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Laetrile-Induced Agranulocytosis

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PROPONENTS of laetrile claim it is beneficial and safe. Opponents point to the lack of proof of its efficacy, the delay in seeking more effective therapy its use may entail, and the risk of death or illness from cyanide poisoning resulting from its use. We report the case of a patient in whom agranulocytosis developed, apparently due to laetrile.

Report of a Case

On May 10, 1980, a 61-year-old woman who had been treating herself with laetrile for five years was admitted to Greenwich (Conn) Hospital because of sudden onset of rigors with fever (temperature to 39.4 °C). She had had a simple right mastectomy with axillary lymph node dissection for infiltrating ductal carcinoma in 1966. In 1975 a second primary developed and she underwent a left modified radical mastectomy, followed by a course of fluorouracil. She received five doses of 500 mg intravenously during June and July 1975, but discontinued treatment because of nausea and vomiting. In March 1976, she obtained laetrile from an undisclosed source and began taking one 500-mg tablet twice a day without interruption over the next five years, except for a two-month hiatus during January and February 1980 when she ran out of the drug.

In addition to laetrile, the patient had had recent exposure to flurazepam hydrochloride (Dalmane), a laxative preparation containing yellow phenolphthalein (Feen-a-mint), chlorothiazide (Diuril), meprobamate (Miltown), secobarbital sodium and amobarbital sodium (Tuinal), oxycodone hydrochloride (Percodan), and methocarbamol (Robaxin).

Her medical history included *Salmonella* septicemia in 1960, pyelonephritis in 1964, pneumococcal bronchopneumonia in 1967, and acute bronchitis in 1968. She had an appropriate leukocyte response to each of these illnesses, and complete blood cell (CBC) counts during intervening and subsequent observations were normal on numerous occasions. There was no family history of blood dyscrasias.

She was seen by her physician two weeks before admission, at which time a CBC count showed 3,800 WBCs per cubic millimeter, with 38% polymorphonuclear leukocytes and 47% lymphocytes (Table).

Her admission physical examination was unremarkable except for bilateral mastectomy scars. There were no localizing signs to suggest a site of infection. Her total WBC count was 3,400/cu mm, with a differential cell count showing 0% neutrophils, 0% band forms, 47% lymphocytes, 5% eosinophils, and 48% atypical monocytoid cells with prominent cytoplasmic vacuolization (Table). Chest x-ray film showed no infiltrate, and urinalysis findings were unremarkable. Urine, throat, and multiple blood cultures proved negative. Bone marrow aspiration was performed, showing a preponderance of early myeloid forms, most in the promyelocyte stage, with virtual absence of segmented neutrophils. Marrow differential showed 4% blast cells, 27% promyelocytes, 4% myelocytes, 2% band forms and seg-

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Complete Blood Cell Counts, November 1978 to May 1981*

Date	11/78	4/29/80	5/10	5/14	5/15	5/16	5/18	5/27	6/11	6/14	6/16	6/20	6/23	6/24	6/30	11/80	2/81	5/81
Total WBCs, $\times 10^3$/cu mm	5.1	3.8	3.4	4.2	4.6	4.5	6.3	4.6	3.3	2.4	3.7	3.2	4.6	4.9	3.9	3.8	5.3	6
% Neutrophils	56	38	0	1	8	16	46	48	9	0	0	6	21	37	48	50	51	50
% Band forms	1	0	0	2	1	1	3	0	0	1	0	1	3	0	0	0	0	0
% Lymphocytes	33	47	47	51	57	49	47	36	71	65	74	76	62	53	44	47	37	37
% Eosinophils	4	2.6	5	2	4	5	0	1.3	4	0	4	2	4	1	2.4	2	3	2
% Basophils	0	1	0	0	1	0	0	1	0	0	1	1	1	1	1.4	1	0.4	1
% Monocytes	6	11	48	44	29	29	4	11	16	34	21	14	8	7	4	0	8	10
% Myelocytes	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
Hemoglobin, g/dL	13.8	...	13	13	14	13	13	12	14	14	13	13	13	13	12	...	14	13
Hematocrit, %	40	...	41	38	43	38	40	38	44	40	41	41	41	39	39	...	42	38
Platelets, $\times 10^3$/cu mm	Adeq	...	187	...	...	275	264	...	Adeq	214	205	244	277	264	205	...	...	...

*Ellipses indicate data not available; Adeq, adequate.

mented neutrophils, 2% plasma cells, 1% monocytoid, 2% eosinophils, 16% lymphocytes, and 42% nucleated RBCs. Megakaryocytes were adequate and of normal appearance. The clinical diagnosis was granulocytic maturation arrest, cause unknown.

The patient was placed in reverse isolation and laetrile was withheld. She was febrile (temperature to 38.3 °C) during the first three hospital days and thereafter was afebrile. No antibiotic therapy was given. The WBC count and differential cell count returned to normal by the ninth hospital day (Table). She was discharged on the tenth hospital day and was instructed to avoid all medications, especially those to which she had been exposed before admission.

She omitted all medications for the next three weeks and at that time had a normal WBC count and polymorphonuclear percentage (Table). On May 31, 1980, she resumed laetrile self-administration, 500 mg orally twice a day. On June 7, 1980, chills, aches, and malaise developed. Her WBC count on June 11 was 3,300/cu mm, with 9% neutrophils, no band forms, 70% lymphocytes, 4% eosinophils, and 16% monocytes. On June 13 a paronychia of the right middle finger and sores on the right aspect of the tongue were noted. She was asked to discontinue taking the laetrile. Later that day, temperature to 39.4 °C with severe headache developed. She was given erythromycin ethylsuccinate, taking a total of three 400-mg tablets. She had also taken a single capsule of amobarbital and secobarbital at bedtime on June 11 only.

She was readmitted to Greenwich Hospital on June 14, 1980, appearing ill with temperature of 39.6 °C, a pulse rate of 112 beats per minute, and blood pressure of 124/70 mm Hg. Small vesicles on the right aspect of the tongue and a paronychia of the right middle finger were present.

Her WBC count on admission was 2,400/cu mm, with 0% neutrophils, 1% band forms, 65% lymphocytes, and 34% monocytes. Urinalysis and chest x-ray film showed no abnormal findings. Appropriate cultures were negative. Bone marrow aspiration findings were similar to those of the original aspirate except that myelocytes rather than promyelocytes were predominant in the myeloid series.

The patient was placed in reverse isolation and was treated with intravenous cefamandole nafate (8 g/day) and warm soaks to the right middle finger. She was febrile on the day of admission but afebrile thereafter. The paronychia gradually improved. She had development of herpes of the lips, tongue, and mouth and also blepharitis of the left lower eyelid. These resolved with local measures. Her WBC count slowly improved over the next ten days, with return of adequate neutrophils toward the end of hospitalization. She was discharged on a regimen of oral cephradine (Velosef) and was instructed to avoid laetrile.

Since her discharge from the hospital on June 24, 1980, the patient has avoided use of laetrile and her health has remained good. Periodic CBC counts have shown return to a normal pattern (Table).

Comment

This patient experienced reversible agranulocytosis on two occasions, most likely related to the use of laetrile. Laetrile, as it is available to the public, has often been found to contain contaminants and impurities.[1,2] Therefore, it is impossible to state categorically that amygdalin rather than some contaminating substance was the responsible agent.

The toxic effects of laetrile are chiefly due to the release of hydrogen cyanide by the action of β-glucosidases on amygdalins in the gut.[1-4] Hematologic effects have not been a prominent feature in reported cases.

The mechanism responsible for the agranulocytosis in our patient remains speculative. Perhaps relevant to our patient is the study by Koeffler et al,[5] who found nonselective inhibition by amygdalin of colony formation by acute myelogenous leukemia cells and normal bone marrow granulocyte-monocyte precursors in vitro. They found 50% reduction in colony formation at roughly 3 to 4 mg/mL concentrations of two different amygdalin preparations and virtual total suppression of colony formation at 9 mg/mL. Preincubation of amygdalin preparations with β-glucosidase enhanced the cytotoxic effect. There was no selective toxicity against leukemic cells compared to normal bone marrow cells. They concluded that hydrogen cyanide had a role in the inhibition of colony formation, although the exact mechanism was not determined in their study.

The facts of this case suggest that agranulocytosis may result from the use of laetrile. Physicians and the general public should be aware of this potential toxicity.

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