Acute Leukostasis Pulmonary Distress Syndrome

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A 75-year-old woman in accelerated-phase chronic myeloid leukemia with hyperleukocytosis presented with acute respiratory distress syndrome. Despite early and aggressive pulmonary support and cytoreductive chemotherapy, the patient died. Autopsy confirmed the presence of the leukostasis syndrome. The clinical, radiologic, pathophysiologic, and therapeutic aspects of this entity are reviewed.

Key words. Chronic myelogenous leukemia; leukostasis; hyperleukocytosis; adult respiratory distress syndrome.

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Respiratory distress in leukemic patients is commonly related to pulmonary opportunistic infections; however, other causative considerations include drug-induced injury, hemorrhage, infarction, congestive heart failure, and the leukemic process itself.[1] The latter may be related to leukemic interstitial infiltrates or intravascular leukostasis. We report the case of a 75-year-old woman in an accelerated phase of chronic myeloid leukemia who presented with acute pulmonary distress syndrome.

Case Report

A 75-year-old woman presented to LaGuardia Hospital with a 2-day history of weakness, shortness of breath on minimal exertion, dizziness, palpitations, and cough. She denied having fever, chills, or chest pain. She had a 10-year history of Philadelphia chromosome-positive chronic myeloid leukemia, and she was maintained on hydroxyurea.

The patient's temperature was 99.3°F; pulse, 96 beats per minute; respiration rate, 18 breaths per minute; and blood pressure, 120/78 mm Hg. On physical examination, the patient was pale. Her lungs were clear to auscultation and percussion, and heart sounds were normal with no murmurs. The abdomen was nontender, the liver was palpated 4 cm below the right costal margin, and the spleen was markedly enlarged, firm, and extended 26 cm below the left costal margin (Figure 1). Other physical examination findings were within normal limits.

The patient's hemoglobin was 69 g/L with a hematocrit of 24%. The white blood cell count (WBC) was 419,000/mm^3 (41.9 × 10^9/L) with 27% segmented neutrophils, 14% bands, 41% myelocytes, 4% blasts, 4% metamyelocytes, 4% lymphocytes, 4% monocytes, and 2% basophils. Her chest radiograph (Figure 2) and her electrocardiogram were normal.

Shortly after admission, the patient developed acute respiratory distress with bilateral pulmonary rales. A specimen of arterial blood showed that the partial pressure of oxygen was 39 mm Hg, the partial pressure of carbon dioxide was 20 mm Hg, and the pH was 7.43. Chest radiograph showed bilateral pulmonary woolly infiltrates (Figure 3). The patient was intubated and put on mechanical ventilation with positive end expiratory pressure (PEEP). Aggressive chemotherapy with hydroxyurea (2 g every 6 hours through nasogastric tube) and cytosine arabinoside (100 mg intravenously every 8 hours) was started, and administration of an antibiotic, vancomycin, was begun. Although her WBC dropped to 187,000 (18.7 × 10^9/L) after 3 days of therapy, the patient remained hypoxemic and restless despite increasing concentrations of inspiratory oxygen (FIO_2) and a PEEP of +10. Her condition was too poor for transfer to another center for leukapheresis. The patient died on the 5th day of hospitalization. Postmortem examination of the lungs showed fibrosis, atelectasis, pneumonitis, and prominent pulmonary congestion with features of leukostasis (Figure 4).

Discussion

Pulmonary infiltrates in leukemic patients are a common diagnostic challenge. Tenholder and Hooper[2] reviewed the records of 139 adult patients with leukemia. They found that 82% of localized pulmonary infiltrates were related to

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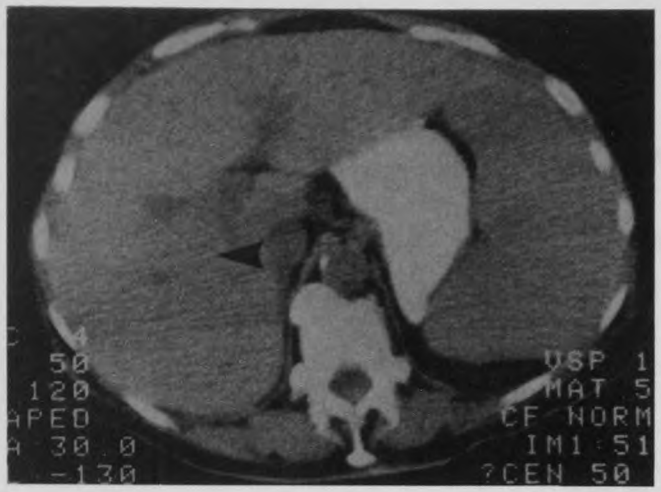

Figure 1. Computed tomography scan of abdomen showing hepatomegaly and massive splenomegaly (arrow).

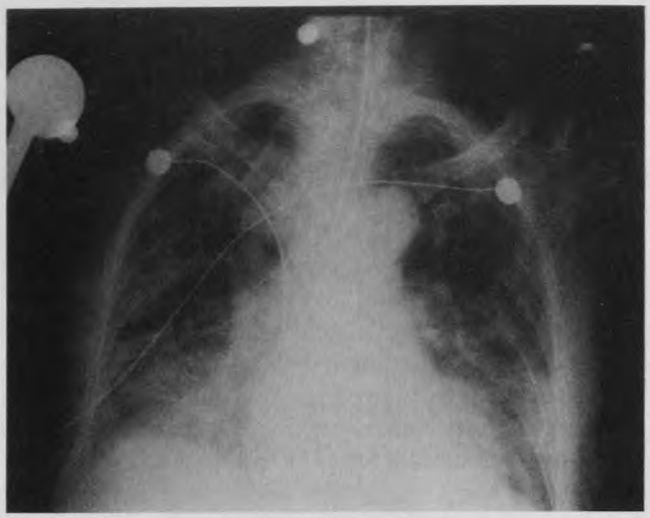

Figure 3. Roentgenogram of chest showing woolly infiltrates in both lung fields with normal cardiac silhouette.

an infectious etiology and none were directly related to the leukemic process. This was in sharp contrast to the infiltrates of diffuse lung disease in which the infectious etiology accounted only for 35% of the cases and the leukemic infiltrates were responsible for 20% of the cases.

Respiratory distress caused by the leukemic process may be due either to diffuse interstitial infiltration of the alveolar septae with neoplastic cells[3–5] or simply to formation of intravascular leukocyte thrombi and aggregates (leukostasis).[6] Leukemic cells of the monocytic lineage seem to favor the interstitial infiltrative process, recapitulating in a way the physiological circulation of monocytes into pulmonary macrophages.[5] In an autopsy population of 201 leukemic patients, McKee and Collins[6] found that in lymphatic leukemias, leukostasis was seldom associated with mortality and morbidity. In myelogenous leukemias, however, leukostasis was often associated with pulmonary hemorrhage and infarction and was presumed to have contributed to death in 24% of the cases.

Clinically, leukostasis can be suspected in patients with unexplained fever, respiratory failure, or cerebral dysfunction (headache, dizziness, mental confusion, deafness, papilledema)[7] because the brain and the lungs are the two most commonly affected organs with the leukostasis syndrome. Van Buchem et al[7] correlated the terminal chest radiographs and the autopsy findings of 10 patients with pulmonary leukostasis. In 6 patients, no abnormalities attributable to leukostasis were seen on

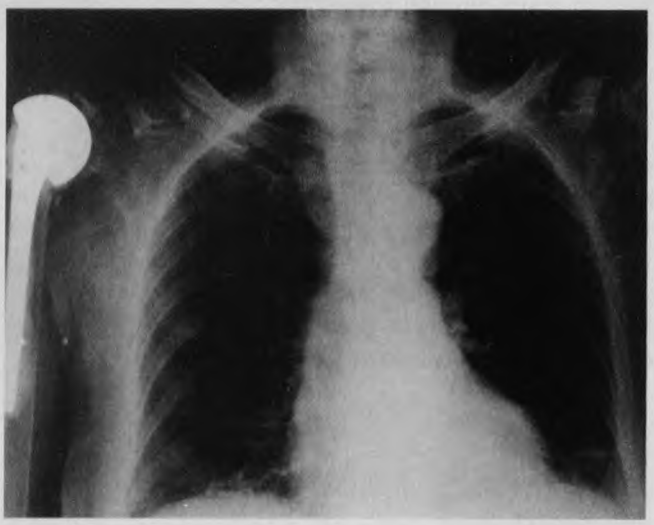

Figure 2. Initial roentgenogram shows essentially clear lungs with normal heart size. Right shoulder prosthesis is also seen.

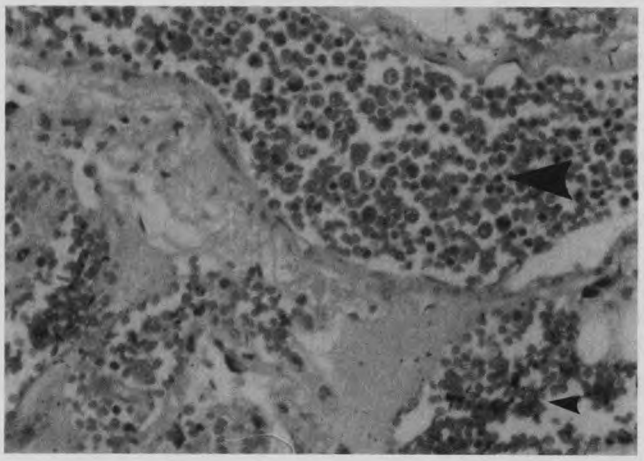

Figure 4. Photomicrograph: The upper part depicts an interalveolar septum with a distended capillary that shows extensive leukostasis (large arrow). The alveolar spaces shown in the lower part are filled with edema and red cells (small arrow).

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chest radiographs, and in 4 patients, diffuse alveolar consolidation was caused by alveolar edema following leukostasis. They concluded that leukostasis should be considered in leukemia patients with severe dyspnea who have normal chest radiographs or diffuse alveolar edema. Lichtman and Rowe[8] showed that in patients with hyperleukocytosis (WBC counts greater than 100,000 [100×10^9/L]) the bulk viscosity of blood is usually not increased despite the high fractional volume of leukocytes (leukocrit). This is due to the usual decrement in the fractional volume of erythrocytes that accompanies the increase in leukocytes. Nevertheless, excessive numbers of leukocytes adversely affect the microcirculation of the lungs by forming white cell thrombi in small veins, by competing locally for oxygen, and by invading alveolar tissue. This ultimately leads to vessel wall damage followed by septal and intra-alveolar edema.

The excessive consumption of oxygen by leukemic cells has been shown in vitro to be responsible for artificially low partial pressure of oxygen in blood samples within seconds of stopping oxygenation.[9]

The high frequency of the leukostasis syndrome during acute myeloid leukemia and the acute phase of chronic myeloid leukemia has been attributed to the low deformability of the myeloblasts.[10] Vernant et al[11] further observed that the hyperleukocytic acute myeloid leukemias with no leukostasis syndrome were all characterized by a stable or slowly increasing leukocytosis (raising the probability of microcirculatory adaptation). In contrast, the hyperleukocytic myeloid leukemias with a rapid blood leukocyte doubling rate are more commonly associated with the leukostasis syndrome. One recent case of pulmonary leukostasis related to postoperative hyperleukocytosis in a patient with chronic myeloid leukemia in remission seems to confirm this hypothesis.[12]

Respiratory failure due to leukostasis is a reversible syndrome,[13] especially with prompt and vigorous therapy. This would include intensive pulmonary support and aggressive cytoreductive chemotherapy. It is also important to avoid the unnecessary increase of blood viscosity associated with the unmitigated use of diuretics and blood transfusions. More recently, emergency aggressive leukapheresis[14,15] using continuous-flow cell separators has been used effectively in reversing the leukostasis syndrome. In a study of 43 patients, Lester et al[16] found pulmonary leukostasis as the single worst prognostic factor in patients with acute myeloid leukemia and hyperleukocytosis. They observed that although therapeutic leukapheresis may improve survival in patients whose WBC can be controlled, those patients in whom leukocytosis rapidly returns to pretreatment levels do not seem to be helped.

Our patient depicts a case of chronic leukemia of myeloid lineage with a rapidly increasing WBC, dyspnea, and essentially clear lung fields on chest radiography, ie, a constellation of findings most characteristic of early stage leukostasis syndrome. Despite treating the patient with aggressive chemotherapy and supportive care, the rapid progression toward interstitial and intra-alveolar edema led to the patient's death. This case highlights the notion that leukostasis syndrome should be considered a medical emergency. It should trigger the most aggressive cytoreductive modalities at hand (chemotherapy, leukapheresis, or both) in combination with the most vigorous pulmonary supportive care available in order to abort the inexorable progression toward the irreversible stages of alveolar damage, edema, and hemorrhage.

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