

Expansion of $\gamma\delta$ T cells in an infant with severe combined immunodeficiency syndrome after disseminated BCG infection and bone marrow transplantation

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$\gamma\delta$ T cells typically comprise less than 5% of human blood lymphocytes. In contrast to conventional $\alpha\beta$ T cells that recognize peptides presented by HLA, cells of the major human blood $\gamma\delta$ T-cell subset recognize non-peptidic phosphoantigens contained in some bacterial extracts.¹ However, the physiologic function of $\gamma\delta$ T cells remains unclear. We report the case of an infant with severe combined immunodeficiency (SCID) syndrome and BCG septicemia who showed a striking in vivo expansion of $\gamma\delta$ T cells after HLA-compatible bone marrow transplantation (BMT). This unique clinical situation may exemplify a protective role for human $\gamma\delta$ T cells in mycobacterial diseases.

CASE REPORT

After BCG vaccination in the neonatal period, hepatosplenomegaly, fever, and multiple skin nodules developed in a 5-month-old male infant. Skin biopsy revealed acid-fast bacteria-loaded histiocytes in the absence of infiltrating lymphocytes. The BCG strain *Mycobacterium bovis* was isolated from the skin, urine, and gastric aspirates, and antimycobacterial therapy was initiated. One maternal half brother of the patient and the brother of his mother had died of septicemia in early childhood. Further laboratory studies, including molecular analysis of the common IL-2 receptor γ -chain, confirmed the diagnosis of X-linked SCID (subtype T-B⁺).

At the age of 12 months, the infant was referred for non-T cell-depleted BMT from his HLA-compatible half brother, with 7×10^8 nucleated cells per kilogram being infused. No immunosuppression was given before BMT. Cyclosporine prophylaxis of graft-versus-host disease (GVHD) was discontinued 4 weeks after BMT when there was no evidence of GVHD. An exacerbation of the mycobacterial septicemia with fever and generalized maculopapular skin nodules on day 7 of the posttransplant period was treated by intravenous isoniazid, rifampin, and ethambutol for 3 months, followed by oral medication for an additional 18 months. The symptoms of

Abbreviations used

BMT: Bone marrow transplantation
GVHD: Graft-versus-host disease
PPD: Purified protein derivative of tuberculin
SCID: Severe combined immunodeficiency
TCR: T-cell receptor

generalized BCG infection slowly regressed, with complete resolution about 1 year after BMT. The immunologic reconstitution is shown in Table I. As early as 6 weeks after BMT, increased levels of $\gamma\delta$ T cells were noted in the boy's blood. $\gamma\delta$ T cells were absent in blood samples drawn before BMT. Ten months after BMT, 50% of all blood lymphocytes, or 65% of total T cells (CD3⁺ cells), expressed the T-cell receptor (TCR) $\gamma\delta$, a striking increase compared with healthy age-matched control subjects (about 2% of T cells). As soon as 10 months after BMT, T-cell proliferation to purified protein derivative (PPD) of tuberculin in vitro became detectable (although at low levels), whereas PPD skin test responses remained negative (Table I). Analysis of the expanded $\gamma\delta$ T-cell subsets 18 months after BMT demonstrated 28% V δ 1 T cells and 15% V γ 9/V δ 2 T cells of all lymphocytes. Typical values of age-matched control subjects were less than 1% for V δ 1 lymphocytes and less than 2% for V γ 9/V δ 2 lymphocytes, as determined in our laboratory. At 2½ years of age, the patient was thriving without signs of active BCG infection. Although markedly elevated levels of $\gamma\delta$ T cells persisted, the lymphocyte count and most other parameters of his immune function were in the normal range.

DISCUSSION

This infant had X-linked SCID associated with disseminated BCG septicemia after BCG vaccination.² The SCID syndrome was cured by BMT from his HLA-compatible family donor without clinical evidence of GVHD. A striking in vivo proliferation of $\gamma\delta$ T cells after BMT paralleled complete clinical control of the BCG infection, allowing discontinuation of the antimycobacterial therapy. It is conceivable therefore that expansion of $\gamma\delta$ T cells may have contributed to the favorable clinical outcome in this case. Practically all human V γ 9/V δ 2 T lymphocytes, the major subset of human blood $\gamma\delta$ T cells, display a natural reactivity towards phosphoantigens that are produced by mycobacteria and other microorganisms.¹ Thus the V γ 9/V δ 2 lymphocyte expansion can be explained by the mycobacterial septicemia, although the

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TABLE I. Immunologic status of the infant with SCID before and after BMT

	Before BMT*	3 months after BMT	10 months after BMT	18 months after BMT
Lymphocytes (/μL)	475	936	1927	3422
Percentages of lymphocyte subsets†				
CD3+	0	64	77	45
CD4+	0	44	8	17
CD8+	0	20	51	29
CD19+	94	6	19	36
TCR αβ of CD3+	0	80	35	40
TCR γδ of CD3	0	20	65	60
T-cell mediated immunity to:				
PPD in vitro‡	—	—	+	+
PPD in vivo§	—	—	—	—
<i>Tetanus, Candida</i> in vivo§	—	—	—	—
Immunoglobulins (mg/dL)				
IgG	122	Substituted	Substituted	480
IgM	8	584	71	26
IgA	7	47	132	24

*Before BMT at the age of 9 months.

†Percent specific binding of mAbs by flow cytometry.

‡Proliferation of lymphocytes to PPD in vitro was considered positive if the stimulation index (proliferation [cpm] to antigen/proliferation to medium alone) was greater than 3.

§Delayed-type hypersensitivity skin test.

Vδ1 T-cell proliferation is perplexing because Vδ1 T lymphocytes do not recognize bacterial antigens.¹ Data on variable region use are only available for time points later than 18 months after BMT. Thus we do not know whether the initial in vivo proliferation of γδ T lymphocytes, detected as early as 6 weeks after BMT, might have exclusively involved the Vγ9/Vδ2 T-cell subset. Expansion of Vδ1 T cells might have followed at a later stage and been induced by other stimuli.

Because the HLA-matched bone marrow donor of our patient had normal levels of γδ T cells in his peripheral blood, it is rather unlikely that increased levels of γδ T cells after BMT resulted from transfer of unusually high numbers of γδ T lymphocytes. Because γδ T cells in the patient's blood were not detectable before BMT (Table I), the patient's γδ T cells could not have originated from his mother by diaplacental transfer.³ These γδ T cells must have been of donor origin because our patient with X-linked SCID could not rearrange the TCR genes of his own thymic T-cell precursors. Although γδ T-cell expansions after allogeneic BMT for leukemia in the absence of mycobacterial infections have been observed in a minority of patients, they were usually lower, transient, and associated with acute or chronic GVHD.⁴ We did not observe γδ T-cell expansions after BMT in 7 other patients with SCID in the absence of BCG infections. Thus this patient's expansion of γδ T cells in vivo may

very likely have been caused by the BCG infection. Because disseminated BCG infections are common in primary immunodeficiencies,² elevated levels of γδ T cells may have been missed in earlier reports of similar clinical situations. The present case represents a unique experiment of nature that suggests a specialized role of γδ T cells in mycobacterial infections. Corresponding findings have been obtained in SCID mice that were able to control BCG infections after engraftment with lymph node cells depleted of conventional αβ T cells.⁵

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