Case report

Pure red cell aplasia

A preleukemic state

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Significant progress has recently been made in the characterization of the preleukemic phase of acute nonlymphocytic leukemia (ANLL). In addition to the well-defined syndromes which have been found to precede ANLL, a number of less well-defined and poorly understood preleukemic states have been described.[1] The well-defined syndromes associated with increased risk of ANLL include exposure to myelotoxic agents such as chloramphenicol,[2,3] benzene,[4,5] phenylbutazone,[6] and arsenic;[7] exposure to ionizing radiation;[8] several chromosomal abnormalities including Down's syndrome,[8] Klinefelter's syndrome,[9] and Turner's syndrome;[10] Fanconi's congenital marrow hypoplasia;[11] congenital agranulocytosis;[12] idiopathic aplastic anemia;[13] ataxia telangiectasia;[14] and paroxysmal nocturnal hemoglobinuria.[15]

The syndrome of acquired pure red cell aplasia (PRCA) with or without antecedent exposure to marrow toxins has only rarely been reported as a preleukemic phase of ANLL. PRCA may be defined as a normocytic, normochromic anemia without reticulocytes, but with normal leukocytes and platelets in the peripheral blood; normal marrow granulocytic and megakaryocytic elements with a virtual absence of erythroblastic

elements, and no evidence of extramedullary hematopoiesis.[16] The following case illustrates idiopathic PRCA as a preleukemic manifestation of ANLL.

Case report

A 56-year-old man was found to be anemic at another hospital in December 1970 following surgery for a renal calculus. A bone marrow aspirate was interpreted as showing aplasia. No history of exposure to organic toxins, insecticides, or chloramphenicol could be elicited. Empiric trials of prednisone and pyridoxine failed to improve the anemia, and he required frequent transfusions to maintain adequate hemoglobin and hematocrit. On admission to the Cleveland Clinic Hospital he was obese and mildly Cushingoid with normal blood pressure and pulse. No abnormalities were found on physical examination; the liver and spleen were not enlarged to palpation and percussion. Initial hematologic parameters were hemoglobin, 5.3 g/dl; hematocrit, 16%; reticulocyte count, less than 0.1%; MCV, 87 fl; MCH, 31 pg; MCHC, 35%; WBC, 5200/μl with a differential count of 45% segmented neutrophils, 33% lymphocytes, 9% monocytes, 5% metamyelocytes, and 4% myelocytes; and 140,000 platelets/μl were present. Direct and indirect antiglobulin tests were negative. Serum iron, iron-binding capacity, and vitamin B_{12} levels were not measured. Bone marrow aspirate (*Figs. 1 and 2*) revealed a normocellular marrow with normal megakaryocytes, an M/E ratio of 32:1 with a granulocytic precursor differential count of 10% myeloblasts, 3% promyelocytes, 9% myelocytes, 22% mature neutrophils and bands, and 51% lymphocytes. A diagnosis of PRCA was made. Extensive search for a thymoma by roentgenography was unrewarding. He received transfusions at 3- to 5-week in-

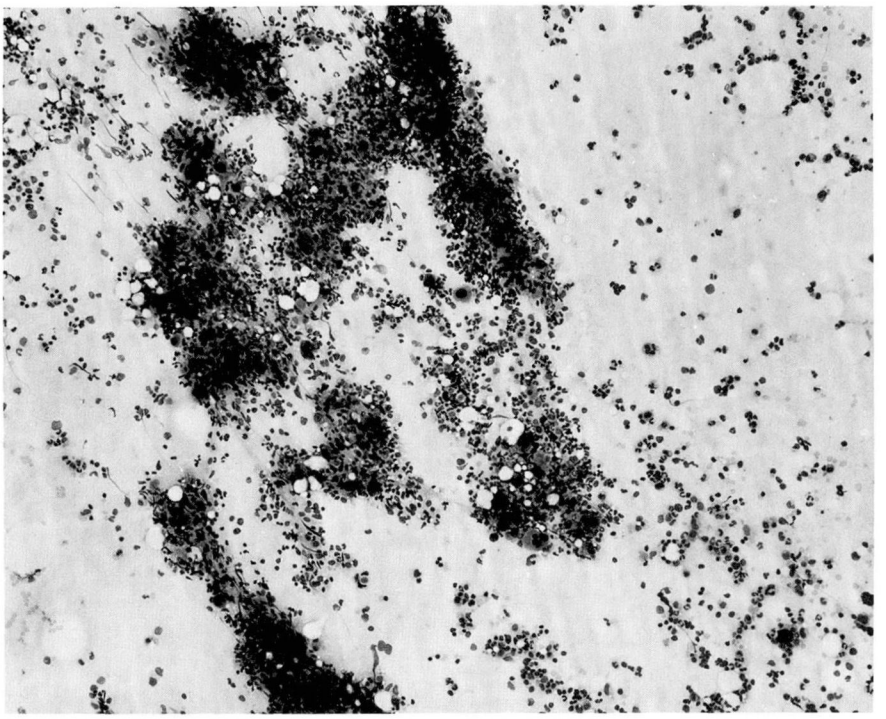

Fig. 1. Initial bone marrow aspirate showing normal cellularity and normal megakaryocytes (Wright's stain, ×64).

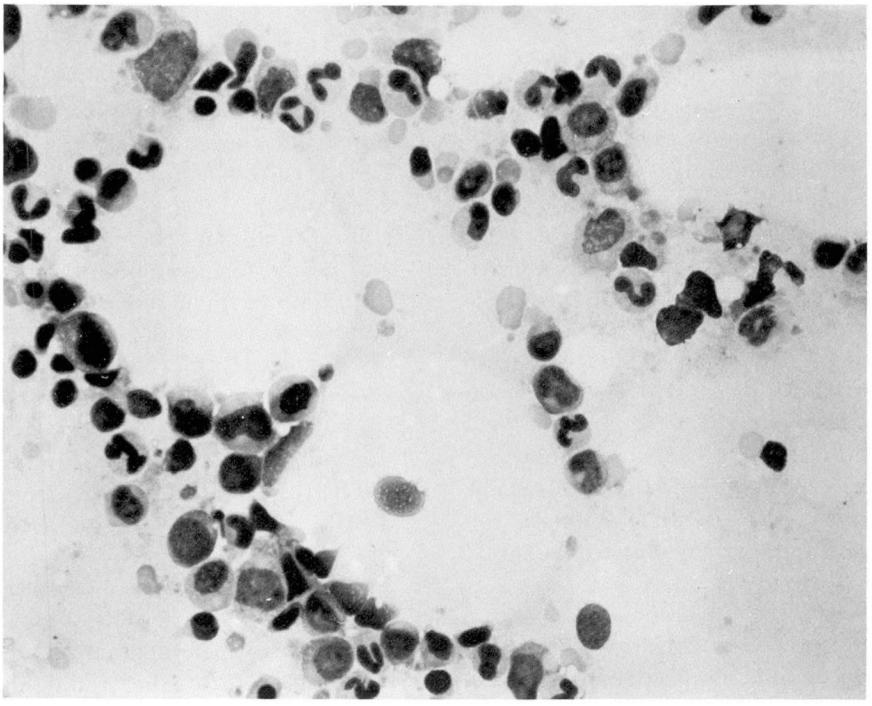

Fig. 2. High magnification of initial bone marrow aspirate. All cells present in field are granulocytes or lymphocytes (Wright's stain, ×400).

tervals; this therapy maintained his hemoglobin level between 6 and 9 g/dl. Therapy with azathioprine, prednisone, 6-mercaptopurine, oxymetholone, and dexamethasone in various combinations failed to produce reticulocytosis. During his course the majority of reticulocyte counts remained below 0.1%. Except for several episodes of herpetic stomatitis and febrile nonhemolytic transfusion reactions which appeared late in his course, he remained well. In all he received 93 units of whole blood, packed cells, and leukocyte-poor packed cells in a period of 23 months.

Twenty-one months after his initial examination bronchitis developed which was treated with ampicillin. His peripheral smear at this time showed the following values: hemoglobin, 5.7 g/dl; hematocrit, 17%; WBC, 1600/μl with 46% segmented neutrophils, 4% bands, 32% lymphocytes, and 15% monocytes; and platelet count of 80,000/μl. His symptoms persisted despite antibiotic therapy, and 1 month later he was admitted with fever, splenic pain, and cough productive of yellow sputum. The spleen was now palpable 4 cm below the left subcostal margin, and 5 cm hepatomegaly had appeared. A chest film revealed atelectasis of the middle lobe of the right lung. Examination of the peripheral blood smear showed hemoglobin, 7.4 g/dl; hematocrit, 22%; WBC, 2200/μl with 44% segmented neutrophils, 2% bands, 1% basophils, 26% lymphocytes, 10% monocytes, and 17% blasts. Platelets were reported as markedly decreased. Bone marrow aspirate was hypocellular, but 13% of the identifiable cells were blasts. Five days later, the WBC was 6500/μl with a differential count of 20% segmented neutrophils, 1% bands, 16% lymphocytes, 3% monocytes, 2% metamyelocytes, 1% myelocytes, and 57% blasts. The patient died that afternoon after receiving the first dose of chemotherapy.

Autopsy results

Autopsy examination revealed pulmonary consolidation in both lower lobes (combined weight 2000 g). Severe splenomegaly (weight 2590 g) with reddish-brown expansion of the red pulp and replacement of white pulp was observed. Severe enlargement of lymph nodes was present in all the regions examined. The bone marrow grossly was succulent and deep reddish-brown. The liver was enlarged (weight 3300 g) and on cut section showed whitish nodular expansions of the portal areas. The pancreas was of normal weight but firmer than expected and dark tan to brown.

Microscopic examination of the lungs showed an infiltrate of malignant cells involving alveoli and parenchyma. The cells resembled histiocytes with agranular pink to light blue cytoplasm and folded nuclei with chromatic clumping and occasional, prominent nucleoli (*Fig. 3*). ASD chloracetate esterase and Giemsa's staining failed to reveal specific granules in the immature cells. Numerous hyaline membranes were found along the alveolar septae, and hemosiderin laden macrophages filled many alveoli. Neutrophils were absent from the cell masses. Leukemic thrombi in small vessels with surrounding infarction of lung tissue were present. Sections of spleen and lymph node (*Fig. 4*) showed extensive diffuse infiltration, with the malignant cells entirely obliterating the normal architecture. The spleen also contained foci of extramedullary hematopoiesis. The spleen and several

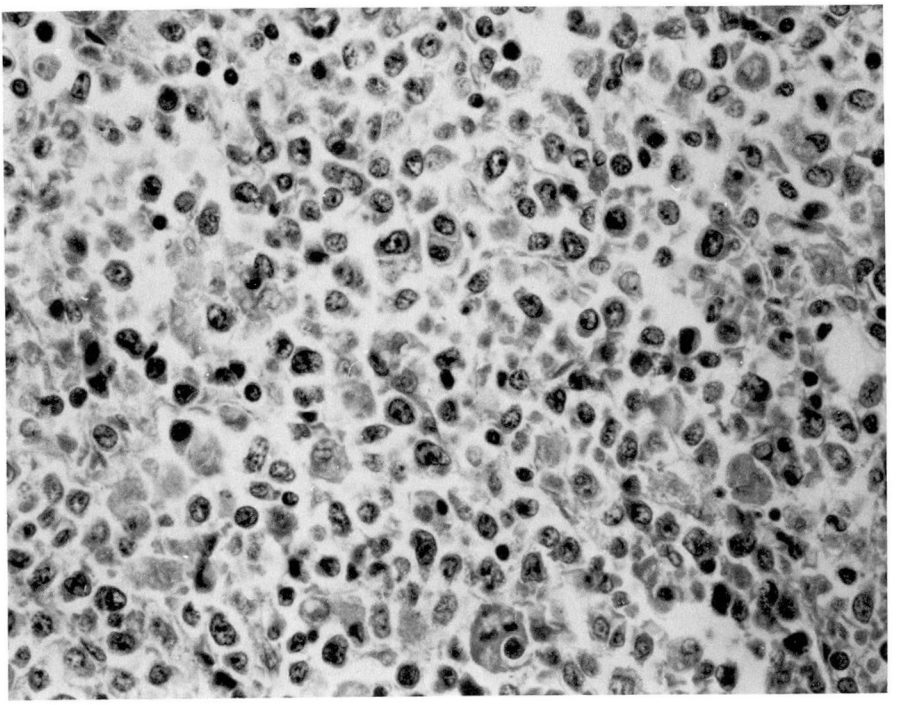

Fig. 3. Malignant cells infiltrating lung at autopsy. Note pleomorphic nuclei with prominent nucleoli. Cells have moderate amount of agranular eosinophilic cytoplasm (hematoxylin and eosin stain, ×400).

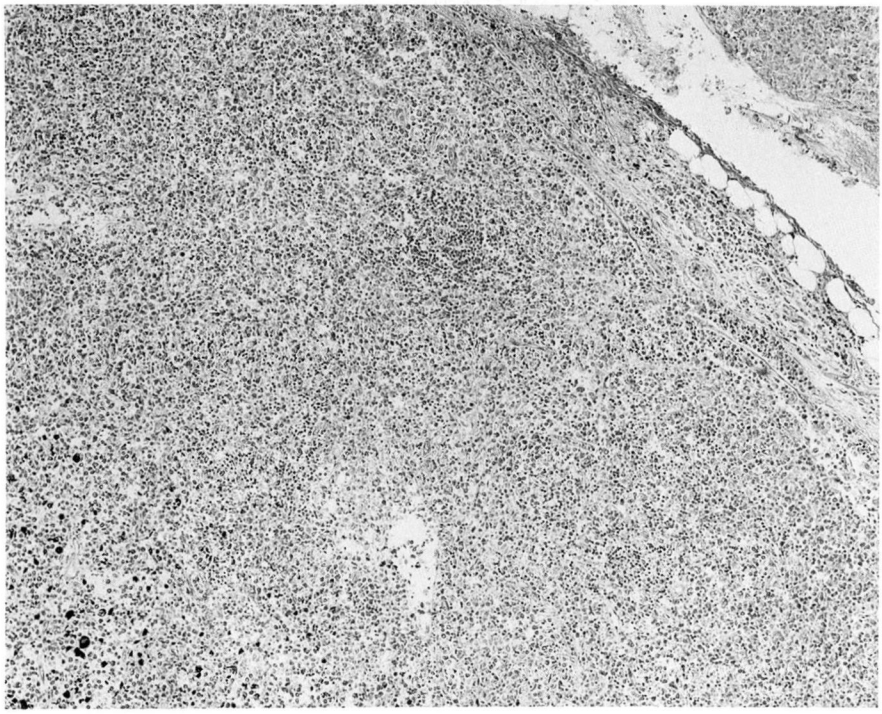

Fig. 4. Section from autopsy lymph node showing obliteration of normal architecture by infiltrating malignant cells (hematoxylin and eosin stain, ×64).

lymph nodes showed leukemic thrombi with infarction similar to those found in the lung. The malignant cells entirely replaced the marrow (*Fig. 5*). The liver (*Fig. 6*) displayed massive portal and periportal infiltration with malignant cells; extensive numbers of Prussian blue positive iron granules were present in the Kupffer cells but not in the hepatocytes. Iron was also diffusely deposited in pancreatic islet and acinar cells, epithelial cells of the pancreatic ducts, and in macrophages. Microscopic infiltration of the malignant cells into kidneys, prostate, testis, thyroid, esophagus, and adrenals was also found.

Discussion

Several reports of PRCA as a preleukemic syndrome have been published.[1, 17–22] In some of the case reports, insufficient information is provided to decide whether these cases meet the criteria needed to make a diagnosis of PRCA.[1, 20, 22] The case reported by Soutter and Emerson[19] does not fit the accepted definition of PRCA, since the patient had a reticulocytosis of 2.1% during his course, and the degree of red cell aplasia in the marrow is not reported. Furthermore, the presence of immature monocytoid cells in the marrow and peripheral blood at the time of the initial diagnosis suggests that this patient may already have had leukemia. The case reported by Mohler and Leavell[17] was shown by marrow aspirate to represent aplastic anemia rather than PRCA. Two cases (14 and 15) reported by Schmid et al[21] (number XX is the patient reported by

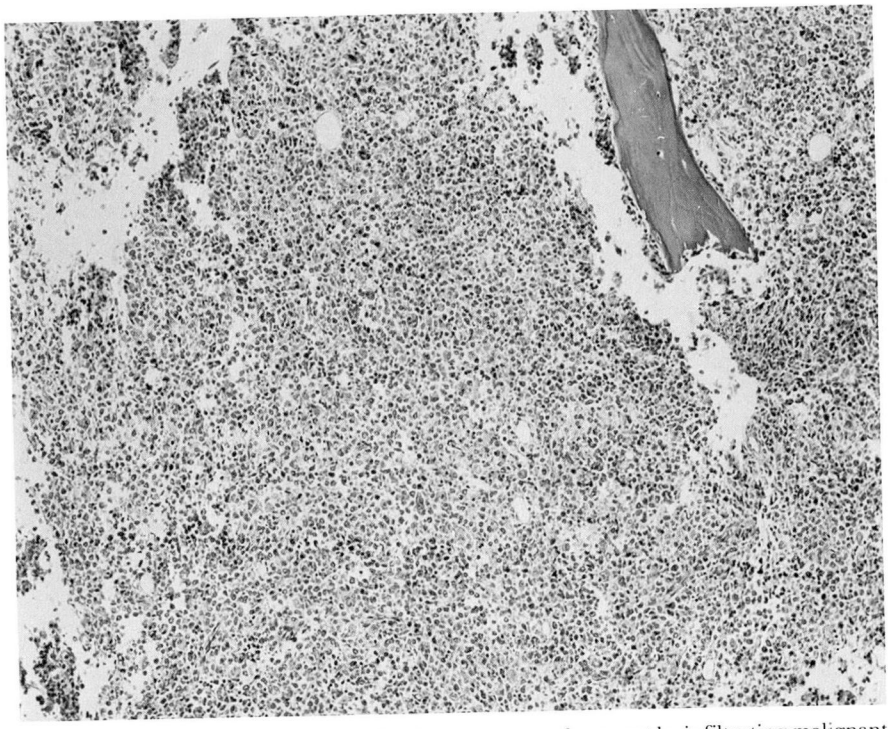

Fig. 5. Section of autopsy bone marrow showing marrow replacement by infiltrating malignant cells (hematoxylin and eosin stain, ×64).

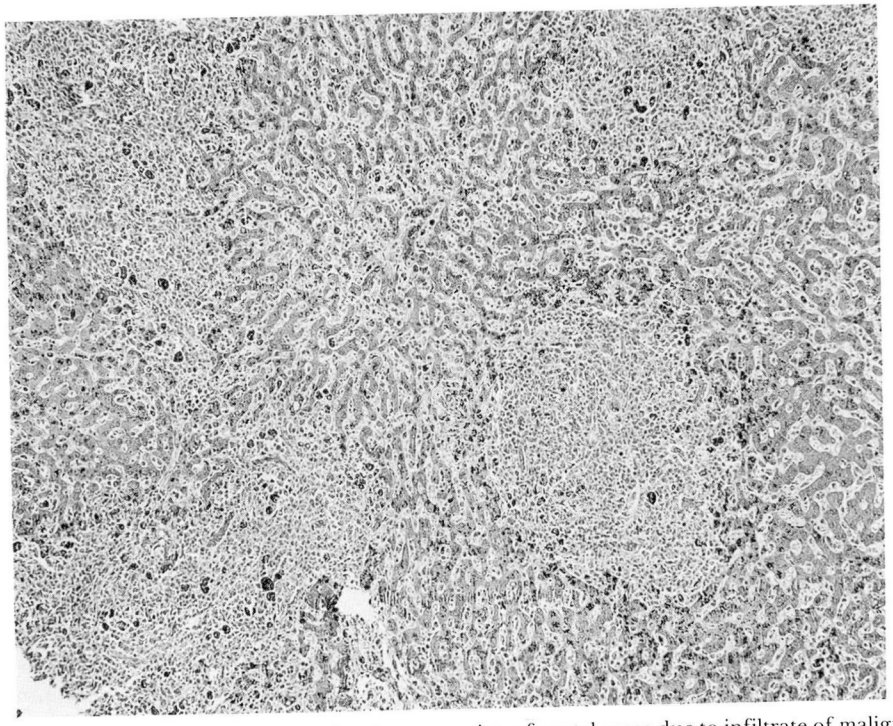

Fig. 6. Segment of liver at autopsy showing expansion of portal areas due to infiltrate of malignant cells. Infiltration of sinusoids and periportal regions is also present (hematoxylin and eosin stain, ×64).

Table. PRCA as a preleukemic state; summary of previously reported cases and present case

	Age/sex	Toxic exposure	Duration of clinical course and type of leukemia
Case 14[21]	56 M	None	2 yr; transformed to acute leukemia
Case 15[21]	47 M	Pentachlorophenol	1½ yr; transformed to acute leukemia
Case[18]	65 F	None	5 mo; transformed to acute granulocytic leukemia
Present case	56 M	None	22 mo; transformed to acute monocytic leukemia

Soutter and Emerson) appear to represent true PRCA as illustrated by marrow differentials. The report by Rubenstein[18] is a case of idiopathic PRCA terminating in acute leukemia.

The four cases accepted as PRCA terminating in acute leukemia are summarized in the *Table*. The average age of the four patients was 56 years, and the duration of disease from diagnosis to death was 17 months. In two cases, the leukemia was nonlymphocytic. In no patient was transient red cell aplasia a preleukemic manifestation, and no patient had a thymoma. In one case, exposure to a toxic myelosuppressive agent was found to be a possible predisposing factor. Comparison with the Mayo Clinic study of preleukemia[1] shows that the age and sex distribution of the 32 patients with preleukemia that subsequently transformed to acute leukemia were similar to the age and sex distribution of the cases in the *Table*. The PRCA patients had a more rapidly progressive course (duration of disease 17 months for PRCA transforming to acute leukemia as compared to 47 months for all preleukemic manifestations which transformed to acute leukemia). PRCA appears to be another member of the ill-defined group of hematologic syndromes termed preleukemia.

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