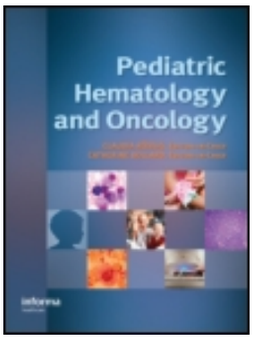

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Letter to the Editor

NEUROBLASTOMA CELLS CIRCULATE IN PERIPHERAL BLOOD

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Neuroblastoma (NB) is the most common extracranial malignant solid tumor of childhood. Disease frequently can be observed in metastatic form at the time of diagnosis.[1] The sites of metastasis strongly suggest that both lymphatic and hematogenous routes are involved in neoplastic dissemination. However, this has been proved only anecdotally.[2]

Peripheral blood (PB) and bone marrow (BM) samples obtained from eight children with stage IV (four at onset and four at relapse) and four with stage I-III NB (all at onset) were evaluated, at the same time, for the presence of NB cells. Mononuclear cells, obtained by density gradient, were stained by immunofluorescence with UJ13A[3] and/or HSAN 1.2[4] monoclonal antibodies (MoAbs) as described.[5]

A variable BM involvement was found in all stage IV patients. Neuroblasts were detected in six out of eight PB samples, sometimes arranged as small clumps composed of three to six cells (Table 1). UJ13A- and/or HSAN 1.2-positive cells were detectable in PB for a median time of 15 days during treatment. PB smears stained with May-Grunwald-Giemsa failed to reveal neoplastic cells; lymphocytosis ranging from 40 to 60 was reported. However, in two of the four cases examined, PB mononuclear cells cytospin analysis revealed small clumps typically arranged. Cells from patients with localized disease were not stained either in PB or BM. PB mononuclear cells from patient L.A., cultured in vitro, spontaneously eternalized, giving rise to a cell

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TABLE 1. Detection of Neuroblastoma Cells in Peripheral Blood and Bone Marrow in Eight Children with Stage IV Neuroblastoma

			Bone marrow		Peripheral blood	
Patient	Sex/age (mo)	Stage	UJ13A % +	HSAN 1.2 % +	UJ13A % +	HSAN 1.2 % +
(1) C.V.	F/21	IV O	45	ND	7[a]	ND
(2) L.A.	M/30	IV R	80	80	25	30
(3) B.C.	M/59	IV R	63	15	neg	neg
(4) C.S.	F/37	IV O	90	53	2[a]	neg
(5) C.L.	F/14	IV O	ND	40	ND	7
(6) L.M.	M/15	IV R	3	neg	neg	neg
(7) R.F.	F/45	IV O	90	95	5	1
(8) C.L.	F/26	IV R	55	90	4	neg

[a]Clumps (more than three cells).
[b]Abbreviations: O, onset; R, relapse; ND, not done.

line (GI-LI-N). The new cell line showed peculiar cytogenetic markers and N-myc oncogene amplification and overexpression (Table 2).

The hematogenous dissemination of NB cells has been suspected by examining PB smears[2] and confirmed by the isolation of the cell line CHP-126B1, showing morphologic and enzymatic characteristics of cells of neuroectodermal origin.[6] By simultaneously staining BM and PB mononuclear cells with highly specific MoAbs, we were able to demonstrate the hematogenous circulation of NB cells. This event does not appear to be rare in patients with BM involvement. Interestingly, NB cells were present in PB for a median time of 15 days during chemotherapy. In addition, the persistence of circulating neuroblasts (10% of PB cells) was observed in patient L.A. 1 month from initiation of chemotherapy; at that time, 2% of BM cells were stained with the same MoAbs.

TABLE 2. Molecular and Biological Characterization of GI-LI-N Cell Line

Surface markers (IF)	: UJ13A 96% HSAN 1.2 100%
Cytoplasmatic markers (WB)	: Vimentin +, chromogranin +, neurofilaments +;
N-myc copies (SB)	: 30
N-myc mRNA (NB)	: 50
Doubling time	: 28 h
Karyotype	: 48 , xy, −1, +2 der(1)HSR(1p), 15p+, +mar
Tumorigenity in nude mice	: Median latency time: 42 days
	: Median survival time: 102 days

Abbreviations: IF, membrane immunofluorescence; WB, western blot analysis; SB, southern blot analysis; NB, northern blot analysis.

Recent reports indicate that various malignancies may be treated successfully with massive therapy followed by autologous BM transplantation; in order to avoid tumor cell reinfusion, PB has been evaluated as a source of hematopoietic stem cells.[7] Our findings indicates that tumor contamination may be present also in PB. A careful check of PB mononuclear cells in a larger group of patients with metastatic NB at various time during treatment would allow the establishment of the actual frequency of the reported phenomenon.

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