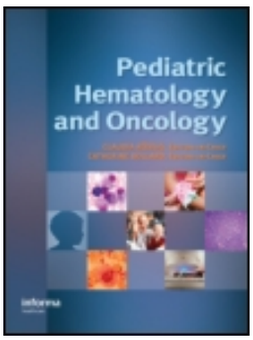

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Letter to the Editor

NATURAL KILLER CELL ACTIVITY IN A PATIENT WITH CHÉDIAK-HIGASHI SYNDROME SUBMITTED TO BONE MARROW TRANSPLANTATION

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Chédiak-Higashi syndrome (CHS) is a rare autosomal-recessive disease that is characterized primarily by partial oculocutaneous albinism, frequent pyogenic infections, and characteristic giant lysosomal granules present in most granule-containing cells. The immunologic relevance of this disease is the selective impairment in natural killer (NK) cell function [1–4]. Previous studies have suggested that this defect may predispose to the subsequent development of lymphoproliferative disorders [3, 4].

Natural killer cells are the first class of cells to appear after bone marrow transplantation (BMT) [5, 6], and there is one report that BMT

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can reverse the defect of these cells in the CHS [7]. Our report confirms these results by studying the behavior of these cells before and after BMT in a patient with CHS.

CASE REPORT

A 6-year-old boy with partial albinism and typical giant leukocyte granules, born to consanguineous parents, presented with several scars of cutaneous abcesses and voluminous hepatosplenomegaly. He had a history of repetitive pneumonias.

Previous to BMT, immunologic evaluation of the patient showed depressed total leukocyte and lymphocyte counts (Table 1). The NK cell activity was determined against K562 cells in a 4-hour chromium release assay. This activity was found to be deficient when compared with the controls, and did not respond to in vitro activation by recombinant human interferon-α (rhIFN-α), Sigma (Table 2).

Bone marrow transplantation was attempted using an identical human leukocyte antigen sibling in July 1990. The conditioning regimen for transplantation consisted of methylprednisolone (1 mg/kg for 8 days), etoposide (400 mg/m^2 twice daily for 3 days), carmustine (200 mg/m^2 daily for 3 days), and cyclophosphamide (50 mg/kg daily for 4 days). Methotrexate was used as a prophylatic regimen against graft-versus-host-disease (GVHD). The infused bone marrow contained 4.5×10^8 cells/kg.

Table 1. Absolute (per mm^3) numbers of leukocytes, CD4 and CD8 peripheral blood lymphocytes of CHS patient and control before and after BMT

Subject tested	Timing	Global leukocytes	Total lymphocytes	Lymphocytes†	
				CD4	CD8
Controls*		8500 (5000–14500)	3400 (2000–5000)	1530 (1224–1904)	782 (476–1394)
Patient					
	Before BMT	3700	1870	673	430
	20 days after BMT	500	40	7	6
	32 days after BMT	2550	892	53	330
	48 days after BMT	4250	1147	218	252
	115 days after BMT	3850	1039	218	518
	178 days after BMT	5900	2655	451	1354
	269 days after BMT	5700	1311	275	537

*Values represent the arithmetic mean of 14 healthy controls ranging in age from 5 to 6 years.

†Lymphocyte subsets assayed by indirect immunofluorescence using Becton-Dickinson (San Jose, Calif., USA) monoclonal antibodies.

Table 2. NK cell activity in CHS before and after BMT: effect of rhIFN-α*

Subject tested	Timing	Interferon (U/mL)	% Cytotoxicity 100:1†	50:1	25:1
	—	0	10	7	6
Control	—	1000	27.5	17	8
	—	5000	20	12	6
CHS	Before BMT	0	1.5	0.6	2
		1000	1.9	1.5	0.2
		5000	0.6	0	0.4
CHS	After BMT				
	Day 18	0	3	1.4	0.8
	Day 20	0	6.6	0	0
	Day 32	0	20	8	2
		1000	11	3.5	1.7
		5000	43	18	2.4
	Day 48	0	16	10	4
	Day 115	0	29	21	7
	Day 178	0	10	7	2
	Day 269	0	4	1.4	0.4

*Recombinant human interferon-α.
†Effector: target ratio.

Engraftment was prompt, and the early clinical course uneventful. The graft was confirmed at day 21 by bone marrow aspirate, and the marrow was normal.

In the peripheral blood the global leukocyte count, total lymphocytes, and lymphocyte subsets (CD4+ and CD8+) increased gradually (Table 1). NK cell activity was determined and a gradual increase was observed from day 20 onward, attaining normal levels after the first month, and there was no longer an interferon-resistant defect (Table 2). By day 160 after BMT the patient suffered from GVHD and received corticoid treatment until day 280. More than 4 years have elapsed since BMT and the patient is well.

DISCUSSION

Similar to what we observed in our patient, a number of workers have demonstrated that the NK cell deficiency in CHS patients is not due to a decreased number of cells or failure to bind to target cells [8], but rather to a defect in the lytic process. This defect can be reversed either by treatment with interferon [9] or by cyclic nucleotides [10].

Since NK cells originate in the bone marrow, this study reinforces that BMT can reverse successfully the intrinsic defect of these cells, and

perhaps should be attempted in a situation in which reversal agents such as interferon are by themselves of no avail.

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