Severe graft versus host disease in a patient with globoid cell leukodystrophy following umbilical cord blood transplantation: resemblance to the twitcher mouse model

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Bone marrow transplantation (BMT) is currently the treatment of choice for patients with globoid cell leukodystrophy (GLD), particularly in the early phases of the disease. Elevated interleukin (IL)-6 levels in the central nervous system of the twitcher mouse, an animal model for GLD, have been held responsible for severe graft versus host disease (GVHD), and IL-6 knock-out mice have shown lower incidence of GVHD after BMT. Here we report an eight-year-old girl with late-onset advanced stage of GLD who developed severe GVHD and died following unrelated 5/6 matched cord blood transplantation. Serum IL-6 levels pre-BMT and at day +38 were elevated (20 pg/ml and 15 pg/ml, respectively). This observation may support the findings in twitcher mice suggesting a possible role for IL-6 in the pathogenesis of GVHD in transplanted patients with GLD.

Key words: globoid cell leukodystrophy, interleukin-6, bone marrow transplantation, graft versus host disease, twitcher mouse.

Globoid cell leukodystrophy (GLD) is a rare neurodegenerative disorder characterized by a marked deficiency of the lysosomal enzyme β-galactosidase and accumulation of psychosine leading to destruction of oligodendroglia and progressive demyelinization in the central and peripheral nervous system. Patients develop spasticity, dementia, and peripheral neuropathy, leading to chronic vegetative state and early death. Bone marrow transplantation (BMT) in the early phases of the disease allows glial cells of donor origin (derived from blood monocytes) to participate in reversal of demyelinization and improvement or stabilization of neurological symptoms[1,2,3].

The twitcher mouse is an experimental model of GLD. An increased incidence of graft versus host disease (GVHD) has been described in the twitcher mouse, in which the expression of interleukin (IL)-6 is greatly enhanced in the central nervous system[4,5]. Although serum IL-6 levels have not been measured in those mice, the increased production of IL-6 has been linked with induction of GVHD. Investigators have described a significant decrease in the incidence of GVHD in IL-6 deficient knock-out mice and suggested that IL-6 might play a key role in GVHD in patients with GLD as well[4].

The incidence of GVHD in patients with GLD is not well defined due to the small number of patients transplanted[1-3]. Krivit et al.[1] described mild GVHD occurring in three of five patients with GLD following BMT. Choi et al.[6] reported fatal GVHD in teenage twins. Here we describe a case with GLD who underwent unrelated cord blood transplantation (CBT) during an advanced stage of the disease and died of grade-4 skin GVHD. Stored serum samples were used to measure IL-6 levels based on the studies in twitcher mice.

Case Report

A previously healthy 6 $^{9/12}$-year-old girl presented with an 11-month history of decreased visual acuity, deterioration of school performance, decreased strength in the upper and lower extremities and ataxia. A diagnosis of late-onset GLD was made with decreased leukocyte galactocerebrosidase activity and brain magnetic resonance imaging (MRI) showing cerebral white matter involvement with periventricular abnormal areas of increased signal intensity. There was no family history of systemic disease but consanguinity was present. Due to the lack of matched family donor for BMT, an unrelated search was initiated. The patient's clinical condition deteriorated and she underwent unrelated CBT at an advanced stage of disease seven months after diagnosis. The cord blood was provided by St. Louis Blood Bank (USA) and was 5/6 matched (mismatch at DRB1 locus), ABO incompatible. The conditioning regimen consisted of busulfan (16 mg/kg), cyclophosphamide (200 mg/kg) and ATG (thymoglobulin). Cyclosporine A (CsA) and methotrexate were given as GVHD prophylaxis. She received 9.3x10e7 nucleated cells/kg, 7.9x10e5 CD34+cells/kg and 7.3x10e4 CFU/kg. The patient had a stormy immediate post-transplant period. Following the neutropenic and febrile period, she developed massive epistaxis on day +8 leading to respiratory arrest and endotracheal intubation. She was extubated shortly; however, metabolic problems consisting of fluid overload, electrolyte imbalance, and hypertension led to worsening of her clinical status. On day +18 she experienced a generalized convulsion that was responsive to anticonvulsive management initially, but then had repeated tonic clonic seizures. Cranial computerized tomography (CT) ruled out bleeding; EEG revealed diffuse slow waves consistent with encephalopathy and was attributed to CsA toxicity. Considering the underlying neurological disease and the previous documentation of elevated serum cyclosporine levels (517 ng/ml), CsA was discontinued, and standard dose methylprednisolone was started instead. White blood cells engrafted on day +19. At day +23 the patient developed mild maculopapular rash and was diagnosed as grade-1 skin GVHD (biopsy proven). There was no liver or gastrointestinal system involvement. She was treated with high dose methylprednisolone and CellCept (mycophenolate mofetil). Unfortunately, her clinical condition worsened and progressed to grade-4 GVHD and she died on day +39.

Serum IL-6 levels were determined in samples taken consecutively on days -15, day +18, and day +38 and frozen at -70°C. Enzyme linked immunosorbent assay (ELISA) test at Pasteur Cerba laboratories (France) was used, with a normal range of serum IL-6 being <3 pg/ml. The pre-transplant day -15, day +18 and day +38 levels were found as 20, <3, and 15 pg/ml, respectively.

Discussion

It has been reported that central nervous system manifestations of late-onset GLD can be reversed by allogeneic hematopoietic stem cell transplantation, particularly in the early stages of the disease. Even patients with the infantile form (Krabbe disease) may benefit if transplanted before the initiation of the clinical symptoms[1]. Replacement of the missing enzyme by the donor-derived cells and maintenance of normal enzyme activity in the brain may contribute to favorable clinical response[1-3]. Unrelated cord blood was used as stem cell source for our patient who lacked a related donor and was already in an advanced stage of disease when transplanted. The disease had significantly progressed during donor search and preparation for transplant. The development of severe GVHD was unexpected for this child who underwent cord blood infusion. Although discontinuation of CsA prophylaxis in this patient might have contributed to development of GVHD, we retrospectively studied serum IL-6 levels of the patient to search for an underlying predisposing condition as described in the twitcher mouse. IL-6 is a pro-inflammatory cytokine that induces acute phase proteins, stimulates hematopoietic cell growth, thrombopoiesis[9], and may potentiate GVHD[7-8]. In patients with acute GVHD, serum IL-6 has been shown to gradually increase before the onset of GVHD and decrease when controlled[8].

Experimental studies have shown that the GVHD incidence is increased in the twitcher mouse. Biswas et al.[4] recently showed that IL-6 deficiency (IL-6 knock-out) in the twitcher mouse is associated with a decreased incidence

of GVHD and longer survival. A few cases with GLD and GVHD have been reported in humans[1,3,6], but the particular susceptibility is not known due to the small number of cases. The report of fatal GVHD in teenage twins with GLD may suggest a genetic susceptibility perhaps involving IL-6 gene[6].

It may be speculated that elevated pre-transplant IL-6 levels in the present patient might have contributed to development of fatal GVHD as in the twitcher mouse. Serum IL-6 levels were high before the initiation of the conditioning regimen and also on day +38 in this patient. This may suggest a possible contributory role of this cytokine in development of and resistance to treatment of GVHD. Interestingly, serum IL-6 level was within the normal range on day +18. We attribute this decrease to cyclosporine use since CsA has been shown to suppress IL-6 levels (10). In the present case, we believe that both withdrawal of CsA and intrinsically increased IL-6 levels might have contributed to the development of fatal GVHD.

The report of this interesting case may represent a human model for the twitcher mouse findings and may perhaps suggest a therapeutic role for IL-6 suppression in these patients as a preventive measure for GVHD. We think this case is instructive for the unexpected severity of GVHD and the possible role of IL-6, and it suggests a beneficial role for potentiation of GVHD prophylaxis in GLD patients.

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