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CASE REPORT

Fulminant isolated adenovirus hepatitis 5 months after haplo-identical HSCT for AML

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Key Clinical Message

The principal limitation of allogeneic hematopoietic stem cell transplantation except relapse remains the transplant-related mortality (TRM). In addition to graft-versus-host disease (GvHD), infections contribute to TRM in many patients. We describe herein a case of an adult patient presenting 5 months after haplo-identical transplantation an isolated fulminant hepatitis due to adenovirus.

Keywords

Adenovirus, allogeneic HSCT, haploidentical HSCT, viral hepatitis.

Background

Although numerous progresses were made, the principal limitation of allogeneic hematopoietic stem cell transplantation (HSCT) except relapse remains the transplant-related mortality (TRM). In addition to graft-versus-host disease (GvHD), infections contribute to TRM in many patients. Infections occur rapidly after transplantation during the immunosuppressed period, which is a consequence of conditioning regimen, serotherapy, progressive reconstitution of immune system, and administration of immunosuppressive agents. Besides fungal and bacterial infections, there is also a risk of reactivation and viral infection. Herpes viruses (HSV, VZV, and HHV6), Epstein–barr virus (EBV), cytomegalovirus (CMV), and adenovirus (ADV) are the most important in this setting. In severely immunocompromised patient, ADV causes severe respiratory disease, hepatitis, colitis, encephalitis, pancreatitis, hemorrhagic cystitis, and keratoconjunctivitis [1–3]. Disseminated ADV disease is the most common presentation of the disease in allogeneic HSCT patients [1–5]. The incidence is 1–7% with a reported mortality of 8–26% [1–5]. ADV infection is more frequent in the pediatric population and risks factors for development of this infection include GvHD and the use of immunosuppressive agents [1–6]. We describe herein a case of an adult patient presenting, 5 months after haplo-identical allogeneic HSCT, with an isolated fulminant hepatitis due to ADV.

Case Presentation

A 27-year-old woman presented with acute myeloblastic leukemia (FAB 6) secondary to myelodysplastic syndrome in August 2012. On diagnosis, the karyotype was normal; in molecular biology, there were WT1+, a single mutation of CEBPa (mutation TAD1 from CEBPa), and no mutation of NMP1. A complete response was obtained after induction chemotherapy. As a consolidation therapy, she received two cycles of high-dose Ara-C associated with pegfilgrastim. She relapsed on April 2014 and she received Ara-C and idarubicine as salvage therapy. The patient was a single child and a search for unrelated HLA-identical donor was started at the time of relapse. A second complete response was obtained. No HLA-identical unrelated donor was identified after 12 weeks of

research and a haplo-identical allogeneic HSCT from her mother was scheduled. The conditioning regimen was an association of fludarabine, cyclophosphamide, busulfan, antithymocyte globulin, and cyclophosphamide post graft infusion [7]. The GvHD prophylaxis consisted on the association of tacrolimus (Tac) and mycophenolate mofetil (MMF) [7]. The stem cell source was peripheral blood stem cells (PBSC) with 4.32 × 10e6 CD34+/kg. The recipient was CMV+, HSV+, HHV6+, TOXO+, EBV+, and VZV+. The transplantation was not complicated except for the beginning of sinusoidal occlusive syndrome (SOS) treated with diuretics and ursodeoxycholic acid (the dosage reached was – 750 mg three times a day). At day 21, Tac was stopped as she developed schizocytes, and MMF was continued alone with a progressive tapering with an aim to stop at 6 months after transplantation. Hematological recuperation occurred on day 18 with a chimerism of 100% donor on both peripheral blood (PB) and bone marrow (BM). She was discharged on day 27 after transplantation. During the first three months of follow-up at outpatient clinic, EBV, HHV6, Toxoplasmosis, CMV and ADV PCR were regularly examined in blood [8–10]. She received monthly serum immunoglobulin. Her posttransplantation course was characterized by CMV reactivation at day 56 and she was treated with valgancyclovir (one box obtained from compassionate use of the Belgian Hematopoietic Society (BHS) program) during for 6 weeks. At routine follow-up of 3 months after transplantation, there was no evidence of relapse; the chimerism was 100% donor on both PB and BM. Her blood tests showed – CD3 count:16 × 10e3/mm^3, CD4 count: 4 × 10e3/mm^3, CD8 count: 12 × 10e3/mm^3 with a CD4:CD8 ratio of 0.33; IgG: 9.07 g/L, IgA 0.59 g/L and IgM 0.08 g/L; Hg 8.1 g/dL, white cells (WC) count: 2.0 × 10e3/mm^3 with neutro 1.61 × 10e3/mm^3, and Platelets count: 89 × 10e3/mm^3. We decided on account of these results, to collect donor lymphocytes in case of new CMV reactivation [11]. After 3 months of follow-up, we continued to watch the PCR for CMV in blood every week. A second CMV reactivation occurred on day 121 and the patient was treated with valgancyclovir (two boxes were obtained in the compassionate use of BHS program), but the dose had to be reduced after 1 week as she developed severe toxic pancytopenia (Hg: 7.0 g/dL, neutro: 0.5 G/L, Plat 30 × 10e3/mm^3). Granulocyte-colony stimulating factor (G-CSF) was started three times a week and she received serum immunoglobulin weekly as supportive care. A donor lymphocyte injection (DLI) of 1 × 10e5 CD3+/kg was administrated on day 134 to improve the immune antiviral response.

Three weeks after the DLI, she was admitted in the Hematological Department with fever (38.5°), nausea, vomiting, loss of weight, loss of appetite, and severe oral candidiasis. Her blood tests showed Hg: 9.1 g/dL, WC: 2.7 × 10e3/mm^3, Plat: 56 × 10e3/mm^3, CRP: 86 mg/L, Na: 135 mmol/L, K: 3.0 mmol/L, Protein: 67 g/L, creatinine: 1.06 mg/dL, T Bili: 0.2 mg/dL, D Bili <0.1 mg/dL, AST: 228 U/L, ALT: 136 U/L, ALP: 105 U/L, and gamma GT 75 U/L. Posaconazole was stopped because a toxic cause was suspected and ursodeoxycholic acid for a first time was reintroduced with an improvement in hepatic test in for a first time. She started on Ceftazidim and Caspofungin. A gastric fibroscopy with biopsies was performed to search GvHD. Within 48 h of admission, she developed diarrhea. Bacteriological, viral, and fungal stool analyses were performed and Ceftazidim was replaced empirically by Tazocillin and Metronidazole. Tests for fecal biomarkers were also performed to exclude GvHD. MMF was discontinued and a short course of steroids was started. At this time, Foscavir was started to replace valgancyclovir because the absorption of the medication was not optimal due to diarrhea. During hospitalization, CMV PCR was realized two times a week and the number of copies decreased progressively. There is no evidence of GvHD on gastric biopsies and oral candidiasis secondary to Candida albicans was confirmed. Chest, abdominal, and pelvic CT showed several large hypodense lesions in the right liver with confluence (Fig. 1). A liver biopsy was scheduled but postponed because she developed a sepsis with Staphylococcus hominis in blood cul-

Table 1. Values of liver tests.

Patient	Day 144	Day 147	Day 150	Day 154	Day 155	Day 156	Day 157	Day 158	Day 159	Day 160
AST	228	220	214	333	350	383	806	1339	2419	4424
ALT	136	150	187	244	243	277	511	821	1201	1561
LDH	448	600	696	884	978	922	1265	1696	2510	5540
ALP	105	99	94	100	113	105	94	97	122	139
Gamma GT	75	62	81	109	159	148	145	175	207	188
T bil	0.2	0.1	0.2	0.3	0.4	0.5	0.6	0.7	1	1.9
D bil	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	0.3	0.3	0.6	1.4
Albumin	28.1		19.9	26.9			23.7	23.7	19.9	18.7

AST (U/L); ALT (U/L); LDH (U/L); ALP (U/L); gamma GT (U/L); Total Bilirubin (mg/dL); Direct Bilirubin (mg/dL); albumin (g/dL).

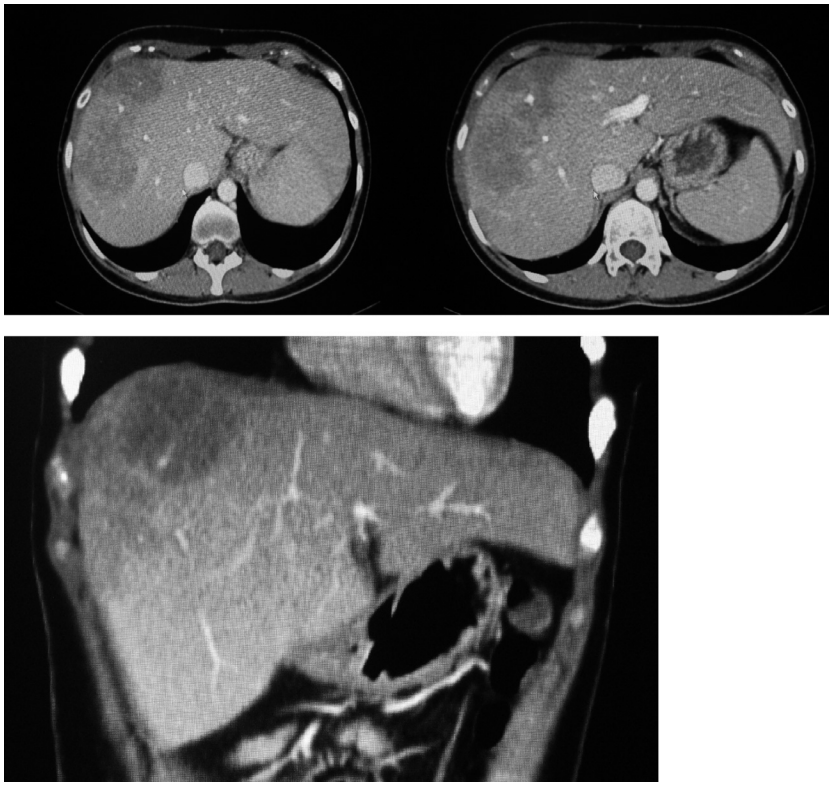

Figure 1. CT of abdomen shows several hypodense lesions in the right liver with confluence into a single lesion (10 × 6 cm).

tures on port at day 148. Vancomycin was started and the port was pulled. The diarrhea stopped without evidence of GvHD and the dose of steroids was rapidly decreased. At day 154, she presented a rash on 20–25% of corporeal surface and profuse diarrhea (>1 L/24 h), biopsies of gut and skin were realized and the steroids were reached to 2 mg/kg/day for 4 days. Within 3 days, she developed hepatomegaly with pain, ascitis, edema, and fever reaching 40°C. At day 158, the blood test showed pancytopenia (with severe neutropenia despite G-CSF), severe hepatic cytolysis, and cholestasis (Table 1). CMV, EBV, HHV6, toxoplasmosis, adenovirus, HBV, and HCV PCR were realized in blood samples. A BM aspiration was been realized to search for haemophagocytosis (because she developed a rash associated with pancytopenia, she had a CMV reactivation, elevation of ferritine level, and severe perturbation of hepatic tests) [12]. There was no evidence of haemophagocytosis or viral infection on BM but there were signs of myelotoxicity due to drug toxicity. At day 159, a liver biopsy was obtained by transjugular approach, after that, she developed disseminated intravascular coagulation with continued bleeding in jugular vein. The patient died from hepatic failure, 2 days later in the Intensive Care Department despite a maximum supportive care. Seven days after her death, we obtained the results from viral PCR on blood and biopsies. There was no evidence of viral infection or GvHD on gut and skin biopsies but the PCR for ADV was positive. All other results were normal and the chimerism on BM was 100% donor.

The liver biopsy showed a patchy necrosis in the perivenular, parenchyma, and periportal areas. Around the necrotic areas, many hepatocytes showed nuclear inclusion bodies. These features suggested viral-induced hepatocytic necrosis, especially adenovirus and herpes virus. Immunohistochemically, the nuclear inclusion bodies in the hepatocytes were positive for adenovirus. Therefore, we conclude the pathological diagnosis as a confluent hepatic necrosis due to adenovirus infection (Fig. 2). Concerning the macrophage activation syndrome, there were some macrophages showing hemophagocytosis, but in very limited number, insufficient to diagnose hemophagocytosis.

Conclusions

Hepatitis has been previously reported as part of systemic adenovirus infections where other organs are more seriously affected. Death from isolated hepatitis with hepatic failure is rare in adult after allogeneic HSCT and <10 cases

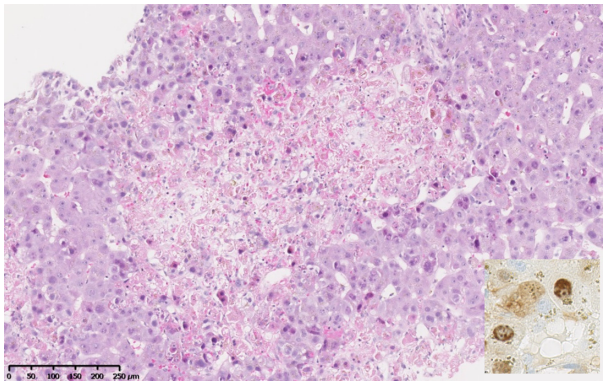

Figure 2. Hepatic parenchyma shows patchy necrosis. Many hepatocytes show nuclear inclusion bodies, which are positive for adenovirus immunohistochemistry (Hematoxylin and Eosin staining, insert: Adenovirus immunohistochemistry).

are described in medical literature. This case shows that 5 months after haploidentical allogeneic HSCT, our patient remains deeply immunosuppressed despite one injection of donor lymphocytes. The differential diagnosis was very difficult because GvHD and drug toxicity were also suspected; moreover, the result from the adenovirus PCR in blood was not rapidly available (7 days in this case) to start an appropriate treatment. The lack of rapid diagnosis lead to recommend to check very regularly adenovirus PCR in haplo-identical allogeneic HSCT patients until complete immune reconstitution in the aim to start rapidly a preemptive treatment in case of reactivation or infection.

Consent

Written informed consent was obtained from the next of kin of the patient for publication of this Case report and any accompanying images.

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Conflict of Interest

The authors declare no conflict of interest.

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