Hepatic cirrhosis in two patients with neuroblastoma receiving hematopoietic stem cell transplantation

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Abstract

Hepatic cirrhosis is a very rare complication of hematopoietic stem cell transplantation (SCT) and of neuroblastoma. We encountered two patients developing cirrhosis after SCT against neuroblastoma. A 6-year-old boy who had received allogeneic bone marrow transplantation developed cirrhosis 10 years after the SCT with the massive upper gastrointestinal hemorrhage. A 27-year-old man receiving allogeneic cord blood transplantation against recurrence of neuroblastoma, died of liver failure due to histological cirrhosis 1 year after the SCT. We could not detect the definite etiologic candidates of cirrhosis; however, careful monitoring appears warranted to avoid overlooking the onset and progression of cirrhosis after SCT.

Introduction

Hepatic cirrhosis is a very rare complication of hematopoietic stem cell transplantation (SCT), with estimated cumulative incidences of 0.6% by 10 years and 3.8% by 20 years after SCT [1)]. Similarly, the complication of cirrhosis with neuroblastoma is rare and only one report is available that describes hepatic cirrhosis in two patients with neuroblastoma [2)]. No previous reports appear to have described the development of cirrhosis after SCT in patients with neuroblastoma.

Case Descriptions

Case 1

A 6-year-old boy with no prior history of note presented with a mass under the right costal margin. Computed tomography (CT) demonstrated a tumor with huge cysts and partial calcification between the right lobe of the liver and kidney, arising from the right retroperitoneum (Figure 1A). No evidence of bone marrow infiltration or other metastases was seen. Open biopsy demonstrated amplified *MYCN* gene and revealed neuroblastoma of round cell type, poor prognosis group. The tumor was classified as high-risk group with stage L2 disease based on the International Neuroblastoma Risk Group Staging System (INRGSS)[3)]. He received three courses of chemotherapy including cyclophosphamide (CPM), vincristine (VCR), pirarubicin (THP), cisplatin (CDDP), etoposide (VP-16), and ifosfamide. Then he underwent right segmental liver resection, right nephrectomy, and partial diaphragm resection due to direct tumor invasion, followed by two courses of chemotherapy and irradiation with 15 Gy to the entire abdomen and 30 Gy to the left supraclavicular fossa and posterior mediastinum under the shielding of the liver and the kidneys. Allogeneic bone marrow transplantation (BMT) from a sibling was then performed after myeloablative conditioning with total body irradiation (TBI), VP-16 and cyclophosphamide (CY). Methotrexate was used for graft-versus-host disease (GVHD) prophylaxis. Grade I acute GVHD manifested as exanthema but resolved spontaneously. After BMT, he received additional chemotherapy with CPM, dacarbazine and VCR. Treatment was completed

in 2 years when he was 8 years old. Ten years after that, the patient was hospitalized due to massive gastrointestinal hemorrhage. Upper gastrointestinal endoscopy revealed ruptured esophageal varices, and CT demonstrated portal vein aneurysm with extensive collateral vein formation (Figure 1B). He met the clinical criteria for hepatic cirrhosis and portal hypertension, although liver enzymes remained within normal limits. His severe condition settled and he was discharged, but the patient committed suicide 1 year after this event at 19 years old, 11 years after BMT.

Case 2

A 24-year-old man with no prior history of note presented with pain in the lower back and pancytopenia. Bone biopsy revealed neuroblastoma cells, and CT showed an abdominal mass arising from the right adrenal gland. Infiltrations into bone marrow and bone throughout the body were identified. INRGSS high-risk *MYCN* -non-amplified stage M neuroblastoma was diagnosed. He received 5 courses of chemotherapy with VCR, CPM, THP and CDDP and underwent autologous peripheral blood SCT (PBSCT) with myeloablative conditioning comprising busulfan (BU) and CY. He then underwent tumor resection and irradiation to the whole spine and right adrenal gland (19.8 Gy), and to the skull, pelvis and femur (5.4 Gy). Secondary aplastic anemia was developed, and oral administration of cyclosporine (CsA) was initiated. Due to the frequent blood transfusions, iron overload gradually progressed but rapidly improved by administration of deferasirox. He was discharged 10 months after the PBSCT. One and a half years after discharge, bone marrow and bone recurrence occurred. He received 4 cycles of chemotherapy with irinotecan, VP-16 and carboplatin, followed by allogeneic cord blood transplantation (CBT) with myeloablative conditioning of BU, VP-16 and CY. CsA and methylprednisolone were used for GVHD prophylaxis. Moderate veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) was treated with danaparoid sodium and ursodeoxycholic achieving rapid improvement. Grade II acute GVHD manifesting as diarrhea was controlled with additional prednisolone. Cytomegalovirus (CMV) antigenemia was also well controlled by administration of ganciclovir. From around 50 days after transplantation, pleural effusion and ascites retention gradually worsened along with deterioration of renal function. Relapse of neuroblastoma was negative, but his condition had gradually worsened. Ten months after CBT, CT showed liver atrophy and marked ascites retention. Blood Mac-2-binding protein glycosylation isomer index and the 15-min retention rate of indocyanine green was elevated, both suggesting development of cirrhosis. Upper gastrointestinal endoscopy showed no esophageal varices. His general condition continued to worsen, and he died of liver failure 1 year after CBT, at 29 years old. Histological examination of needle liver autopsy demonstrated characteristics of bridging and pericellular fibrosis with architectural distortion and spotty necrosis, consistent with cirrhotic changes, and severe hepatocyte damage with slight infiltration of inflammatory cells (Figure 2A, B). Fibrotic hyperplasia and mild infiltration of inflammatory cells were also evident around the portal vein. No histological evidence of GVHD or sinusoidal obstruction was seen. A definitive histological diagnosis of cirrhosis was made.

Discussion

In our institution, we have over 120 patients receiving SCT against hematological malignancies and solid tumors in childhood, adolescence or young adulthood so far. However, we have encountered only two patients that developed hepatic cirrhosis after SCT, and both suffered from neuroblastoma. Neither case showed evidence of hepatitis virus infection including hepatitis C virus (HCV), which has been accepted as the most frequent cause of cirrhosis [1)4)]. Treatment, conditioning before SCT and other characteristics of our two cases differed markedly from each other except for the underlying disease, neuroblastoma. Speculation on the involvement of the underlying disease in the onset of cirrhosis is thus natural. The liver is known as an organ to which neuroblastoma frequently metastasizes, and a previous report showed that the frequency of neuroblastoma metastasis to the liver at the time of diagnosis was 29.6% [5)]. However, since very few patients undergo liver biopsy at diagnosis or during treatment, and evaluation is usually made only by imaging, the exact frequency of liver involvement remains unclear. Another speculation regarding underlying condition is that some congenital predisposition (such as DNA repair defects, telomere disorders and so on) and autoimmunity had some impact on massive hepatic damage. Both our cases had no medical history, family history or congenital malformations that suspected them. Other possible causes of cirrhosis would

be TBI, VOD/SOS, GVHD, CMV infection and iron overload. Regarding TBI, a previous report showed that radiation-induced liver disease is unlikely to occur after a mean liver dose around 30 Gy in conventional fractionation [6]. Neither case was exposed to 30 Gy at the liver in our patients. Liver damage associated with VOD/SOS[1], GVHD [7], CMV infection[8] and iron overload [9] could conceivably have contributed to the onset of cirrhosis. In our cases, however, these conditions would not play a direct inducer of hepatic cirrhosis since these were properly handled by medications and achieved clinical improvement. We have made a number of considerations on the causes or mechanisms that induced hepatic cirrhosis in our two patients but could not get any definitive conclusion.

To the best of our knowledge, this report represents the first of hepatic cirrhosis after SCT against neuroblastoma. Since high-risk neuroblastoma could metastasize to various organs including the liver and requires multidisciplinary treatment, various severe complications can occur. Our cases demonstrated that hepatic cirrhosis could develop at any time after treatment for neuroblastoma including SCT, and careful life-long monitoring of the liver is warranted to detect cirrhotic events before progression to hepatic failure.

Conflict of Interest Statement

The authors have no conflicts of interest or funding to disclose.

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Figure legends

Figure 1. CT of Case 1. **A)** CT on admission showing a tumor (white arrow) with huge cysts and partial calcification between the right lobe of the liver and the right kidney. **B)** CT at the time of rupturing of esophageal varices revealing portal vein aneurysm (black arrow) with extensive collateral vein formation.

Figure 2. Histological examination of a needle liver autopsy of Case 2 (**A** , 40× magnification; **B** , 100× magnification).

Masson trichrome staining of hepatocytes demonstrates characteristic bridging and pericellular fibrosis with architectural distortion and spotty necrosis, together with severe hepatocytic damage with slight infiltration of inflammatory cells. Fibrotic hyperplasia and mild infiltration of inflammatory cells are also seen around the portal vein.

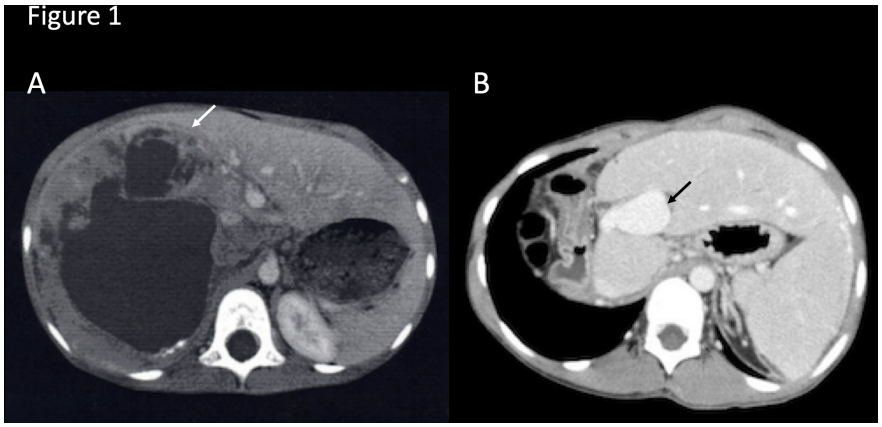

Figure 2