Hyperacute graft-vs.-host disease after related HLA-identical umbilical cord blood transplantation

The term “hyperacute” refers to the pre-engraftment manifestation of GVHD (1). The main clinical manifestations of haGVHD are unexplained fever, skin rash, hepatic dysfunction, and diarrhea (1). Sullivan et al. (2) first described the clinical manifestations of haGVHD in allogeneic BMT in 1986. To the best of our knowledge, the present case is the first to have developed haGVHD in a fully matched CBT and without precipitating factors may suggest the role of still undefined and perhaps individual contributory factors.

Case report

A four-yr-old girl with AML in second complete remission underwent CBT from her HLA-identical brother in November 2005. The conditioning regimen consisted of i.v. busulphan (busulfex, 12.8 mg/kg over four days), melphalan (140 mg/m² · 1 day), and cyclophosphamide (120 mg/kg). GVHD prophylaxis consisted of CsA, beginning with an i.v. dose of 3 mg/kg/day on day +2; with dose then adjusted according to blood levels. The CB nucleated cell dose was $12.2 \times 10^7$ cells/kg and $6 \times 10^5$ CD34 cells/kg was given. The patient developed fever on day +3 for which she was treated with i.v. antibiotics. The fever persisted and she developed widespread erythematous plaques on her neck, face, axilla, and waist. Purplish-red lichenoid papules were then noted on the trunk, glutea, and extremities on day +6 (Fig. 1). Histopathological examination of lesional skin punch...
biopsy revealed focal vacuolization of the basal cell layer, spongiosis, and dyskeratotic keratinocytes in epidermis. Dyskeratosis was present in hair follicles and occasional perivascular lymphocytes were noted. The eccrine glands and vascular structures were normal. A histopathological diagnosis of acute GVHD, grade II was made (Fig. 2). MP was initially started at a dose of 2 mg/kg and was increased to 5 mg/kg upon the appearance of watery diarrhea. Fever disappeared, skin lesions regressed following two days of MP treatment, and diarrhea resolved completely in five days. Physical examination, urine analysis, chest X-ray, and throat and recurrent blood cultures were negative, and no pathogenic microorganisms were isolated from stool specimens. Weekly assessment for galactomannan antigenemia and cytomegalovirus viremia failed to show an infectious etiology. MP dose was decreased to 1 mg/kg on day +17 and was discontinued on day +34. Neutrophil engraftment occurred on day +17, platelets +26, and the last red blood cell transfusion was administered on day +15. Full donor hematopoietic chimerism was determined by molecular method and cytogenetics on day +26. At the seven-month follow-up, the patient was in full remission with 100% donor chimerism, and off immunosuppressive treatment.

Discussion

Cord blood is an alternative source of HSC, and has some advantages over bone marrow and peripheral blood cells. The "naive" nature of CB lymphocytes permits the use of HLA-mismatched grafts at 1–2 loci without higher risk for severe GVHD relative to BMT from a full-matched unrelated donor (3). Investigators have reported decreased incidences of acute and chronic GVHD following CBT (4). haGVHD has not been described following CBT except in one case of mismatched CBT associated with Ralstonia pickettii bacteremia (5).

The overall incidence of haGVHD ranges between 14% and 38% in allogenic settings (1, 6). The diagnostic criteria of haGVHD include: (i) unexplained fever, before engraftment, of >38.3°C on two occasions (each occasion lasting more than three days) with a lack of resolution after a minimum of three days of treatment with antibiotics and antifungal agents, including amphotericin B; (ii) rapid development of skin rash, before engraftment, with the exclusion of other causes, such as drug eruption; (iii) hepatic dysfunction before engraftment, especially increased alkaline phosphatase and bilirubin levels, with the exclusion of other causes, such as VOD/SOS, drug-induced hepatitis, or right-sided heart failure; and (iv) development of mucoid, greenish diarrhea, with more than five stools/day, with the exclusion of mucositis (1). The diagnosis is established based on the presence of the above-mentioned criterion (i) in addition to one of criteria (ii)–(iv) with or without histological confirmation, and is supported by the resolution of the above clinical findings with steroid treatment (1). The diagnosis of haGVHD in the present case was made due to the presence of fever without focus of infection, appearance of skin rash before engraftment, diarrhea, and improvement of symptoms following steroid treatment. In addition to these findings, histological confirmation was made by skin biopsy (Fig. 2). In this patient, the skin rash appeared on day 6 as has been reported in...
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previous studies (day 4–7) (1). Alternatively, the clinical findings in this patient were also suggestive of engraftment syndrome/peri-engraftment clinical abnormalities (7). However, the neutrophil and platelet engraftment days were +17 and +26, respectively, the clinical findings of the patient occurred in the first post-transplant week, and skin biopsy was consistent with acute GVHD. Therefore, engraftment syndrome was not considered in this patient. Moreover, the diagnosis of haGVHD in the present patient is also in accordance with the definition of haGVHD in a very recent report by Saliba et al. (8). The authors have defined haGVHD as a diagnosis of acute GVHD within the first 14 days after HSCT (8).

The risk factors for haGVHD include: a mismatched related or matched unrelated donor, a myeloablative conditioning regimen, more than five prior chemotherapy regimens, donor–recipient sex mismatch (8), use of an alternative donor (1), and sudden discontinuation of post-transplant immunosuppression (2). Donor pretreatment with granulocyte colony-stimulating factor has been shown to suppress haGVHD in murine models and clinical studies (9, 10).

The results of CBT have been found to be comparable to those obtained by BMT (11), whereas time to engraftment is delayed and the incidence and severity of GVHD are reduced (4, 12, 13). The apparent reduced immunogenicity of the CB was evidenced by the lower than expected incidence of severe GVHD reported following both related and unrelated CBT, even in mismatched transplants (14, 15). The present case of haGVHD was unusual considering the use of HLA-identical CB graft from a sibling donor, standard immunosuppressive treatment, myeloablative conditioning, and the disease remission status. To the best of our knowledge, the present case is the first to have developed haGVHD after related and matched CBT.

The use of high-dose corticosteroids (i.v. 3–5 mg/kg/day) for five days was found to be very effective in treating haGVHD, leading to abrupt resolution of fever in the majority of patients (1). The clinical response to steroid therapy was remarkable in the present case, as expected.

It has been shown that haGVHD is associated with later development of acute and chronic GVHD, lower response rate to first-line therapy and a higher rate of non-relapse mortality in patients with a mismatched related or matched unrelated donor graft (1, 7, 8). The lack of acute and chronic GVHD in the present case was attributed to the slow tapering of steroids and the adjustment of CsA dose to blood levels. At the seventh-month follow-up, the patient was in full remission with 100% donor chimerism, and off immunosuppressive treatment.

In conclusion, the unexpected development of haGVHD following HLA-matched CBT from a related donor is described in this report. The development of haGVHD in a fully matched CBT and without precipitating factors may suggest the role of still undefined and perhaps individual contributory factors.

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