Reactivation of Chagas disease after a bone marrow transplant in Italy: first case report

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Introduction

Chagas disease is a protozoan zoonosis caused by the haemoflagellate *Trypanosoma cruzi* (*T. cruzi*). In continental Latin America, it is transmitted to humans mainly by insect vectors (*Triatominae*). Transmission can also occur by blood transfusion[1,2], transplantation of infected organs, tissues or cells[1-3] or from mother to child[1], even in countries in which the disease is not endemic.

In Latin America about 8-10 million people are affected[4] and it has been calculated that 667,000 disability-adjusted life years are lost annually[5]. Most of the infected people are not aware of their status because the disease frequently causes few or no symptoms during the acute phase and evolves commonly to a clinically silent (indeterminate) phase; only in 20-30% of patients is there progression to a chronic disease, affecting mainly the heart and digestive system. Given the growing amount of international travel and the overall increase in migratory flows, a not negligible number of imported cases are registered also in non-endemic areas[6]. Immunosuppression and immune deficiency states (e.g. a patient with human immunodeficiency virus infection or acquired immunodeficiency syndrome) can lead to reactivation of latent infection which, in some circumstances, may give rise to severe manifestations[1].

We report the first case of Chagas disease reactivation after a bone marrow transplant (BMT) recorded in Italy and the first ever in Europe in a patient of paediatric age.

Case report

A 9-year old Argentinean girl had been diagnosed with acute lymphoblastic leukaemia in 1999 and was successfully treated with the ALL 96/ BFM protocol. In February 2004, following the development of secondary acute myeloid leukaemia, the girl was treated with the AML 97/BFM protocol and obtained a complete remission. In October 2004 she was transferred to Italy in the Unit of Paediatric Haematology/Oncology in Pisa to undergo an allogeneic BMT from a matched, unrelated donor. The pre-transplant evaluation (including electrocardiography and echocardiography) was normal, except for a known cerebral atrophy. A conditioning regimen (fractioned total body irradiation, cyclophosphamide, anti-thymocyte globulin) was administered and 4.34×10^8/kg of haematopoietic stem cells were infused. Graft-versus-Host Disease (GvHD) prophylaxis was given (cyclosporine A and short course of methotrexate). Polymorphonuclear leucocyte and platelet engraftment occurred on day +20 and +28, respectively. Treatment with prednisolone was started on day +26 because of grade II GvHD of the skin. On day +46 the patient was found to have fever with progressive anaemia (lowest haemoglobin level 7.9 g/dL), neutropenia (180 neutrophils/μL) and thrombocytopenia (12,000 platelets/μL), increased lactate dehydrogenase (1,330 U/L) and alanine transaminase (120 U/L) and mildly increased C-reactive protein (59 mg/L). Clinical examination was non-informative and blood, urine and cerebrospinal fluid cultures were negative. Bone marrow aspiration confirmed the leukaemia remission. Echocardiography and total body computed tomography scans were normal. Broad-spectrum antibiotics were started and antifungal therapy was added 5 days later. Epstein-Barr virus reactivation on day +46 was successfully treated with rituximab, with normalisation of virological markers but no effect on the fever. On day +56 the patient's general conditions worsened and she

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developed hepatomegaly and laboratory evidence of abnormal liver function (gamma-glutamyl transferase 425 U/L, alanine transaminase 232 U/L, alkaline phosphatase 830 U/L, lactate dehydrogenase 11,526 U/L). A peripheral blood smear revealed flagellated parasites identified as *T. cruzi* trypomastigotes. Therapy with benznidazole (10 mg/kg/die) was started but 3 days later the patient died from multi-organ failure (day +70).

Discussion

Immunosuppression secondary to BMT and GvHD treatment was probably responsible for the reactivation of Chagas disease in our paediatric patient.

The bone marrow donor (from California, USA) was not tested for Chagas disease. No other information about the donor (in particular, his travel history and ethnicity) could be obtained at the time of this case description. The patient was not transfused in Italy, but in Argentina. The girl's infection was probably acquired in Argentina either congenitally (the mother's serological status is unknown), through a blood transfusion or by vector-borne transmission.

Several cases of acute Chagas disease following BMT or chemotherapy for haematological diseases have been described in South America, but in very few countries in which the disease is not endemic. In Europe two cases have been reported in Spain[2,3], both probably due to blood transfusion.

The clinical picture of reactivation of Chagas disease in immunosuppressed patients includes fever associated with painful skin nodules, myocarditis, anaemia, jaundice, hepatitis and central nervous system involvement[2,3,7]. In our case, little information on the clinical picture was available at the time of the case description, but fever, anaemia and hepatitis were present. Apparently, echocardiography at the beginning of the Chagas reactivation did not reveal signs of myocardiopathy. The clinical picture was particularly insidious in this case because it mimicked other more typical and frequent complications of BMT and immunosuppressive treatment.

Using systematic monitoring, Altclas *et al*.[8] estimated that the incidence of reactivation of Chagas disease was 17% and 40% following autologous and allogeneic haematopoietic transplants, respectively. In a recent review it was suggested that transplant candidates with Chagas disease should be treated prior to transplanation[9]. However, experts from endemic countries consider a pre-emptive approach with *T. cruzi* monitoring in blood and treatment only in case the patient becomes positive, since it has been shown that, with some exceptions, clinical reactivation is preceded by detectable parasitaemia[8]. Pre-emptive treatment has efficiently been applied in BMT recipients with Chagas disease in Latin America[8].

After Spain, Italy has the highest number of Latin American migrants in Europe and it has been estimated that there are more than 5,000 such subjects infected by *T. cruzi*[10]. In Switzerland, 18.5% and 26.2% of migrants with Chagas disease considered donating blood and organs, respectively[11]. In Europe to date, only Spain and France have implemented screening for blood donors, but policies about this topic are under discussion in Italy.

Current JACIE international standards suggest donor evaluation for Chagas disease, but under European regulations, these standards require testing only for those at high risk[12]. American guidelines recommend screening for *T. cruzi* in all donors or recipients who were born (or whose mother was born) in an area in which Chagas disease is endemic or who have lived at least 6 months or received a blood transfusion in such an area[13]. Italian guidelines do not clearly mention the disease. In the case of a donor at risk of potentially transmissible diseases, our practice is to ask for a second opinion from the National Transplant Centre. Transplant donor evaluation guidelines are under revision in Italy. Access to a diagnosis of Chagas disease was not (in 2004) and is still not widely guaranteed in the Italian hospital network.

In conclusion, we draw attention to the fact that a fever (associated or not with panniculitis, myocarditis, encephalitis, or hepatitis) following BMT in Latin American patients or recipients born from Latin American mothers or receiving a transplant from at risk donors should raise the suspicion of Chagas disease also in non-endemic countries. Strategies should be implemented urgently to prevent Chagas disease transmission or reactivation in transplant recipients; directives and guidelines on the selection of donors of organs, cells or tissues and on the evaluation of recipients should clearly suggest

taking into account historical or demographic risk of *T. cruzi* infection, defining subjects at risk as patients (migrants, adopted individuals, long term travellers) coming from or transfused in Chagas disease endemic countries or born from Latin American women.

Keywords: bone marrow transplantation, Chagas disease, immunosuppression.

The Authors declare no conflicts of interest.

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