a chronic inflammatory disorder characterized by interface hepatitis, heightened levels of serum IgG, presence of specific autoantibodies, and a remarkable response to immunosuppressive therapy. The previous reports, as presented in Table 1 [3-7], exhibit indistinguishable clinical characteristics but have confirmed AIH through biopsies. The underlying immune-pathogenesis of these interrelated diseases remains elusive. AIH arises from a breakdown in immune tolerance and involves intricate interactions encompassing genetic susceptibility, molecular mimicry, autoantigen response, and deficiencies in immunomodulation. Dysregulation of effector T cells, regulatory T cells, B cells, and Natural Killer (NK) cells assumes a pivotal role in autoimmune-mediated hepatocyte injury [8]. Conversely, the molecular imbalances

contributing to hepatocyte damage in hepatic GvHD are not yet well comprehended, although they involve the activation and proliferation of donor T cells, culminating in tissue injury. Cytotoxic T cells and NK cells release Fas-ligand and tumor necrosis factor-alpha, thereby inducing direct cytotoxic effects [1]. Limited studies have endeavored to elucidate the immune-pathogenesis and differentiate hepatic GvHD from autoimmune hepatitis. Recent data have revealed significantly higher peak AST levels in the AIH group in comparison to the hepatic GvHD group (AIH: median 780 IU/L, range 508-1,215; hepatic GvHD: median 381 IU/L, range 107-1,358), while ALT levels demonstrated a tendency to be higher in the AIH group, albeit lacking statistical significance (AIH: median 904 IU/L, range 517-1,586; hepatic GvHD: median 654 IU/L, range 216-2,065). Alkaline phosphatase, bilirubin, and lactate dehydrogenase levels were elevated in both groups without significant distinctions. Corticosteroid therapy exhibited a favorable response in all instances of AIH-like hepatitis in this study. Histological analysis revealed a predominant infiltration of CD8-positive T cells in AIH, accompanied by the presence of CD20-positive B cells and CD138-positive plasma cells [9]. Another study aimed to elucidate the dissimilarities in pathology and infiltrating inflammatory cells. Portal and periportal inflammation demonstrated greater prominence in AIH as opposed to GvHD, whereas lobular inflammation and bile duct inflammation were similarly observed in both groups. Semi-quantitative evaluation of immune cells in the portal and periportal areas strikingly manifested an accumulation of CD3/CD4/CD8-positive T cells, CD20-positive B cells, and CD138-positive plasma cells in AIH. Conversely, the aggregation of CD20-positive B cells and CD138-positive plasma cells in GvHD was scarce [10]. In our patient, the clinical manifestation of acute hepatitis with significantly elevated transaminase levels in the context of chronic GvHD was elucidated through the identification of autoimmune markers (positive ANA & LKM-1). Histopathological analysis demonstrated moderate interface and lobular hepatitis, accompanied by positive immunostaining markers for T cells, B cells, and plasma cells. Furthermore, the swift normalization of AST/ALT levels upon the initiation of immunosuppressants serves as additional supportive evidence favoring the diagnosis of autoimmune hepatitis rather than hepatic GvHD. Consequently, the most appropriate diagnosis in this particular case is anti-LKM1 autoimmune hepatitis subsequent to HSCT. In conclusion, the differential diagnosis of liver dysfunction in patients who have undergone HSCT poses a significant challenge, encompassing a range of potential causes such as viral infections, drug-induced liver injury, sepsis-associated cholestasis, malignancy relapse, and graft-versus-host disease. Given the clinical presentation of acute hepatitis, particular attention should be directed towards the hepatic variant of liver GvHD. Recent developments have contributed to a growing understanding of the clinical,

immunological, and histological features of autoimmune hepatitis following HSCT, particularly in cases where transaminase levels are markedly elevated. Thus, it is crucial to include autoimmune hepatitis in the differential diagnosis of patients presenting with unexplained acute hepatitis, with the added value of biopsy-proven pathology. Furthermore, further research endeavors are necessary to gain a comprehensive understanding of the distinct pathogenetic mechanisms underlying autoimmune hepatitis after HSCT and the hepatic variant of liver GvHD.

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