



Case report

Allogeneic bone marrow transplantation-mediated transfer of specific immunity against *Toxocara canis* associated with excessive IgE

G Fischmeister¹, W Holter¹, S Matthes-Martin¹, H Auer², W Emminger-Schmidmeier¹, H Gadner¹ and C Peters¹

¹St Anna Children's Hospital, Pediatric Stem Cell Transplantation Unit, Vienna; and ²Department of Parasitology, Clinical Institute of Hygiene, University of Vienna, Austria

Summary:

A girl with myelodysplastic syndrome (RAEB-T) received HLA-identical bone marrow from her younger brother after myeloablative treatment with busulfan and cyclophosphamide. After bone marrow transplantation, fever, exanthema, pruritis, and a pulmonary infiltrate were treated symptomatically. Bacterial cultures remained negative. Leukocyte engraftment began on day 10, and all blood cell populations proved to be of donor origin on FISH analysis. Increasing IgE levels (21 000 U/ml) on day 14 after BMT, positive RAST, specific IgG-antibodies, and missing *Toxocara* (*T.*) *canis* antigens in the recipient indicated donor-derived seroconversion. Before BMT, the recipient had been negative for *T. canis* in routine parasitological screening, and the donor proved to be positive for *T. canis* antibody by ELISA. This report suggests that the transfer of IgE immunity in the absence of detectable antigens may be responsible for IgE-mediated symptoms consistent with toxocara infection and confirms the need for parasite screening in donor medical examinations. *Bone Marrow Transplantation* (2001) 28, 519–521.

Keywords: allogeneic BMT; *Toxocara canis* seroconversion; IgE elevation

granulomas (ocular larva migrans syndrome), anemia, pneumonia, myocarditis, hemorrhagic rash, seizures and encephalitis.¹ Eosinophilia and elevated gammaglobulin levels, and the detection of specific antibodies against *T. canis* antigens are the diagnostic signs providing presumptive evidence of Toxocarosis. The treatment of Toxocarosis consists of anthelmintics such as albendazole or mebendazole.¹ In cases of myocarditis or encephalitis, corticosteroids should be added.¹

Myelodysplastic syndromes (MDS) in childhood account for less than 10% of all hematological malignancies, and 30% of these children have predisposing conditions. The patient we discuss in this paper showed signs of trilineage bone marrow dysplasia combined with a monosomy 7. Blast production (19% in the bone marrow) defined the condition as RAEB according to the European Working Group of (EWOG)-MDS 98 protocol.² In children with MDS who have not had preceding chemotherapy an event-free survival after allogeneic bone marrow transplantation (BMT) greater than 50% has been reported.²

Transfer of donor-derived specific IgE-mediated hypersensitivity by bone marrow to the recipient after allogeneic BMT has been described,³ and the possibility of donor-derived (adoptive) antibody production against viral infections in the recipient, for instance against cytomegalovirus,⁴ is considered during donor selection. We describe the transfer of a specific B cell-mediated immunoresponse from donor to recipient with *T. canis* seroconversion and elevated IgE levels paralleling the hematological recovery after BMT.

Case report

In a 10-year-old girl with myelodysplastic syndrome (MDS) and monosomy 7 malignant blasts appeared in peripheral blood analyses. HLA-screening of the family revealed her 4-year-old brother to be HLA class I and II identical, and to have the same blood group. No chemotherapy had been given until then, and according to the EWOG-MDS-98 BFM-protocol,² immediate matched sibling donor (MSD)-BMT was performed. Pretransplant examinations revealed eosinophilia and elevated IgE levels in the recipient (14%/344 U/ml) and the donor

Toxocara mostly affects children, and is caused by the helminths *T. (Toxocara) canis* and *T. cati*, natural parasites of dogs, foxes and cats, respectively. Transmission results from ingestion of embryonated eggs from contaminated environment (water, soil). Larvae hatch in the small intestine, penetrate the mucosa and migrate actively (or are transported by the blood stream) into the liver, the lung and via the heart into nearly all organs. Many children remain asymptomatic. However, symptoms like fever, leukocytosis, eosinophilia, hypergammaglobulinemia, and hepatomegaly (visceral larva migrans syndrome) may occur. Severe manifestations include endophthalmitis, retinal

(8%/2088 U/ml), which was explained by pinworms (*Enterobius vermicularis*) found in the stool of the recipient. Both the donor and the recipient underwent treatment with an oral anthelmintic, pyrantel, 2 weeks before transplantation. Serological screening of the recipient for other intestinal parasites (*Ascaris*, *Echinococcus*, *Entamoeba*, *Fasciola*, *Filariae*, *Schistosoma*, *Taenia*, *Toxocara*, *Toxoplasma*, *Trichinella*) was negative. Conditioning (busulfan 16 mg/kg, cyclophosphamide 120 mg/kg and melphalan 140 mg/m²) was tolerated well. The patient developed grade IV skin and mucosal toxicity (WHO), but except for a mild rise in liver enzymes, no other severe organ toxicity was observed.

Bone marrow was collected (3×10^6 CD34⁺ cells/kg; 4.4×10^7 CD3⁺ cells/kg, and 9×10^6 CD19 cells/kg recipient body weight) from the sibling donor and transfused to the patient without problems. Routine supportive treatment consisted of daily oral amphotericin, co-trimoxazole and 400 mg/kg i.v. immunoglobulin (Baxter, Vienna, Austria) every second week. Fever, severe pruritus and a pulmonary infiltrate of unknown origin on day 4 were treated with ceftazidime, netilmicine, vancomycin and continuous intravenous antihistamines. Bacterial, viral and fungal cultures remained negative. The fever decreased and the pulmonary infiltration improved shortly before leukocyte engraftment. Sustained leukocyte engraftment occurred from day 10 on (Figure 1), and FISH analysis showed complete donor chimerism in all FACS-sorted (FACSCalibur, Becton Dickinson, San Jose, CA, USA) blood cell populations. An atypical exanthema of the skin occurred on day 13, despite GVHD prophylaxis with 3 mg/kg cyclosporin A, and was successfully treated with prednisolone. Two months after BMT, GVHD prophylaxis was stopped.

Measurement of immunoglobulin levels on day 14 revealed a total IgE value of 12 000 U/ml (Figure 1). At the same time, plasma cells (20/ μ l) were detected in the peripheral blood. These cells were analyzed by FISH and identified as being of donor origin. Parasitological screening was repeated, and *T. canis* antibodies were now found in the serum of the recipient by ELISA (55 AU), and by Western blot analysis (Figure 2),⁵ as well as in the donor (ELISA 25 AU, positive Western blot), indicating specific seroconversion in the recipient from day 14 onwards

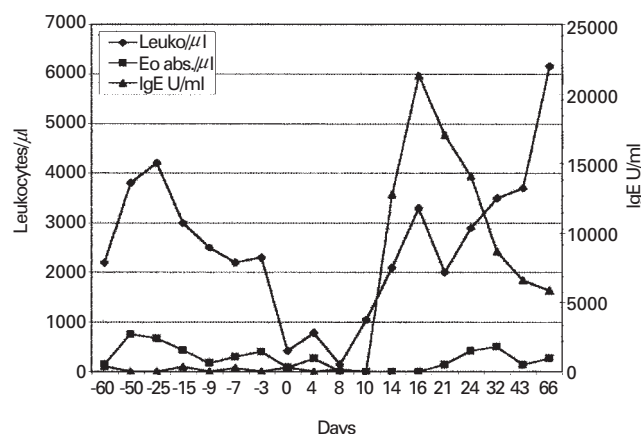


Figure 1 Leukocyte, eosinophil and IgE values before and after BMT.

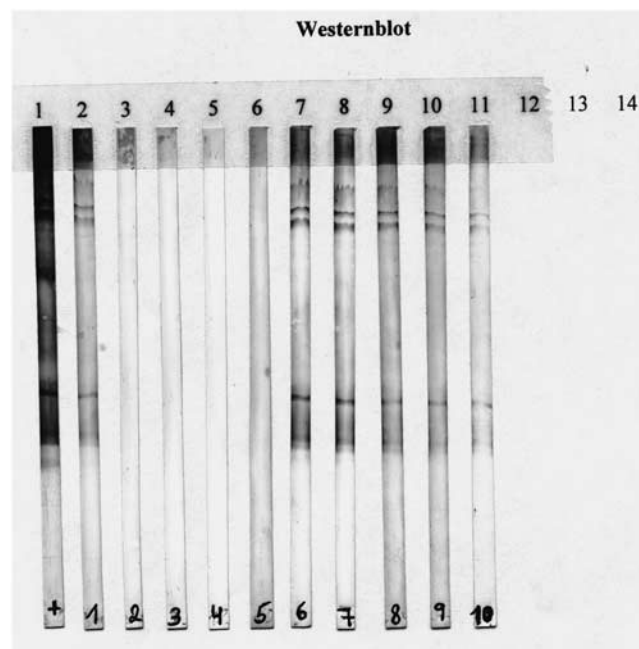


Figure 2 *Toxocara canis* antibody. Western blot, sensitivity 5 ng (the numbers in the lowest line and on the stripes). += positive control; 1 = donor 3 weeks after BMT; 2–4 = recipient before BMT; 5 = day 3 after BMT; 6 = day 14 after BMT; 7 = day 20 after BMT; 8 = day 23 after BMT; 9 = day 27 after BMT; 10 = day 52 after BMT.

(Figure 2). Finally, analyses of these sera by RAST (UniCAP, Pharmacia Diagnostics, Uppsala, Sweden), confirmed the presence of *T. canis*-specific IgE in the recipient (class 3), starting on day 14 after BMT, and also in the donor. The recipient was treated with albendazole (15 mg/kg/day) for 5 days, which, retrospectively, may not have been necessary: *T. canis* antigen was never detectable, and IgE levels had started to decrease before treatment started. During the 6 months after BMT the patient has been virtually asymptomatic, except for a short episode of bronchopneumonia, and IgE levels have decreased below 500 U/ml.

Discussion

Our patient presented with symptoms of fever, pulmonary infiltration, severe pruritus, and skin rash during the first 10 days after BMT, consistent with *Toxocara* infection. At this time neither antigen, nor specific antibodies were found. Only from day 14 after BMT a *T. canis*-specific immunoresponse was detectable, which was of donor origin, because complete chimerism including plasma cells could be demonstrated by FISH analysis. Seropositivity for *T. canis* was also confirmed in the donor.

In Austria 1.4 to 10.9% of the normal population and >30% of exposed people (mainly veterinarians) are seropositive.⁶ Although patients suffering from toxocara infection can be observed in each age group,⁶ children playing in the garden, public parks or in sand boxes are particularly exposed to the infection. *Toxocara* infestations in humans occur world-wide, seroprevalences varying between 0 and >60%.⁷ Visceral toxocara has been associated with chronic

respiratory symptoms and allergic manifestations in children.⁷

Clinical symptoms in toxocara are thought to be caused by parasites and antibody-dependent cell-mediated cytotoxicity against parasites, but our observations suggest that the mere transfer of IgE immunity, even in the absence of detectable antigen, may have been responsible for the symptoms consistent with toxocara infection seen during the first 10 days after BMT. Indirectly, this speculation is supported by results from Obwaller *et al*,⁶ who found a correlation between clinical symptoms and level of IgE/anti-IgE immune complexes in patients with symptomatic *T. canis* infections.

Other reports⁸ associate high IgE values after BMT with acute GVHD, but an increase of IgE has also been observed in recipients without GVHD.⁹ Heyd *et al*¹⁰ describe an indirect association between IgE hyperproduction and acute graft-versus-host disease in allogeneic BMT. They assumed that cell populations required for IgE response (T-, B-, and antigen-presenting cells) may be reconstituted before the regulatory elements (T-suppressor cells) that limit IgE production in healthy subjects become active.¹⁰

Adoptive transfer of immunity has been reported¹¹ in patients receiving allogeneic BMT from donors previously immunized against hepatitis B or with resolved hepatitis B. Protective HBs antibody levels appeared 9–42 days after BMT. The advantage of donor-derived antibody production, for instance against cytomegalovirus infection in the recipient,⁴ is a criterion for donor selection. Transfer of immunity from donor to recipient seems to be a general phenomenon after allogeneic BMT. However, as seen in our case, transfer of immunity may also be responsible for less favorable situations in the recipient. This observation was confirmed by Agosti *et al*³ who reported the transfer of allergen-specific IgE-mediated hypersensitivity, ie allergy, atopy and asthma, by BMT. Apart for toxoplasmosis, parasitologic screening is not routinely performed on healthy donors. In the light of the present case, the possibility of *T. canis* immunity transfer in the allogeneic BMT setting seems to merit attention, and *T. canis* screening should be considered before bone marrow donation by younger siblings or exposed unrelated donors.

References

- 1 American Academy of Pediatrics. *Toxocariasis*. In: Pickering LK (ed). *2000 Red Book: Report of the Committee on Infectious Diseases*, 25th edn. American Academy of Pediatrics: Elk Grove Village, IL, 2000, pp 582–583.
- 2 Niemeyer C. EWOG-MDS 98: prospective study of the diagnosis and treatment of myelodysplastic syndromes in childhood. Gesellschaft für pädiatrische Onkologie und Hämatologie, Freiburg, Germany.
- 3 Agosti JM, Sprenger JD, Lum LG *et al*. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *New Engl J Med* 1988; **319**: 1623–1628.
- 4 Boland GJ, Vlieger AM, Ververs C, De Gast GC. Evidence for transfer of cellular and humoral immunity to cytomegalovirus from donor to recipient in allogeneic bone marrow transplantation. *Clin Exp Immunol* 1992; **88**: 506–511.
- 5 Auer H, Aspöck H. Toxocarose-Forschung in Österreich – Ergebnisse, Probleme, Herausforderungen. *Mitt Österr Ges Tropenmed Parasitol* 1998; **20**: 17–28.
- 6 Obwaller A, Jensen-Jarolim E, Auer H *et al*. Toxocara infestation in humans: symptomatic course of toxocarosis correlates significantly with levels of IgE/anti-IgE immune complexes. *Parasite Immunol* 1988; **20**: 311–317.
- 7 Buijs J, Borsboom G, van Gemund JJ *et al*. Toxocara seroprevalence in 5-year-old elementary school children: relationship with allergic asthma. *Am J Epidemiol* 1994; **140**: 839–847.
- 8 Geha RS, Rappaport JM, Twarog FJ *et al*. Increased serum immunoglobulin E levels following allogeneic bone marrow transplantation. *J Allergy Clin Immunol* 1980; **66**: 78–81.
- 9 Ringden O, Persson U, Johansson SG *et al*. Markedly elevated serum IgE levels following allogeneic and syngeneic bone marrow transplantation. *Blood* 1983; **61**: 1190–1195.
- 10 Heyd J, Donnenberg AD, Burns WH *et al*. Immunoglobulin E levels following allogeneic, autologous, and syngeneic bone marrow transplantation: an indirect association between hyperproduction and acute graft-versus-host disease in allogeneic BMT. *Blood* 1988; **72**: 442–446.
- 11 Ilan Y, Nagler A, Adler R *et al*. Adoptive transfer of immunity to hepatitis B virus after T cell-depleted allogeneic bone marrow transplantation. *Hepatology* 1993; **18**: 246–252.