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LETTERS AND CORRESPONDENCE

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Bradycardia Due to Mitoxantrone Exacerbated by Previous Anthracycline Therapy

To the Editor: Bethell et al. [1] described symptomatic bradycardia due to doxorubicin. Mitoxantrone (MIT), a DNA intercalator, is an effective antitumor drug known to interfere with topoisomerase II function, similar to doxorubicin or daunorubicin [2]. We report on MIT-induced bradycardia exacerbated by previous anthracycline therapy.

Eight pediatric patients with malignant disease received MIT in combination with other anticancer drugs (Table I). We determined the lowest heart rate during the 3 days before and after MIT therapy. None of the patients had fever or progressive anemia during this period. A significant decrease in heart rate was found in all patients after MIT therapy (81.3 ± 12.3 vs. 64.8 ± 14.1/min; $P < 0.05$). Five patients previously received the same doses of MIT with the same protocol (c). The decreased heart rate (Δ/min) was more prominent in patients who had received higher cumulative doses of anthracyclines (19.6 ± 4.6 vs. 7.2 ± 4.1/min; $P < 0.01$). The decreased heart rate improved within 3 or 4 days after the last MIT dose. The *t*-test was applied to determine differences in proportions; $P < 0.05$ is considered significant.

MIT was initially described as noncardiotoxic in animal models, but more recent studies have suggested that MIT is cardiotoxic [3]. While daunorubicin administration resulted in decreased heart rate in rats [4], the development of bradycardia has not been reported after MIT administration. MIT causes cardiotoxicity by a different mechanism from those of doxorubicin and epirubicin, which are probably mediated by oxygen-free radicals [3]. One report indicated that patients treated with MIT may develop late potentials [5]. Another revealed that MIT induced a gradual, competitive β-adrenergic blocking effect against the positive chronotropic action of isoproterenol [6]. Our observations suggest that heart rate monitoring should be performed for 4 days after the last dose of MIT in a patient who received previous anthracycline therapy.

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TABLE I. Lowest Heart Rate Measured 3 days Before and After MIT Administration

Age (yr)	Diagnosis	Heart rate (/min) Pre-MIT	Post-MIT	Δ (pre-post)			Previous cumulative dose of anthracycline (mg/m²)			Protocol[a]
2	Leukemia	90	80	10	—	—	230	—	—	a
9	Leukemia	92	80	12	—	—	300	—	—	b
9	Leukemia	80	60	—	20	—	—	504	—	c
		—	—	—	—	8	—	—	284	c
10	Leukemia	82	70	—	12	—	—	120	—	c
		—	—	—	—	10	—	—	60	c
10	Leukemia	70	50	—	20	—	—	110	—	c
		—	—	—	—	10	—	—	20	c
10	Leukemia	100	76	—	24	—	—	510	—	c
		—	—	—	—	0	—	—	330	c
10	Neuroblastoma	72	60	12	—	—	205	—	—	d
12	Leukemia	64	42	—	22	—	—	270	—	c
		—	—	—	—	8	—	—	180	c
	Mean	81.3	64.8		19.6	7.2				
	±SD	±12.3*	±14.1*		±4.6**	±4.1**				

[a]Protocols: a, MIT 10 mg/m² on days 1–2; b, MIT 12 mg/m² on days 1–3; c, Cyclophosphamide 1,500 mg/m² on day 1; dexamethasone 12 mg/m², on days 1–5; MIT 5 mg/m² on days 2–4, methotrexate 3 g/m² on day 5; d, MIT 60 mg/m² on day 1.

*$P < 0.05$.

**$P < 0.01$. Five patients previously received the same doses of MIT with the same protocol.

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TABLE 1. Hematologic Laboratory Data

	First admission	Just before hydroxyurea therapy	Last admission
Hbg %	8.4	8.1	2
WBC/μl	94,000	370,000	33,000
Blast %	2	4	—
Promyelocyte %	5	6	4
Myelocyte %	25	10	20
Metamyelocyte %	9	2	13
Neutrophil %	30	71	32
Band %	24	4	20
Eosinophil %	—	—	10
Basophil %	—	—	1
Lymphocyte %	4	2	—
Monocyte %	1	1	—
NRBC/100	4	3	1
Platelet/μl	105,000	100,000	9,000
LAP score[a]	2		
LDH IU/L[b]	2,300		
B_{12} pg/ml[c]	827	—	—

[a]Normal range 30–100.
[b]Normal range 200–400 IU/L.
[c]Normal ragne 190–800 pg/ml.

Translocation T(4;21) Associated With the Pelger-Hüet Anomaly in a Patient With Ph Chromosome-Negative CML

To the Editor: A patient with chronic myeloproliferative disorder (MPD), most probably Ph chromosome negative chronic myelogenous leukemia (CML), is presented. The disease was associated with the Pelger-Hüet anomaly and the t(4;21)(p12;q21 or 22). More than 90% of CML patients are Ph chromosome positive (Ph^+CML). About 50% of Ph^-CML patients have a bcr/abl rearrangement (Ph^-bcr^+). The rest of the Ph^-CML are Ph^-bcr^- and it is difficult to discern them from Ph^+bcr^+ merely on a clinical and morphological basis [1]. Recently 11 patients with Ph^-/bcr^- CML were reported. They were clinically and morphologically indistinguishable from those found in the typical cases of bcr^+ CML [2]. We describe a patient with clinical manifestation of Ph^-CML who had a unique t(4;21) (p12;q21 or 22) and in addition had the Pelger-Hüet anomaly.

An 81-year-old female immigrant from Russia was admitted to the Internal Medicine Department of Soroka Medical Center in November 1993 because of high fever, cough, and dyspnea. Her past history was remarkable for hysterectomy because of ectopic pregnancy in 1958, cholecystectomy for cholelithiasis in 1981, and choledocholitotomy for recurrent obstructive jaundice in 1981. Physical examination on admission revealed pallor, fever of 39°C, spleen palpable at 5 cm below the left costal margin, and hepatomegaly (4 cm below the right costal margin).

Laboratory data are shown in Table I. On peripheral blood smears all cells of myeloid origin had the Pelger-Hüet anomaly. Liver and renal function tests were normal. Bone marrow biopsy and aspiration were consistent with myeloproliferative disorder. No fibrosis was documented. All bone marrow cells showed the pelgroid nuclei. Normal karyotype was found in peripheral lymphocytes, while cytogenetic analysis of the bone marrow showed 46, XX, t(4;21) (p12;q21 or 22). A diagnosis of Ph negative CML was most likely. The patient was treated with cefuroxime for presumed infection. Later, obstructive jaundice occurred and bile stones were removed by papillotomy. After recovery, she received treatment with hydroxyurea, 1.5 g/day, and allopurinol, 600 mg/day, because of hyperleukocytosis of 370,000/μl (Table I). June 17, 1994 she was admitted again because of dizziness, multiple ecchymoses, and a blood count of 2 g%Hb, a white blood cell (WBC) count of 33,000/μl with shift to the left (Table I), and a platelet count of 9,000/μl. Lactic acidosis was documented. Despite intensive supportive therapy, the patient succumbed due to cardiac arrest. Autopsy was refused. We have no blood smears prior to admission to the hospital, and no molecular analysis could be carried out because of lack of a bone marrow specimen.

The only CML case so far reported is that by Donti et al. [3], who described a blast crisis with t(4;21) (p16;q22) in a patient previously defined as having typical CML with variant Ph t(2;9;22). However, no Pelger-Hüet anomaly was decomented, and the translocations are at variance from our case.

Acquired Pelger-Hüet anomaly, as described by Pelger, is sometimes observed in MPD, dysmyelopoietic syndromes, severe infections, and in other clinical entities such as Hodgkin Disease, non-Hodgkin lymphoma, post-bone marrow transplantation and after valproic acid treatment [4]. The anomaly in these clinical settings has been found together with various chromosomal aberrations, such as trisomy 18, t(5;17), t(7;17), del 17p i(17q), and $22p^+$ (5-8). The present case had Pelger-Hüet anomaly and t(4;21) in the bone marrow cells. Therefore, hereditary Pelger-Hüet anomaly, which is not usually associated with such chromosomal aberration, is unlikely. Moreover, the dysplastic morphological changes in the patient's bone marrow concur with the diagnosis. It is possible that the (4;21) translocation is etiologically associated with her disease, as well as with the Pelger-Hüet anomaly.

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