Acute Hepatitic Onset of Liver GVHD Occurring 9 Months Post-transplant

16

Howard M. Shulman and Keith R. Loeb

Clinical History

A 40-year-old woman received an allogeneic-matched sibling transplant. The only post-transplant problem consisted of mild skin GVHD which responded to prednisone. At 8.5 months post-transplant, she finished a 2-week course of famciclovir for zoster. Two weeks later her liver function tests (LFTs) (Fig. 16.1) revealed normal bilirubin with mild elevations of alkaline phosphatase (AP) 405 IU/L, SGOT 112 IU/L, and SGPT 133 IU/L. Within 2 weeks SGOT had markedly risen to 2086 IU/L, SGPT 1641 IU/L, and AP 347 IU/L. The first liver biopsy was performed 26 days after the onset of the liver elevations at 10 months post-transplant (Fig 16.2). Foscarnet was given preemptively for treatment of presumed zoster hepatitis. Tests for hepatitis A, B, and C were negative, as were CMV studies by PCR. There was no potential exposure to hepatotoxic drugs to cause her symptoms. In the ensuing month, transaminases and AP levels declined; however, her SGOT again rose to 475 IU/L, and her bilirubin continued to rise to a peak of 30 mg 33 days later when a second liver biopsy was done at 11 months post-transplant (Fig. 16.3). Follow-up treatment with high-dose steroids and cyclosporin led to rapid improvement in liver tests with normalization of bilirubin in 2 months.

H. M. Shulman (✉) · K. R. Loeb
Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA

Pathology Section, Seattle Cancer Care Alliance, Seattle, WA, USA
e-mail: tigermaya@comcast.net; kloeb@seattlecca.org

C. C. S. Yeung, H. M. Shulman (eds.), *Pathology of Graft vs. Host Disease*,
https://doi.org/10.1007/978-3-319-42099-8_16

Diagnosis

Nine months post HSCT solitary onset of liver GVHD clinically presenting as an acute hepatitis after cessation of IS.

Key Pathology Features

1. Presentation as a lobular hepatitis with markedly elevated transaminases >2000 iu.
2. Marked lobular inflammation with numerous acidophilic bodies (necrotic hepatocytes).
3. Enlarged portal spaces containing a mixture of lymphocyte plasma cells and scattered eosinophils.
4. Interface inflammation.

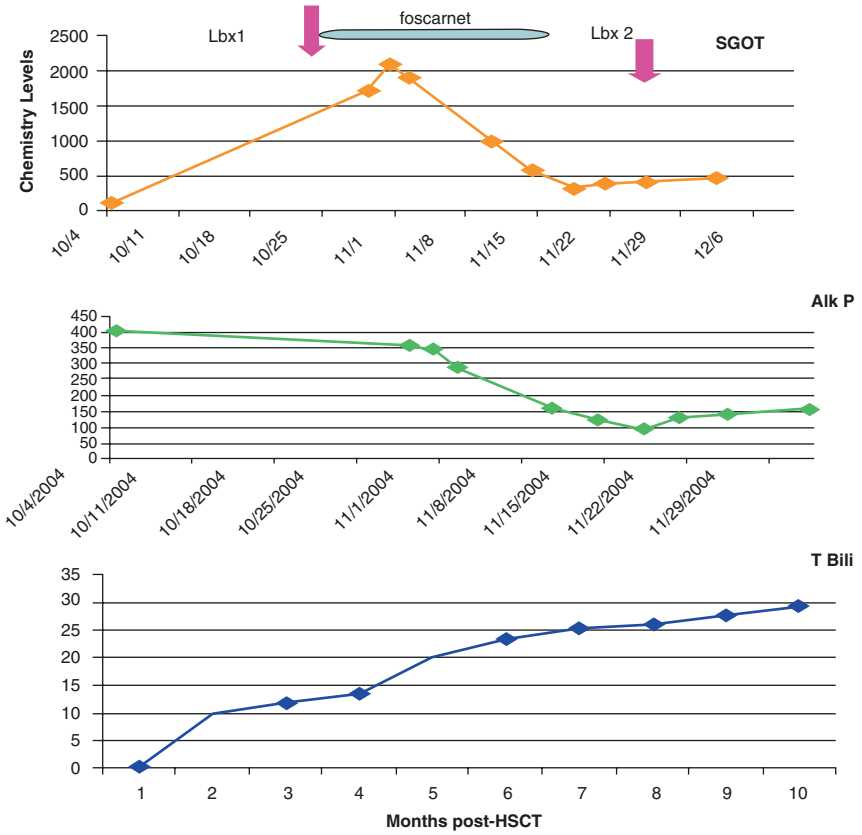

Fig. 16.1 Timeline of liver test abnormalities

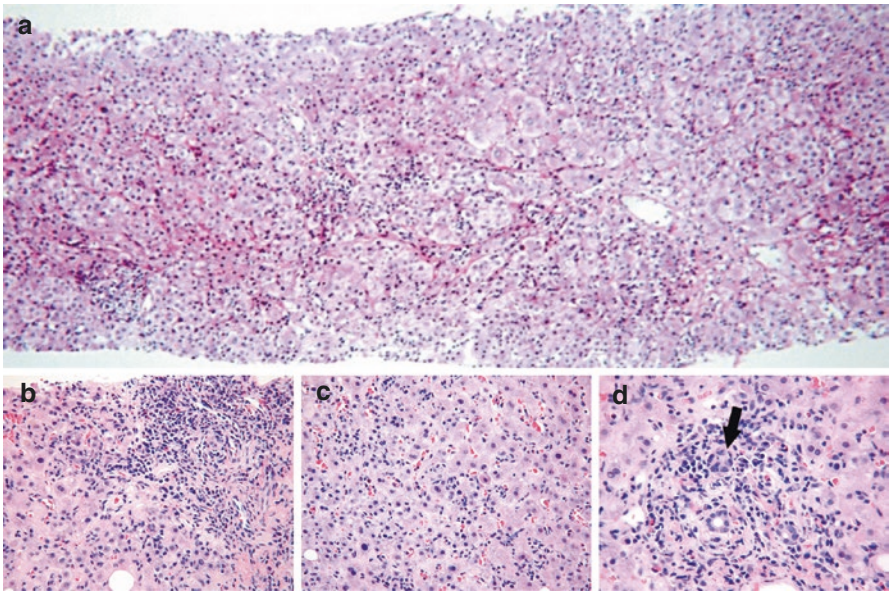

Fig. 16.2 The first liver biopsy was performed at 1 month from the initial onset of LFT elevations. It had a striking lobular hepatitis with disarray of the hepatocyte cords, hepatocyte unrest with many sinusoidal lymphocytes, prominence of Kupffer cells (**a**), and many scattered acidophilic hepatocytes (**b**). The expanded portal spaces contained a mixed infiltrate of lymphocytes and macrophages, as well as a few eosinophils and plasma cells, spilling over into the surrounding periportal plate (interface inflammation) (**c**). The larger bile ducts were unremarkable; however, some of the smaller bile ducts (one is indicated by the arrow) had swollen cytoplasms with nuclear dyspolarity, anisonucleosis, or segmental loss of nuclei and contained a scattering of intraepithelial lymphocytes (**d**)

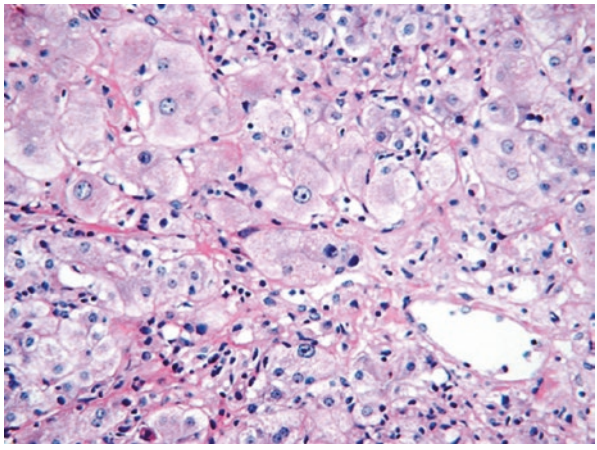

Fig. 16.3 The second liver biopsy, performed at 11 months, displayed pronounced cholestatic changes in the hepatocytes with canalicular bile plugs and marked swelling of pigment-laden hepatocytes in zone 3. This was associated with focal hepatocytolysis, perivenular lymphocytic inflammation, and sinusoidal fibrosis

5. Bile ducts obscured by inflammatory cells. Bilirubin rise occurs after spike in transaminases.
6. Follow-up biopsy taken has more pronounced bile duct damage and hepatocellular cholestasis including perivenular hepatocytolysis.
7. Initiation of steroid treatment before bile duct destruction led to complete clinical resolution.

Discussion

The typical presentation of liver GVHD in long-term survivors with concomitant cGVHD in other organs is an indolent or slowly progressive cholestatic liver disease. In contrast, we have a patient recently off immunosuppression (IS), with no other signs of GVHD, with an explosive onset of a hepatitis-like clinical picture with extremely high transaminases [1]. Her bilirubin which was initially normal became markedly elevated. The initial elevation of transaminases was related to the effect of cytokines on the Fas and Fas Ligand (Fas-FasL) interaction causing necrosis of hepatocytes preceding the actual damage to the bile ducts. It was interesting that in this case the initial biopsy mainly showed the hepatitic features, while small bile duct changes were less pronounced (Fig. 16.4). The pronounced portal inflammation contained a mixture of inflammatory cells which included eosinophils and many plasma cells. The second biopsy showed obvious bile duct damage, hepatocellular cholestasis, and perivenular hepatocytolysis [1]. It is important to recognize this acute hepatitic presentation of GVHD since delay of treatment can lead to severe loss of bile

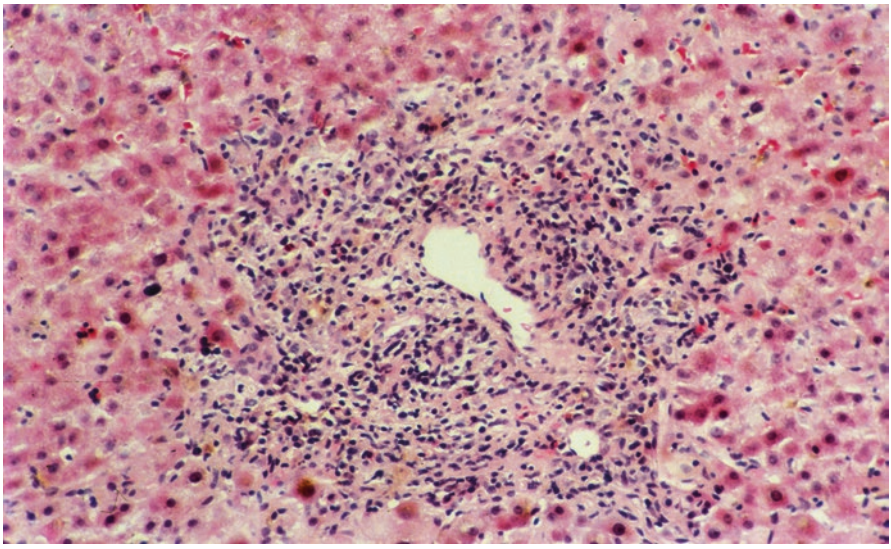

Fig. 16.4 A separate case of acute hepatitic GVHD with marked portal inflammation with plasma cells and some eosinophils with interface inflammation. Small bile ducts are not overtly damaged early after onset, consistent with the concept that the early changes are mostly related to cytokines and later to cellular-mediated damage

ducts and irreparable liver damage. Antiviral therapy should be started as a precautionary measure even before the diagnosis is established. Similar acute hepatitic presentations of GVHD have been reported by other studies [2, 3], especially following donor lymphocyte infusions given in an attempt to stimulate a graft-versus-leukemia response, though the transaminase elevations were less pronounced [4].

A rare, slowly progressing inflammatory and fibrosing non-infectious hepatitis resembling autoimmune-like hepatitis (AIH) has been reported [5, 6]. It has been described in recent literature as a histopathological overlap of primary biliary cirrhosis (PBC) and progressive systemic sclerosis (SSc): "PBC/SSc overlap syndrome" [17]. In our clinic, some of these cases developed many years post-allogeneic HSCT, in the absence of either protracted aGVHD or stigmata associated with cGVHD. We propose that the name for this form of hepatitis be called "chronic alloimmune hepatitis," abbreviated to "CAIH," as the immune system in cases described in the literature is derived from fully allogeneic donor hematopoietic cells. The corresponding histology displays expanded portal spaces filled with lymphoplasmacytic inflammation, damage to and/or destruction of small bile ducts, interface inflammation. and portal and lobular fibrosis tending toward cirrhosis. Some cases had high titers of autoantibodies to LKM type 2 [7] (personal communication: GB McDonald). Some cases had autoantibodies of non-organ specificity (ANA and ASMA) that overlapped with some of the same sera antibodies as those in cGVHD [8]. Sporadic cases of cirrhosis that occur 5-15 years post-HSCT and are attributed to GVHD isolated to the liver may well be a late manifestation of CAIH [15, 16]. To summarize, CAIH may be viewed as an autoimmune-like manifestation, similar to those in Chap. 20, whose genesis develops in the milieuof an altered immune reconstitution after allogeneic HSCT.

In the early era of HSCT, liver GVHD was posited to be pathogenetically related to PBC. These early studies reported positive anti-mitochondrial antibodies (AMA), a marker specific for PBC, in 5–81% of patients with cGVHD. In 1999, Quaranta et al. evaluated sera from 89 cGVHD patients for AMA using more precise analytes and methodology. None of the 89 patients had positive AMA, but they did have a variety of other non-disease-specific autoantibodies. Finally, immunohistochemistry (IHC) in GVHD-affected liver biopsies for PDC-E2 by the PBC-specific monoclonal antibodies against the epithelial luminal antigens of PBC bile ducts was negative in all 89 cGVHD patients. In summary, hepatic GVHD is not a model for PBC because of the rarity of cirrhosis, absence of granulomata, sparing of large bile ducts, and absence of specific IHC staining against the epithelial luminal mitochondrial target of PBC [8].

The remaining clinical differential possibilities are the same as those discussed in Chap. 15 including viral hepatitis caused by HAV, HCV, HBV, and that more recently ascribed to HEV [9, 10]. Rapid diagnosis using DNA/RNA PCR on serum and tissue IHC staining is needed to avoid a fatal outcome since these infections have effective antiviral treatments. Additional viral infections, though rare, include hepatitis from several herpes group viruses. Herpes simplex hepatitis causes massive hepatic necrosis (Figs. 16.5 and 16.6). Varicella-zoster hepatitis may present with severe abdominal pain from visceral involvement without skin lesions. Zoster hepatitis produces random foci of hepatocellular necrosis and involvement of bile ducts (Fig. 16.7). EBV lymphoproliferative syndrome causes massive infiltration of the portal spaces by plasmacytoid cells (Figs. 16.8 and 16.9). EBV is readily identifiable by finding elevated plasma PCR DNA levels and histologically by EBER in situ hybridization

studies. HHV6B hepatitis has been described after liver allograft. Though HHV6 viruses are ubiquitous in transplant recipients, there is only a single case report of HHV6B hepatitis after HSCT documented by PCR and in situ hybridization of the liver which histologically had periportal necrosis [11]. CMV infection in the liver is usually part of disseminated CMV, especially with concomitant gut involvement. Nonetheless, it rarely results in significant liver dysfunction [12, 13]. Therefore, performing IHC for CMV with clinical acute hepatitic presentation is unnecessary and should not be regarded as the explanation [14]. Adenovirus hepatitis produces random punched-out foci of necrosis with the diagnostic virally infected cells along the periphery. In such cases, the ALT elevations are not as great as those caused by other viral infections (Figs. 16.10 and 16.11). If there is coexisting chronic HCV or HBV infection, fibrosing cholestatic hepatitis should be considered (Chap. 15). In addition to any infectious etiologies, any known hepatotoxic drugs should be discontinued.

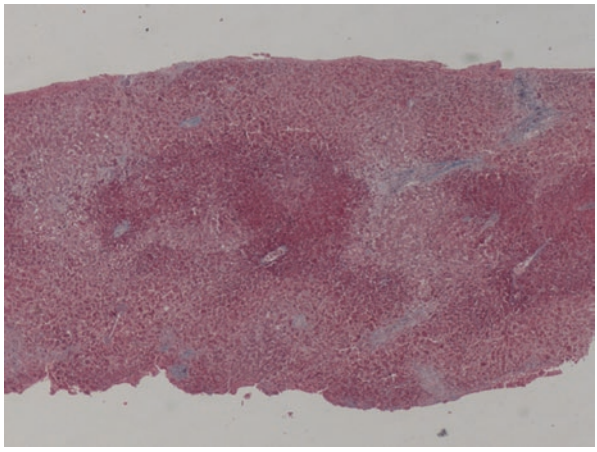

Fig. 16.5 Herpes simplex hepatitis at low magnification shows regular foci of hemorrhagic necrosis

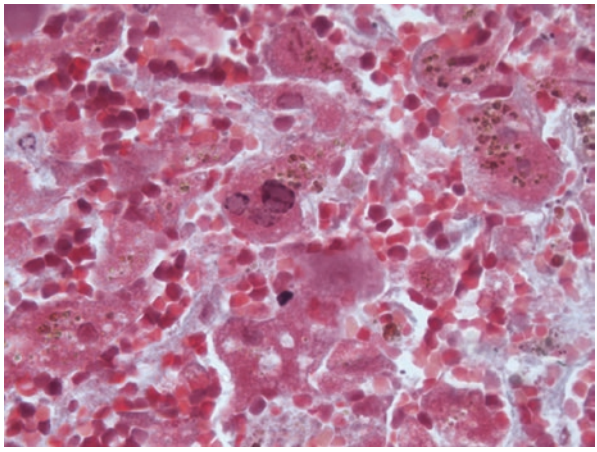

Fig. 16.6 High magnification shows degenerating hepatocytes containing smudgy nuclear inclusions of Herpes Simplex Virus

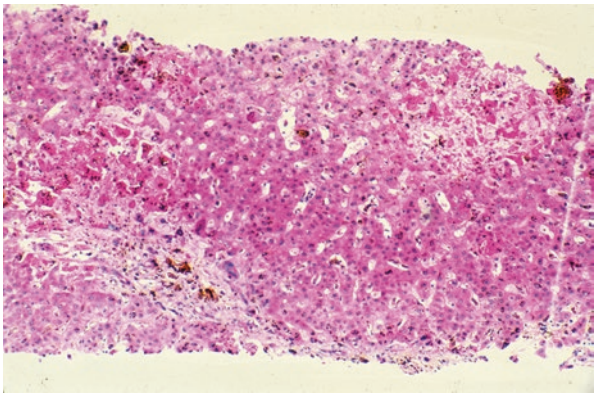

Fig. 16.7 Random foci of hepatocellular necrosis and involvement of bile ducts in a patient with viceral herpes zoster

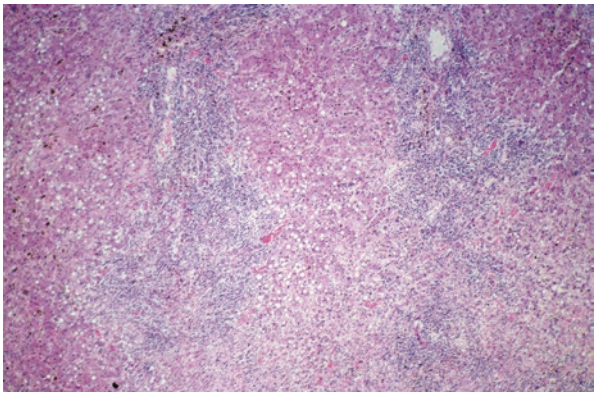

Fig. 16.8 EBV-driven post-transplant lymphoproliferative disease in the liver arising after T-cell depletion. Lower power view shows massively infiltrated portal spaces

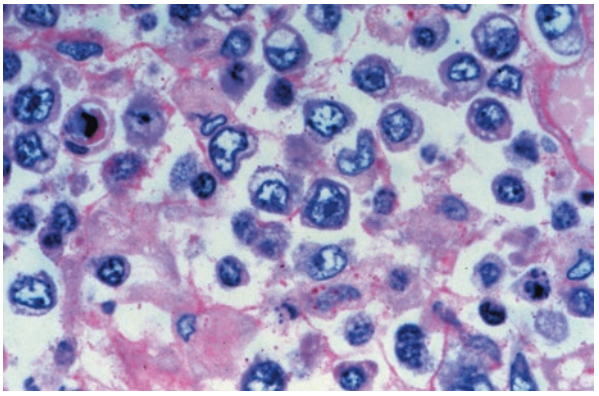

Fig. 16.9 High power view of the same biopsy as Fig. 16.8 shows the neoplastic cells with a plasmacytoid appearance

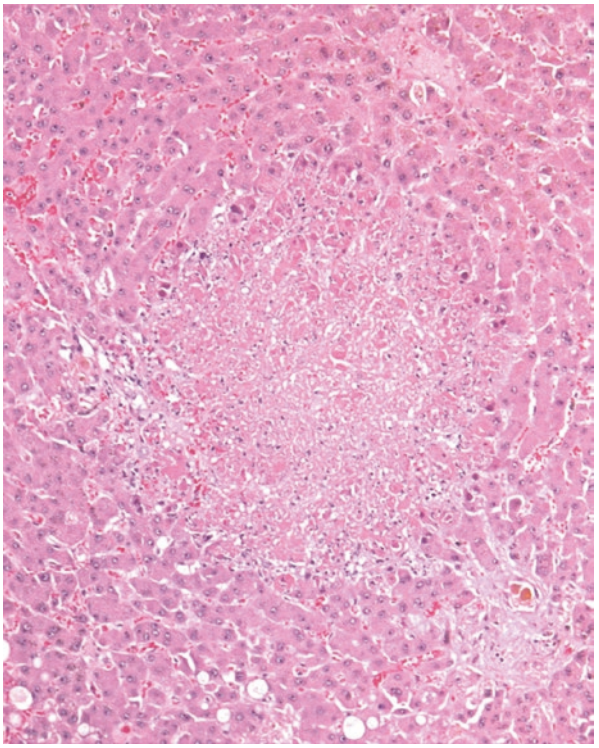

Fig. 16.10 Randomly punched-out necrotic focus from adenovirus in the liver

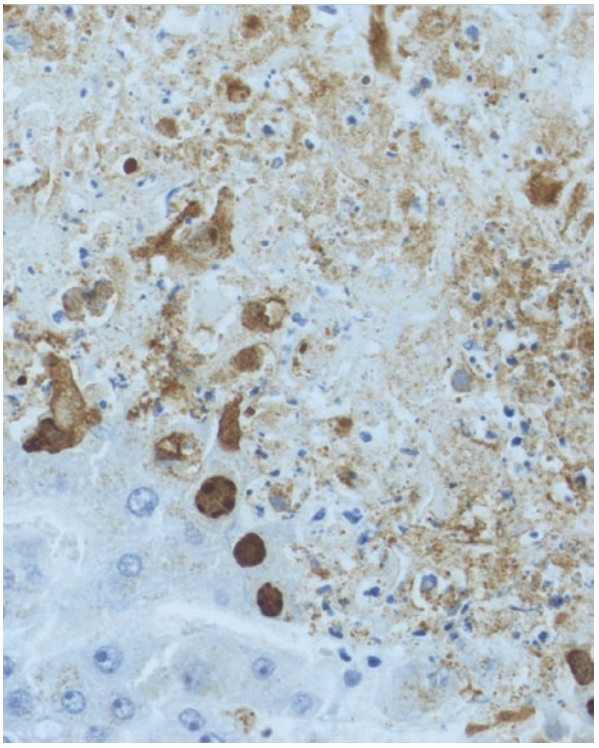

Fig. 16.11 IHC for adenovirus of the punched-out lesion shows many infected cells along the periphery

Teaching Points

- The acute hepatitic onset of liver GVHD presents with high aminotransferases following cessation or tapering of IS.
- The bilirubin rise may lag behind the marked transaminases. This is related to hepatocyte acidophilic body formation secondary to cytokine activation.
- Acute hepatitic onset may follow infusion of donor lymphocytes given to promote a graft-versus-leukemia effect.
- Histology of acute hepatitis onset shows a lobular hepatitis with interface inflammation with a necroinflammatory infiltrate that may include eosinophils and many plasma cells in the portal areas. Damaged bile duct changes may be more evident later, but portal inflammation may be reduced if IS treatment has been initiated.
- Differential diagnosis includes viral infections which must be ruled out. Antiviral treatment should be started even before there is positive confirmation.

Questions

1. What is the usual setting when the acute hepatitic onset of liver GVHD develops?
2. What is the differential diagnosis?
3. Why does the marked rise in aminotransferases occur before the appearance of histologic signs of bile duct damage and histologic changes?

Answers

1. Answer: Following tapering or cessation of IS
2. Answer: Viral infection caused by HBV, HCV, HSV, VZV, EBV, and adenovirus. Any potential hepatotoxic drugs should be stopped.
3. Answer: The initial rise in liver enzymes reflects the effect of IL-6 and IL-2 cytokines' nonspecific FAS-FASL interactions with hepatocytes, resulting in hepatocyte death and subsequent release of aminotransferases (the innocent bystander effect). The actual immunologic targets (the bile ducts) are later injured due to cellular attack.

References

1. Strasser SI, Shulman HM, Flowers ME, et al. Chronic graft-versus-host disease of the liver: presentation as an acute hepatitis. Hepatology. 2000;32(6):1265–71.
2. Ma SY, Au WY, Ng IO, et al. Hepatitic graft-versus-host disease after hematopoietic stem cell transplantation: clinicopathologic features and prognostic implication. Transplantation. 2004;77(8):1252–9.
3. Baniak NM, Kanthan R. Autoimmune-like hepatitis: a "Hepatitic" manifestation of chronic graft versus host disease in post-stem cell transplant. Int J Surg Pathol. 2016;24(2):146–52.

4. Akpek G, Boitnott JK, Lee LA, et al. Hepatitic variant of graft-versus-host disease after donor lymphocyte infusion. Blood. 2002;100(12):3903–7.
5. Narita A, Muramatsu H, Takahashi Y, et al. Autoimmune-like hepatitis following unrelated BMT successfully treated with rituximab. Bone Marrow Transplant. 2012;47(4):600–2.
6. Koyama D, Ito M, Yokohata E, et al. Autoimmune-like hepatitis after allogeneic hematopoietic stem cell transplantation: humoral hepatic GvHD. Bone Marrow Transplant. 2017;52(1): 151–3.
7. Granito A, Stanzani M, Muratori L, et al. LKM1-positive type 2 autoimmune hepatitis following allogenic hematopoietic stem-cell transplantation. Am J Gastroenterol. 2008;103(5):1313–4.
8. Quaranta S, Shulman H, Ahmed A, et al. Autoantibodies in human chronic graft-versus-host disease after hematopoietic cell transplantation. Clin Immunol. 1999;91(1):106–16.
9. Carre M, Thiebaut-Bertrand A, Larrat S, et al. Fatal autochthonous fulminant hepatitis E early after allogeneic stem cell transplantation. Bone Marrow Transplant. 2017;52(4):643–5.
10. Willemse SB, Bezuur DL, Blom P, et al. Hepatitis E virus infection and hepatic GvHD in allogeneic hematopoietic stem cell transplantation recipients. Bone Marrow Transplant. 2017;52(4):622–4.
11. Hill JA, Myerson D, Sedlak RH, Jerome KR, Zerr DM. Hepatitis due to human herpesvirus 6B after hematopoietic cell transplantation and a review of the literature. Transpl Infect Dis. 2014;16(3):477–83.
12. Rees GM, Sarmiento JI, Myerson D, Coen D, Meyers JD, Mcdonald G. Cytomegalovirus hepatitis in marrow transplant patients: clinical, histologic and histochemical analysis. Gastroenterology. 1990;98:A470.
13. Snover DC, Hutton S, Balfour HH Jr, Bloomer JR. Cytomegalovirus infection of the liver in transplant recipients. J Clin Gastroenterol. 1987;9(6):659–65.
14. Larson AM, McDonald GB. Hepatobillary infections after solid organ or hematopoietic cell transplantation. In: Ljungman P, Snydman DR, Boeckh M, editors. Transplant infections. 4th ed. Cham: Springer International Publishing AG; 2016. p. 653–73.
15. Strasser SI, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. Blood. 1999;93(10):3259–66.
16. A Xhaard, P Nahon, M Robin, C Baudry, L Ades, R Peffault de Latour, G Socié, (2012) Hepatic GVHD leading to cirrhosis after allogeneic hematopoietic SCT. Bone Marrow Transplantation. 47(11):1484–5.
17. Assandri R, Serana F, Montanelli A. Development of PBC/SSc overlap syndrome in chronic GVHD patient: immunological implications in the presence of mitochondrial, nucleolar and spindle midzone autoantigens. Gastroenterology and hepatology from bed to bench. 2017;10(4):323–31.