Ann Hematol (2002) 81:407–409
DOI 10.1007/s00277-002-0478-z

CASE REPORT

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Severe regimen-related toxicity occurring in a patient with XYY syndrome receiving allogeneic peripheral blood stem cell transplantation

Received: 7 June 2001 / Accepted: 30 April 2002 / Published online: 21 June 2002

Abstract A 23-year-old man with chronic myelocytic leukemia (CML) in the first chronic phase underwent allogeneic peripheral blood stem cell transplantation (PBSCT) from his HLA-identical sibling. Pretransplant evaluations showed that he had a low risk of transplantation-related mortality and that the interval between the diagnosis of CML and PBSCT was only 6 months. However, he developed a variety of complications, including acute renal failure requiring hemodialysis, severe hepatic damage, hemorrhagic cystitis, and gastrointestinal hemorrhage leading to hypovolemic shock. Pathological examination of the colonic mucosa showed vascular endothelial damage and thrombotic lesions, leading to the diagnosis of thrombotic microangiopathy. Later, we found that he had the constitutional abnormality XYY. XYY syndrome is a frequent congenital abnormality, and mental disorders and congenital abnormalities of kidney and liver are common manifestations. Considering his clinical course, it was interesting that complications were severe in the organs which are frequently involved in cases of XYY syndrome. These organs may have poor function or poor reserves and may be more vulnerable to endothelial damage caused by high-dose cytotoxic chemotherapy. Patients with XYY syndrome might have a high risk of transplantation-related mortality.

Keywords Peripheral blood stem cell transplantation · XYY syndrome · Thrombotic microangiopathy · Constitutional chromosomal abnormality

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Introduction

Constitutional chromosomal abnormality is frequently associated with the development of leukemia [1], and it frequently involves multiple organ dysfunction. The toxicity of cytotoxic chemotherapy may be severe in the treatment of hematological malignancies occurring in these patients [2,3]. Especially in the setting of hematopoietic stem cell transplantation (HSCT), it may be desirable to avoid organ damage caused by high-dose preparative regimens or graft-versus-host disease (GVHD).

Few reports have been published on HSCT in the case of patients with constitutional chromosomal abnormality. We have little information on the possible risks associated with transplantation procedures in the case of these patients. We recently encountered a patient with XYY syndrome who received transplanted stem cells from his HLA-identical sister for the treatment of chronic myelocytic leukemia (CML). To our knowledge, this is the first report on HSCT in a patient with XYY syndrome. His clinical course suggests the risk of transplantation associated with this constitutional chromosomal abnormality.

Case report

A 23-year-old man was referred to our hospital because of a persistent fever in November 1999. He was 183 cm tall with a long mandible. Surprisingly, he had as many as 20 dental caries, requiring extensive treatment of the teeth before HSCT. He had a leukocyte count of 56.4×10^9/l. A bone marrow aspirate showed myeloid hyperplasia, and karyotype analysis revealed t(9;22) with an extra Y chromosome (Fig. 1). He was therefore diagnosed as having CML in the first chronic phase.

After treatment of the decayed teeth, he underwent peripheral blood stem cell transplantation (PBSCT) from his HLA-identical sibling 6 months after the diagnosis. The conditioning regimen consisted of busulfan and cyclophosphamide. Plasma levels of busulfan were not monitored in this patient. We used short-term

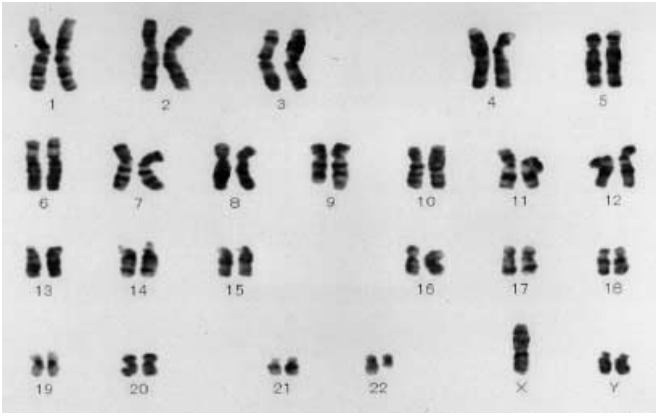

Fig. 1 G-banded karyotype analysis of a bone marrow cell showing Ph1 translocation and an extra Y chromosome

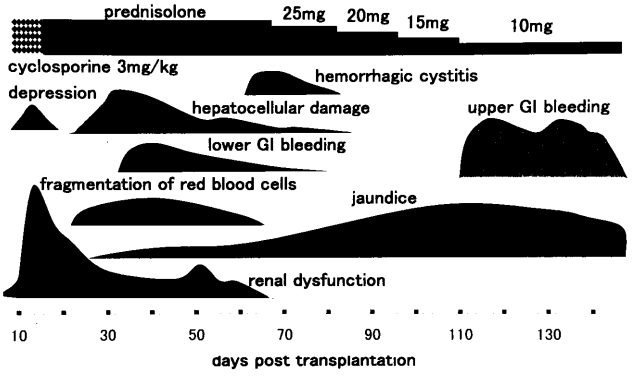

Fig. 2 A series of posttransplant complications occurring in this patient

methotrexate (MTX) and cyclosporin for GVHD prophylaxis. His clinical course had been uneventful until day 12, when oliguria developed. The blood test showed azotemia, and serum levels of creatinine reached 106 μM. Hematuria and proteinuria were evident on urinalysis. The patient was diagnosed as having acute renal failure. While blood cyclosporin levels had been in the normal range between 250 ng/ml and 350 ng/ml, we discontinued cyclosporin and initiated prednisone at a dose of 0.5 mg/kg. The serum creatinine level was elevated at 645 μM on day 15 when he received hemodialysis. We withheld nephrotoxic agents including amphotericin B and aminoglycosides. Renal function improved gradually, and the serum creatinine level became normal on day 55. This episode was the beginning of a series of complications. His clinical course is shown in Fig. 2.

Around day 16, the patient became listless and indifferent. Except for some complaints concerning general fatigue, he did not talk with the medical staff. He was diagnosed as being in reactive depression. Depression is a common problem associated with XYY syndrome, and treatment through individual and family psychotherapy has been reported to result in a good outcome [4]. Thus, we permitted the patient to contact members of his family. After the first contact with his mother, the depression improved dramatically.

On day 19, fragmentation of red blood cells developed, and the number of fragmentocytes increased to 4.6% on day 46. Because the patient developed renal failure, thrombocytopenia, fragmentation of red blood cells, and persistent fever, he was diagnosed as having thrombotic microangiopathy (TMA) based upon the criteria reported by Pettitt et al. [5].

On day 27, the patient complained of general malaise. Elevation of serum levels of alanine aminotransferase (ALT) suggested the presence of hepatocellular damage. It progressed rapidly and the serum ALT and total bilirubin levels reached 1926 IU/μl and 186 μM, respectively. Infection did not seem to be the causative factor because repeated culture of blood, urine, and stool samples failed to show any causative organisms. Results of tests for hepatitis virus B and C were negative. With supportive care, the hepatic damage gradually improved by day 60, although moderate jaundice persisted. Because of the presence of bleeding tendency, biopsy of the liver could not be performed.

On day 32, he developed watery diarrhea with occasional abdominal cramps. The volume of diarrhea rapidly increased to 5000 ml/day on day 37, and the diarrhea became bloody on the same day. We increased the dose of prednisone from 0.5 mg/kg to 2.0 mg/kg, but to no avail. Pathological examination of the colonic and gastric mucosa showed microhemorrhage with schistocytes around the capillaries and extensive crypt depletion. No evidence of acute GVHD was observed in these specimens. The bloody diarrhea was diagnosed as microangiopathic ischemic enterocolitis. We considered that the hemorrhagic enterocolitis represented a manifestation of TMA. With supportive treatment consisting of hydration, hyperalimentation, octreotide, and administration of albumin and fresh frozen plasma, the diarrhea gradually improved by day 80.

On day 62, he complained of moderate back pain, and macrohematuria developed the next day. Any causative bacteria, fungi, and virus were cultured from urine. Adenovirus-specific DNA sequences were not detected in analysis of the urine by the polymerase chain reaction method. Considering his clinical course, the hematuria was diagnosed as a manifestation of TMA. With supportive treatments, the hematuria disappeared by day 80.

On day 107, massive bloody diarrhea recurred, necessitating repeated transfusion. Immediate colonic and gastric endoscopy revealed massive hemorrhage from the gut. Hemorrhage was restricted to the antrum showing marked vascular ectasia. Thus, the lesions were diagnosed as gastric antrum vascular ectasia (GAVE) [6]. The bleeding improved with repeated endoscopic laser photocoagulation and repeated transfusion of platelets. The total amount of transfused red blood cells reached 230 units. After the gastric hemorrhage improved, the patient developed acute respiratory distress syndrome associated with massive transfusion. He was intubated on day 113, and managed by mechanical ventilation. The respiratory condition gradually improved, and he was extubated on day 126.

While moderate jaundice persisted, all the other complications subsided, and the patient is alive at present, on day 150. Except for moderate jaundice, probably caused by TMA, no signs of GVHD are now evident.

Because his clinical course was entirely different from our expectation, we reviewed his pretransplant status. The additional Y chromosome was initially thought to be related to the clonal evolution of leukemic cells. However, the chromosomal abnormality 47, XY, +Y, t(9;22)(q34;q11) has been rarely reported in cases of CML [7], and a congenital abnormality was suspected. He has a high stature, 183 cm, 20 decayed teeth, and a long mandible. An abdominal ultrasound showed that both kidneys were enlarged. Wechsler adult intelligence scale-revised (WAIS-R) revealed that his IQ score was 78. Such findings are frequently observed in cases of XYY syndrome. To confirm that the additional Y chromosome was congenital, we performed chromosomal analysis using mucosal cells from the oral cavity. The chromosomal abnormality 47, XYY was also observed in analysis of these cells, and we finally diagnosed this patient as an XYY male.

Discussion

The 47, XYY sex chromosomal constitution is one of the most frequent chromosomal abnormalities, occurring in approximately 0.1% of all newborn males [8]. In 1965, Jacobs et al. reported that aggressive behavior, depression, and mental retardation are characteristics associated

with XYY syndrome [9]. Besides the psychological dysfunction, XYY males have several clinical characteristics including increased stature [9], urinary tract malformation including renal agenesis or cystic dysplasia [10], craniofacial abnormality [11], increased enamel thickness [12], and abnormality of the hepatobiliary system [13]. Although there are some reports on the development of hematological malignancies in XYY individuals [14], there is no evidence indicating that XYY syndrome is a risk factor for hematological malignancies.

Because this young patient had not received either intensive cytotoxic chemotherapy or interferon before transplantation and had received allogeneic PBSCT from an HLA-identical sister 6 months after the establishment of the diagnosis of CML, he had a low risk of transplantation-associated morbidity or mortality. However, a variety of life-threatening complications occurred after transplantation, consisting of acute renal failure, severe hepatic damage, reactive depression, hemorrhagic enterocolitis, hemorrhage from the stomach due to GAVE, and hemorrhagic cystitis. Pathological and microbiological examinations showed that neither acute GVHD nor infection was responsible for the complications, and TMA and GAVE were the most probable cause of these complications. TMA is a disseminated form of endothelial cell injury, and a variety of organs can be involved in this disorder. The kidney and the brain are the most common targets of this disorder [5]. GAVE is a rare cause of gastric hemorrhage and has been associated with female gender, older age, chronic liver disease, and achorhydria [15]. Early theories included trauma secondary to prolapse of the pyloric mucosa and ischemic or degenerative changes associated with age. Some reports have been published on GAVE after HSCT [6], but the etiology of GAVE following HSCT remains obscure. A microangiopathic lesion was not pathologically identified in the gastric mucosa in this patient, and it remained unknown whether GAVE was a manifestation of TMA. However, it is quite interesting that the end-organ dysfunction was severe in the case of the urinary organs, the liver, and the alimentary tract. In contrast, organ damage was absent in the case of the skin, heart, and neurological system.

Apart from the alimentary tract, malformation of the kidney and malformation of the liver are common abnormalities observed in the case of patients with XYY syndrome [11,14]. These organs may have poor function or poor reserves and may be more vulnerable to endothelial damage caused by high-dose cytotoxic chemotherapy. While it is impossible to make a strong statement concerning the possible association between XYY syndrome and severe regimen-related toxicity observed in this patient, this case suggests that XYY syndrome may be a risk factor for complications after HSCT.

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