
Disseminated toxoplasmosis after CD34+-selected autologous peripheral blood stem cell transplantation

A patient with adult T-cell leukemia/lymphoma was successfully treated by autologous CD34+-purified autologous PBSCT with conventional chemotherapy and cyclophosphamide. The combination of CD34+-cell-selected PBSCT and TBI regimen resulted in a delayed immune-cell reconstitution and rendered the patient susceptible to disseminated toxoplasmosis.

We report a case of disseminated toxoplasmosis which occurred 4 months after a CD34+-selected autologous peripheral blood stem cell transplantation (PBSCT) for adult T-cell leukemia/lymphoma (ATLL). While the patient achieved a sustained molecular remission after transplantation, immunosuppression as a consequence of T-cell depletion and resultant toxoplasma gondii reactivation ruined the promising outcome. A prudent clinical attitude toward immunologic fragility, and awareness of the occurrence of toxoplasmosis in transplantation of selected CD34+ cells, are needed.

A 49-year-old female was found to have an acute-type of ATLL and treated to hematologic remission with conventional chemotherapy. Peripheral blood progenitor cells were harvest and subjected to CD34+ cell selection by an immunomagnetic bead method (Isolex system; Nexell Therapeutics Inc., Irvine, CA, USA). Assessment of the purging efficacy of CD34+ positive selection by inverse polymerase chain reaction revealed an apparent reduction of ATLL cells. After pre-transplant conditioning consisting of 1,200 cGy of total body irradiation (TBI), cytarabine 8 g/m2, and cyclophosphamide 120 mg/m2, a total of 6.0×107 CD34+ cells (1.2×106/kg) were infused. Engraftment was uneventful and the patient was discharged in sustained hematologic and molecular remission. However, four months after transplantation, she suffered a persistent fever and became dyspneic. A chest X-ray demonstrated interstitial ground glass shadowing (Figure 1A); she underwent a bronchoscopy with alveolar lavage, which failed to reveal any specific etiology. Over 24 hours she developed acute respiratory failure, deteriorated rapidly (Figure 1B), in spite of intensive supportive therapies, and eventually died without any definite diagnosis having been made. At autopsy, cysts of Toxoplasma gondii were detected in several organs (Figure 1C, D, E), but there was no evidence of recurrence of ATLL or other opportunistic infections. The serologic test retrospectively performed on sera from the storage sample obtained before transplantation suggested reactivation of the parasite (Table 1).

Toxoplasma gondii is a widespread opportunistic parasite of humans, but rarely seen in transplanted patients. In North American reviews, toxoplasmosis occurred in 0.31 cases per 100 allogeneic transplantations, but no case of toxoplasmosis after CD34+-purified autologous PBSCT has been previously reported. The acute infection is asymptomatic but establishes itself within many organs, persisting...
for the life of the host. In the latent infection, parasite-specific T-lymphocytes release high levels of gamma interferon, which is required to activate and synergize macrophages for toxoplasmacidal activity. Therefore, delayed immune reconstitution after transplantation puts patients at risk of reactivation of latent infection. The precise kinetics of immune reconstitution after CD34+ cell-selected PBSCT are unknown, and consequently increased incidence of opportunistic infection have been reported. In our case, it is likely that the combination of CD34+ cell-selected PBSCT and TBI regimen resulted in a further-delayed immune-cell reconstitution and rendered the patient susceptible to disseminated toxoplasmosis. Although more studies need to be done to improve the understanding of immunologic impairment responsible for toxoplasmosis reactivation, prophylactic therapy for toxoplasmosis could be beneficial for seropositive patients especially in cases of CD34+ positive selected transplantation with TBI regimen.

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Key words: CD34 selection; toxoplasmosis; adult T cell leukemia/lymphoma.

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Table 1. Evaluation of antitoxoplasma antibodies.

<table>
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<tr>
<th>Antibodies</th>
<th>ELISA</th>
<th>Feldman dye test</th>
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<tbody>
<tr>
<td>pre-transplantation</td>
<td>189</td>
<td>negative</td>
</tr>
<tr>
<td>day 143</td>
<td>44</td>
<td>negative</td>
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IgG and IgM antibodies were quantified with use of an ELISA, titers are expressed in units per milliliter (IU/mL). A patient is considered seropositive if titers are over 10 IU/mL. Pre-transplant serologic status positive for IgG but negative for IgM indicated past toxoplasma infection. On day 143, IgG titer decreased and IgM were not still detectable, in spite of definite proof of infection of toxoplasma in multiple tissues. These findings may be a reflection of impaired cellular and humoral immunity after transplantation, and may also indicate serologic status is not an appropriate tool for early diagnosis. The Feldman dye test is a more sensitive and specific neutralization test in which the organisms are lysed in the presence of IgG antibody and complement. The patient is considered to have a chronic infection if titers are over 16 X. In case of acute infection, titers are normally over 1,024 X.

References

Frequency of Gilbert’s syndrome associated with UGTA1 (TA) polymorphism in Southern Italy

We screened 685 subjects from Southern Italy for a promoter polymorphism of the UDP-glucuronosyltransferase (UGTA1) gene tightly linked to Gilbert’s syndrome (GS), consisting in the insertion of a TA repeat in the TATA box. The frequency of the polymorphism was 0.387 which is similar to the frequencies reported for other investigated populations of different ethnic backgrounds and is consistent with the antiquity of this polymorphism.

Sir,

Gilbert’s syndrome (GS) is an inherited form of mild unconjugated hyperbilirubinemia, characterized by decreased bilirubin UDP-glucuronosyltransferase activity (UGTA1). Serum bilirubin levels vary according to time, intercurrent illness or fasting.

The recent identification of the UGTA1 locus, which encodes for a family of UGTA1 isofoms, has provided tools for molecular studies and for the correct definition of inheritance pattern. Although heterozygous missense mutations have been identified in patients with GS, the majority of cases are associated with a length polymorphism in the promoter region. As a matter of fact, an unusual TATA box exists in 2 different forms, A(TA)nTAA and A(TA)nTAA, due to the presence of six or seven TA repeats. The presence of this expanded element reduces the efficiency of transcription of the UGTA1 gene.

The incidence of GS can be evaluated by analysis of the promoter polymorphism; however, it is clear that forms due to exon (1 to 5) mutations may be underestimated.

The precise incidence of GS is not known, mainly because this condition is difficult to diagnose. After the description of the association of the (TA)n with GS, some studies focused on the relationship between GS and inherited red cell defects (spherocytosis, G6PD deficiency, thalassemia) and neonatal jaundice. The aim of our study was to establish the gene frequency of the TA repeat promoter polymorphism in a