Arsenic Intoxication as a Cause of Megaloblastic Anemia

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We have described a case of chronic arsenic intoxication associated with pancytopenia and megaloblastic erythropoiesis. The patient had the typical laboratory manifestations of ineffective erythropoiesis due to a megaloblastic process, including macroovalocytes, mild pancytopenia, low reticulocyte index, increased marrow cellularity with erythroid hyperplasia, and morphologic evidence of megaloblastic maturation in the marrow. The patient's serum folate and vitamin B₁₂ were normal, and the anemia regressed without therapy. Our case suggests that the combination of megaloblastosis with normoblastic or megaloblastic karyorrhexis, should raise the suspicion of arsenic intoxication in the mind of the observer. In addition, arsenic should be added to the list of agents causing a reversible megaloblastic anemia.

ARSENIC INTOXICATION has been well described as a cause of bone marrow depression. The peripheral hematologic abnormalities associated with arsenic poisoning are, in order of frequency, leukopenia, anemia, and thrombocytopenia.¹⁻⁵ In their report of six cases of arsenic intoxication, Kyle and Pease⁵ found anemia and neutropenia in all patients and thrombocytopenia in three of the six. In this latter report, the peripheral erythrocytes were reported to be basically normochromic and normocytic with some variation in size and shape. Bone marrow examination showed erythroid maturation to be normoblastic with a few “megaloblastoid” forms and occasional binucleated red cell precursors. The patient described in our report of arsenic intoxication is unusual in that his hematologic dyscrasia included a macrocytic pancytopenia with florid megaloblastic changes, frequent bizarre mitoses, and karyorrhexis in the bone marrow. In our search of the literature, we have not found a case of megaloblastic erythropoiesis due solely to arsenic intoxication, although one case has been reported of coexistent arsenic intoxication and folate deficiency.⁶

CASE REPORT

A 47-yr-old white male was hospitalized on September 20, 1972 because of incapacitating burning paresthesias and weakness of the lower extremities. Approximately 3 wk prior to admission, the patient noticed the onset of numbness of his hands and feet. He reported that the symptoms progressed gradually, culminating in a continuous burning sensation of the feet and severe weakness of his upper and lower extremities. He also complained of intermittent nausea and vomiting of 1 wk duration. Except for these complaints, his review of systems was unremarkable.

He admitted to exposure to a weed spray approximately 2 wk prior to admission. Three to five days following this exposure, he developed periorbital edema and desquamation of the skin over his arms, chest, and abdomen which resolved prior to admission. He admitted taking diazepam...
Table 1. Arsenic Content of Tissues.

<table>
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<th>Urine (mg/liter)</th>
<th>Nails (μg/g)</th>
<th>Hair (μg/g)</th>
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<tbody>
<tr>
<td>Patient</td>
<td>2.2</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>Control</td>
<td>0.1</td>
<td>0-3</td>
<td>0-3</td>
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(Valium) and propoxyphene napsylate (Darvon-N), but denied exposure to other toxins or ingestion of additional drugs. His private physician confirmed that the patient had not received any medications other than those mentioned. He reported a 10-pack year history of cigarette smoking and drinking two to three cans of beer a week.

Physical examination revealed a diffusely pigmented male in mild distress. Hyperkeratosis of the palms and soles and growth arrest lines of the fingernails were present. Examination of the thorax was normal, and examination of the abdomen revealed no masses or hepatosplenomegaly. Neurologic examination revealed a symmetrical decrease in muscle strength in the upper and lower extremities. Biceps, ankle, and knee deep tendon reflexes were symmetrically absent. He had a decrease of pin-prick and vibratory sensation in the hands and feet as well as proprioceptive loss in the toes. Mental status was appropriate.

All laboratory tests were performed in the Pathology Department of the University of Missouri except for the serum folate and B₁₂ levels, which were done at Bio-Science Laboratories, and the heavy metal determinations, which were done at the Trace Metals Laboratories, Space Science Research Center of the University of Missouri. Normal values for laboratory tests are in parentheses.

Admission laboratory values included a hemoglobin of 9.1 g/100 ml; hematocrit, 28%; white blood count, 1600/cu mm with a differential of 25%, neutrophils, 53%, lymphocytes, 18%, monocytes, 3%, eosinophils, 1%, basophils, and 1 nucleated red blood cell per 100 white blood cells; platelet count, 130,000/cu mm; and reticulocyte count, 5.3%, corrected to a reticulocyte index of 1.7. The serum SGOT was 115 mU/ml (740); LDH, 205 mU/ml (100-225); creatinine, 0.7 mg/100 ml; bilirubin, direct, 0.05 mg/100 ml (0.1-1.2), indirect, 0.45 mg/100 ml (0.1-0.3); prothrombin time, 11/12 sec; and Coombs' test direct and indirect was negative. RPR was nonreactive. Serum folate was 10 ng/ml (5-21); serum B₁₂ was 601 pg/ml (170-760); serum lead was 9 g/100 ml (0.60); and urine lead was 21 g/24 hr (0-100). Arsenic content of the urine, nails, and hair was markedly elevated as shown in Table 1. The patient's well water arsenic content was subsequently found to be barely measurable at less than 0.0002 mg/ml.

Additional studies included a liver biopsy which was interpreted as showing minimal hepatitis consistent with drug reaction. Electromyographic and nerve conduction tests revealed a severe peripheral neuropathy with generalized denervation greater distally than proximally. Bone marrow examination was performed on September 22, 1972, and the details of the morphologic examination will be described in the following section.

The patient's hospital course was uncomplicated and was characterized by stopping all medications and beginning physical rehabilitation once arsenic intoxication had been identified as the source of the peripheral neuropathy. The hematologic response of the patient is illustrated in Fig. 1. Unfortunately, a follow-up bone marrow examination was not obtained because the patient refused to return for follow-up examination after discharge from the hospital.

RESULTS

Bone marrow examination revealed hematopoietic hypercellularity due to marked erythroid hyperplasia which produced a myeloid to erythroid ratio of 0.4. Both erythroid and myeloid maturation was megaloblastic. The nuclear maturation defect in erythropoiesis produced relative increases in percentages of promegaloblasts and basophilic megaloblasts. All stages of maturation showed the megaloblastic features of nuclear-cytoplasmic asynchronism, finely dispersed immature nuclear chromatin, and increased cytoplasmic volume. Stains for iron revealed many ringed sideroblasts. Giant metamyelocytes and
hypersegmented neutrophils were evidence of megaloblastic myelopoiesis. Numerous mitotic figures which were frequently bizarre were encountered in normoblasts. Karyorrhexis was equally common, and these features resulted in a great many and multiple Howell-Jolly bodies. Cytoplasmic basophilic stippling of reticulocytes and late-stage normoblasts was prominent. Megakaryocytes were adequate and producing platelets. (Figs. 2–4).

Fig. 1. The patient's hematologic response without therapy. A reticulocyte response was evident at 1 wk; by 3 wk, the peripheral blood counts were within normal limits.

Fig. 2. This magnification of the marrow smear emphasizes the frequent occurrence of normoblast karyorrhexis and (atypical) mitoses with resultant multiple Howell-Jolly bodies. Wrights, x 1125.
DISCUSSION

On the basis of the clinical and laboratory data, we feel that our patient represents a case of chronic arsenic intoxication. The clinical features of chronic arsenic intoxication have been described to include hyperkeratosis of the palms and soles, hyperpigmentation of the skin, and sensory and motor neuropathies.7,9 Our patient demonstrated all of these latter features; and, in addition, he had an elevated SGOT and a liver biopsy that was interpreted as showing minimal hepatitis consistent with drug reaction. Mild liver damage in chronic arsenic poisoning has been previously described by Anthonisen et al.10 Our patient had markedly elevated levels of arsenic in his urine, hair, and nails, consistent with the clinical picture of chronic intoxication, but we were unable
to determine the source of arsenic poisoning. His motor neuropathy cleared slowly during hospitalization, but had not completely regressed at the time of his discharge approximately 1 mo after admission. Follow-up studies were not obtained because the patient refused to return for examination.

The hematologic complications of arsenic intoxication include varying degrees of marrow depression, even aplastic anemia. Neutropenia and anemia are the most common manifestations of arsenic intoxication, and some patients may have pancytopenia. These patients may have a peripheral pancytopenia in the presence of a cellular marrow, indicating that arsenic may exert a direct toxic effect on cellular maturation. The anemia of arsenic intoxication is characteristically normochromic and normocytic with no consistent morphologic abnormalities of the bone marrow. Megaloblastic erythropoiesis has not been heretofore clearly ascribed to arsenic intoxication, although Kyle and Pease do mention that "megaloblastoid" erythroid precursors may be occasionally seen in the bone marrow. Van Tongeren et al. have reported a case of chronic arsenic poisoning in a patient whose anemia was characterized by megaloblastic erythropoiesis in the bone marrow but whose serum folic acid was found to be low. These authors suggested that the megaloblastic anemia was due to folic acid deficiency and that perhaps the arsenic inhibited the enzymatic conversion of folic acid into its biologically active derivatives. In contrast, our patient had evidence of megaloblastic erythropoiesis in the presence of a normal serum folate and vitamin B12 and in the absence of ingesting any drug previously associated with megaloblastic anemia.

Our patient had the typical laboratory manifestations of ineffective production of erythrocytes due to a megaloblastic process which included variation in size of erythrocytes with macrocytes on peripheral smear, low reticulocyte index, increased marrow cellularity with erythroid hyperplasia, abundant marrow iron, and morphologic evidence of megaloblastic maturation in the marrow. This laboratory data is characteristic of the megaloblastic anemias in which there is a nuclear maturation abnormality on the basis of defective DNA synthesis. Although adequate megakaryocytes were present in the bone marrow sections, the patient had a peripheral thrombocytopenia that improved without therapy as did the ineffective erythroid and myeloid production.

The question of how arsenic intoxication can produce megaloblastic erythropoiesis with secondary anemia is an interesting one yet to be answered. The typical megaloblastic cell is considered to have a defect in the synthesis of DNA resulting in the nuclear maturation abnormalities observed morphologically. This impairment of DNA replication stems usually from a deficiency of purine and pyrimidine synthesis or incorporation as a result of a defect in established enzymatic pathways. Limarzi found that when arsenic was fed to patients with pernicious anemia, the marrow megaloblasts developed marked karyorrhexis. This effect of arsenic was not observed in patients with a variety of other hematologic disorders. Skipper et al. have shown that potassium arsenite injected into mice can block the incorporation of 14C-labeled formate into nuclear purines. These observations suggest that arsenic may directly interfere with the synthesis of DNA as evidenced morphologically in our patient.
REFERENCES
1. Loveman AB: Toxic granulocytopenia, purpura hemorrhagica and aplastic anemia following the arsphenamines. Ann Intern Med 5:1238, 1932
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