

Radiologic Features of All-Trans-Retinoic Acid Syndrome

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OBJECTIVE. The treatment of acute promyelocytic leukemia with all-trans-retinoic acid (ATRA) sometimes results in a syndrome characterized by fever, respiratory distress, weight gain, pleural and pericardial effusion, and pulmonary infiltrates. We report the radiologic features of ATRA syndrome.

MATERIALS AND METHODS. During the past 5 years, 69 patients with acute promyelocytic leukemia were treated with ATRA. Of this group, 15 patients developed ATRA syndrome. Serial chest radiographs of the 15 patients with ATRA syndrome were evaluated retrospectively for the presence of pleural effusion, pulmonary nodules, consolidation, ground-glass opacity, septal lines, increased pulmonary blood volume, peribronchial cuffing, and air bronchogram. Also, we measured the cardiothoracic ratio and the vascular pedicle width.

RESULTS. Chest radiographs showed increased cardiothoracic ratio in 13 of the 15 patients, increased vascular pedicle width in 13, increased pulmonary blood volume in 13, septal lines in nine, peribronchial cuffing in nine, ground-glass opacity in nine, consolidation in seven, and nodules in seven. Pleural effusion was noted in 11 of the 15 patients, and air bronchogram was noted in five of the 15 patients. Pulmonary hemorrhage developed in three patients who were being treated with ATRA; they showed bilateral, diffuse, poorly defined nodules and ground-glass opacity on radiography.

CONCLUSION. Most patients with ATRA syndrome have abnormal findings on chest radiographs, and the abnormalities are similar to those of pulmonary edema.

All-trans-retinoic acid (ATRA) is a normal constituent of plasma. It is derived physiologically by intracellular oxidation of plasma retinol that has been absorbed from the intestines [1, 2]. ATRA is used as an accepted therapy for acute promyelocytic leukemia (M3 in the French-American-British classification of acute myelocytic leukemia). ATRA can differentiate acute promyelocytic leukemia blasts into mature granulocytes [3–5]. ATRA is usually well tolerated, but major side effects can be observed, the ATRA syndrome being the most important of them.

Frankel et al. [6] first described this syndrome in nine (25%) of 35 patients who were newly diagnosed with acute promyelocytic leukemia and treated with ATRA. ATRA syndrome is characterized by fever, respiratory distress, pleural and pericardial effusion, weight gain, and pulmonary infiltrates noted on chest radiography. These signs occurred after 2–21 days of treatment and were generally associated with an increasing WBC. Five of the

nine patients described by Frankel et al. required transfer to an intensive care unit and mechanical ventilation, and three of these patients died. However, once a diagnosis of ATRA syndrome has been made, a prompt recovery can be achieved by withdrawing ATRA and treating the patient with prednisolone [6, 7].

In the past, occasional case reports and literature pertaining to ATRA syndrome have been published in the medical literature [6–9], but reports of ATRA syndrome in the radiology literature have been rare [10, 11]. The purpose of our report is to heighten radiologists' awareness of this syndrome, which often manifests as nonspecific clinical and chest radiographic findings.

Materials and Methods

During the past 5 years, 69 patients with newly diagnosed acute promyelocytic leukemia were treated with ATRA at our hospital. These patients received 45 mg/m² (two tablets) per day of ATRA orally for a maximum of 90 days or until they experienced complete remission. Chemotherapy was

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started on day 3 of the ATRA treatment. The patients received a course of 12 mg/m² per day of idarubicin for 3 days and concomitantly 200 mg/m² per day of N(4)-behenoyl-1-β-D-arabinofuranosylcytosine (BH-AC) for 7 days. Among these 69 patients, 15 developed ATRA syndrome, including five men and 10 women ranging in age from 23 to 55 years. Pretreatment chest radiographs showed normal findings in 14 of these 15 patients. One patient showed mild cardiomegaly.

The diagnosis of ATRA syndrome was made on clinical grounds by the association of at least three of the following signs in the absence of other causes: fever, weight gain, respiratory distress, lung infiltrates, pleural or pericardial effusion, hypotension, and renal failure [6, 8]. Chest radiographs were evaluated by three radiologists and a final decision was reached by consensus. For each patient, the observers completed a reading list of pertinent findings (Table 1).

We evaluated the presence of pleural effusion, pulmonary nodules, consolidation, ground-glass opacity, septal lines, increased pulmonary blood volume, peribronchial cuffing, and air bronchogram. We evaluated the zonal distributions of ground-glass opacity, nodules, and consolidation. We also measured the cardiothoracic ratio and the vascular pedicle width. The increased cardiothoracic ratio was more than 0.5 on posteroanterior chest radiographs or 0.6 on anteroposterior chest radiographs [12]. The increased vascular pedicle width was more than 53 mm on both posteroanterior and anteroposterior chest radiographs [13]. High-resolution CT was performed in three of the patients during the disease manifestation.

Once the diagnosis of ATRA syndrome was made at our institution, prednisolone (20–40 mg/day, divided doses) was given immediately, and the administration of ATRA was discontinued. We also evaluated the duration of the disease manifestation, the time required to clear the chest lesion, and the presence of sequelae.

TABLE 1 Radiologic Features of All-Trans-Retinoic Acid Syndrome		
Findings	Patients	
	No.	%
Increased CTR	13	87
Increased VPW	13	87
Pulmonary congestion	13	87
Pleural effusion	11	73
Ground-glass opacity	9	60
Septal lines	9	60
Peribronchial cuff	9	60
Consolidation	7	47
Nodule	7	47
Air bronchogram	5	33

Note.—CTR = cardiothoracic ratio, VPW = vascular pedicle width.

Results

ATRA syndrome developed in patients at an average of 7 days (range, 1–22 days) after the start of ATRA. The major clinical manifestations of ATRA syndrome included respiratory distress (80%), fever (73%), and generalized edema (47%) (Table 2). Leukocytosis was found in seven of 15 patients. All patients showed chest radiographic abnormalities when clinical symptoms developed. Chest radiographs showed increased cardiothoracic ratio in 13 of 15 patients, increased vascular pedicle width in 13, increased pulmonary blood volume in 13, septal lines in nine, peribronchial cuffing in nine, ground-glass opacity in nine, consolidation in seven, and nodules in seven. Ground-glass opacity was bilateral and involved the entire six lung zones in all nine patients. Nodules were noted in six lung zones in six of seven patients and in both upper lung zones in one patient. Consolidations were bilateral in four patients and unilateral in three of seven patients. Locations of consolidations were vari-

able: right upper lung zone in three patients, right middle lung zone in two, right lower lung zone in five, left upper lung zone in three, left middle lung zone in two, and left lower lung zone in three. Pleural effusion was noted in 11 of 15 patients. Right pleural effusion was noted in seven of 11 patients, left effusion in two, and bilateral effusion in two. Air bronchogram was noted in five of 15 patients (Table 1 and Fig. 1).

Pulmonary hemorrhage developed in three patients on the second day, seventh day, and 16th day of ATRA treatment. Of these patients, two developed pulmonary hemorrhage during the course of the ATRA syndrome (seventh day and 16th day), and the third developed pulmonary hemorrhage simultaneously with the ATRA syndrome (second day; acute renal failure and fever). When pulmonary hemorrhage occurred, diffusely bilateral and poorly defined nodules, ground-glass opacity, and consolidation developed on chest radiography (Figs. 2A and 2B). High resolution CT was performed on all patients with pulmonary hemorrhage.

TABLE 2 Clinical Manifestations of All-Trans-Retinoic Syndrome					
Patient	Age (yr)	Sex	Clinical Symptoms ^a	Pulmonary Hemorrhage	Outcome
1	35	Female	Respiratory distress, fever	Absent	Improved
2	55	Female	Respiratory distress, fever, generalized edema	Absent	Died
3	39	Male	Fever, generalized edema	Absent	Improved
4	23	Female	Respiratory distress, fever, generalized edema	Present	Improved
5	43	Male	Respiratory distress, generalized edema	Absent	Improved
6	55	Male	Respiratory distress, fever	Absent	Improved
7	42	Female	Respiratory distress, fever, generalized edema	Absent	Died
8	36	Female	Respiratory distress, acute renal failure, ascites	Absent	Improved
9	43	Female	Respiratory distress, acute renal failure	Absent	Improved
10	50	Female	Respiratory distress, fever	Absent	Died
11	39	Female	Fever, generalized edema	Absent	Improved
12	40	Female	Respiratory distress, fever, acute renal failure, decreased liver function, ascites	Present	Died
13	23	Female	Respiratory distress, fever, hypotension	Present	Died
14	42	Male	Fever, generalized edema	Absent	Improved
15	27	Male	Respiratory distress, fever	Absent	Improved

^aParameters of clinical symptoms: respiratory distress includes symptomatic dyspnea and hypoxia (PaO₂ < 80 mm Hg). Fever is defined as axillary temperature >37.2°C. Acute renal failure is defined as elevation of creatinine >2.0 mg/dL. Hypotension is defined as decreased systolic pressure below 90 mm Hg. Generalized edema includes puffy appearance with pitting edema and weight gain (>2 kg). Decreased liver function involves an elevation of liver enzyme (>40 μ/L) of aspartate aminotransferase and alanine aminotransferase).

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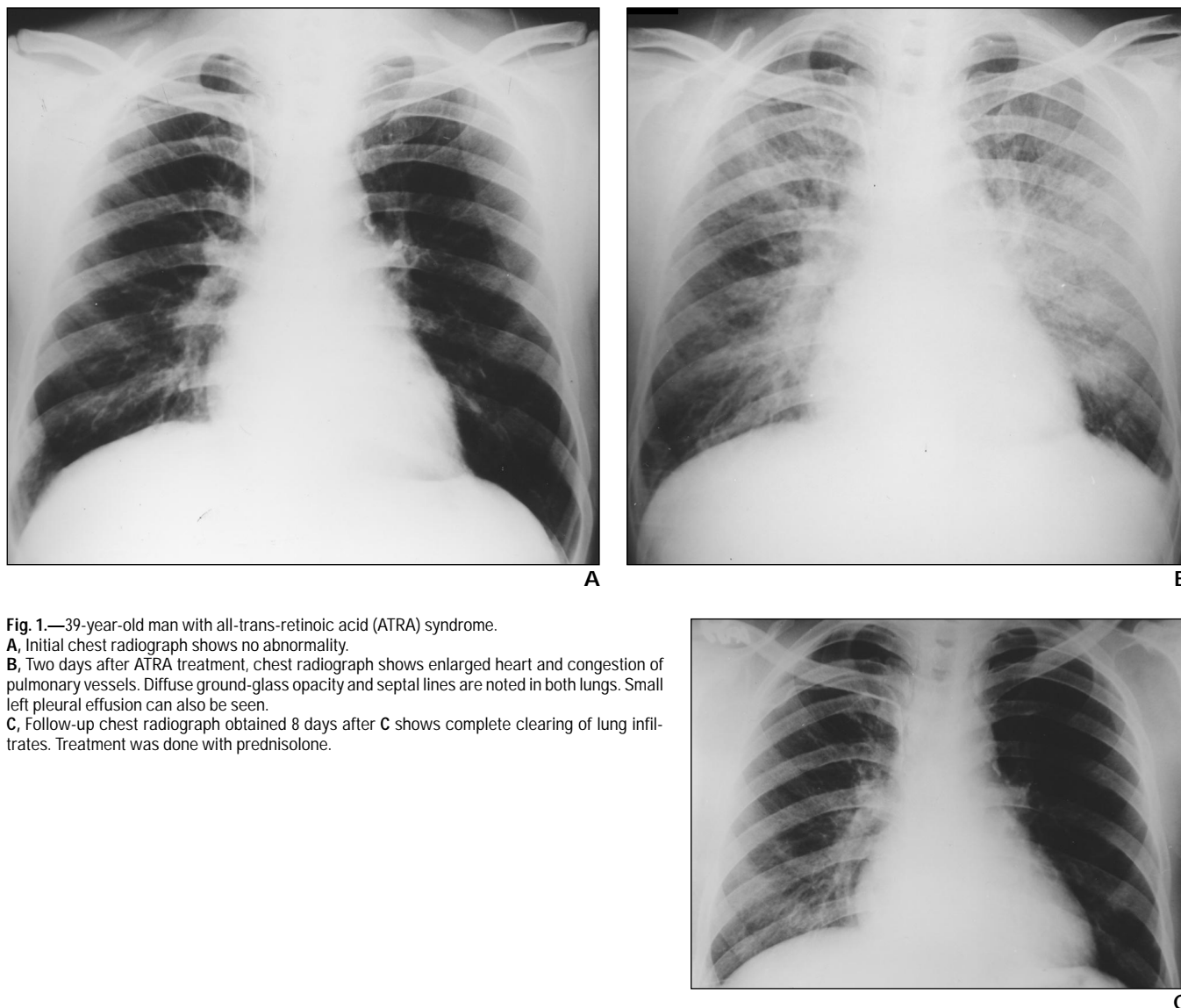


Fig. 1.—39-year-old man with all-trans-retinoic acid (ATRA) syndrome.
A, Initial chest radiograph shows no abnormality.
B, Two days after ATRA treatment, chest radiograph shows enlarged heart and congestion of pulmonary vessels. Diffuse ground-glass opacity and septal lines are noted in both lungs. Small left pleural effusion can also be seen.
C, Follow-up chest radiograph obtained 8 days after C shows complete clearing of lung infiltrates. Treatment was done with prednisolone.

Poorly defined centrilobular nodules and diffuse ground-glass opacity were noted in all patients with pulmonary hemorrhage. Interlobular septal thickening was noted in two patients. Poorly defined consolidation was noted in one patient. The heart was enlarged in all three patients. Pericardial effusion was noted in one patient, and pleural effusion was noted in two patients (Fig. 2C). In three patients with pulmonary hemorrhage, two fell into acute respiratory distress and died.

Treatment was started immediately after the diagnosis of ATRA syndrome. Prednisolone was the treatment of choice in ATRA syndrome (20–40 mg/day, divided doses). After treatment, the radiologic features and clinical symptoms of ATRA syndrome gradually im-

proved in 10 of 15 patients. Five of 15 patients showed the patchy zones of consolidation rapidly coalesce to form massive air-space consolidation in both lungs; these patients fell into acute respiratory distress (Fig. 3). Of these patients, two had ATRA syndrome with pulmonary hemorrhage. All five patients with acute respiratory distress syndrome died despite intensive care on a ventilator.

In the improved patients, the duration for complete resolution of the pulmonary infiltrates and effusion was between 3 and 42 days (mean, 11 days). No residual abnormality was found in eight of the 10 improved patients. In one patient, a chronic linear parenchymal band remained, and in another patient, pleural thickening remained.

Discussion

ATRA syndrome refers to a constellation of findings, including unexplained fever, fluid retention, multiple sites of hemorrhage, organ failure, and thrombotic events [6]. In newly diagnosed acute promyelocytic leukemia patients treated with ATRA, the incidence of ATRA syndrome was 22% in our study. The time of onset of ATRA syndrome varies [7, 8]. The reported median time to the occurrence of ATRA syndrome was 7–12 days [7], which is similar to the time experienced by our patients (mean, 7 days). This syndrome is usually, but not necessarily, associated with hyperleukocytosis and a rapid rise in the leukocyte count.

The pathophysiology of ATRA syndrome is still poorly understood. Clinically, this symptom

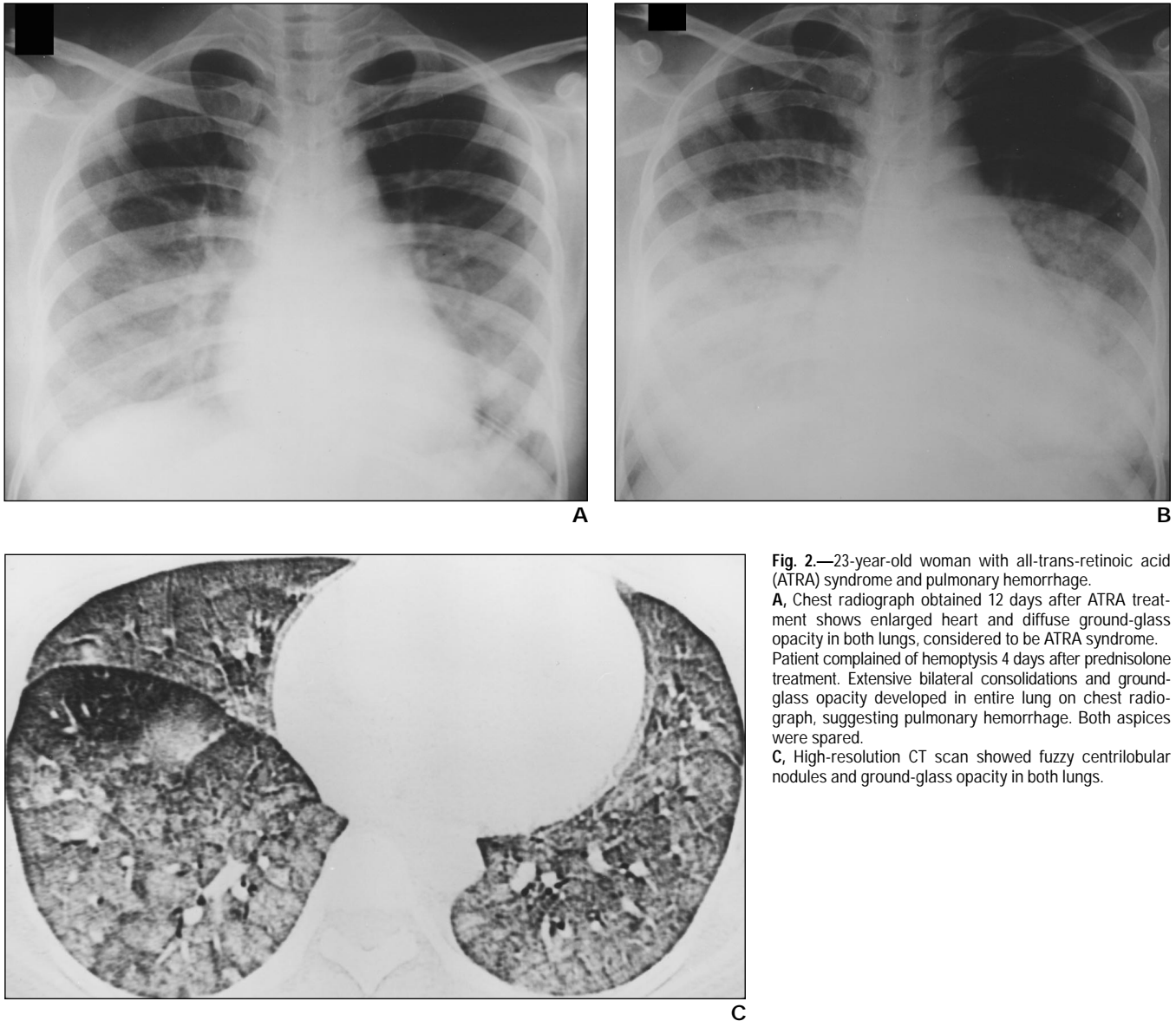


Fig. 2.—23-year-old woman with all-trans-retinoic acid (ATRA) syndrome and pulmonary hemorrhage. **A**, Chest radiograph obtained 12 days after ATRA treatment shows enlarged heart and diffuse ground-glass opacity in both lungs, considered to be ATRA syndrome. Patient complained of hemoptysis 4 days after prednisolone treatment. Extensive bilateral consolidations and ground-glass opacity developed in entire lung on chest radiograph, suggesting pulmonary hemorrhage. Both apices were spared. **C**, High-resolution CT scan showed fuzzy centrilobular nodules and ground-glass opacity in both lungs.

complex most closely resembles the capillary leak syndrome associated with the administration of various cytokines, particularly interleukin-2 [14]. The proposed mechanisms could involve changes in the cytokine secretion and adhesive qualities of acute promyelocytic leukemia cells during ATRA-induced differentiation [15–17]. Drug-induced release of vasoactive cytokines from differentiating leukemic cells (interleukin-1 β , [IL-1 β], IL-6, IL-8, and the tumor necrosis factor α) would explain certain phenomena such as fever, generalized weight gain, and episodic hypotension [15–17].

Organ infiltration by acute promyelocytic leukemia cells found in postmortem studies of the ATRA syndrome suggests that drug-induced maturation of previously undifferentiated leukemic

cells, although still dysfunctional [18, 19], could confer certain functional properties of mature neutrophils, including their migratory capabilities. Migration of these cells into tissues, such as the lung and kidney, could explain the clinically observed respiratory distress and occasional renal impairment.

Finally, leukocyte adherence to capillary endothelial cells and to the extracellular matrix is mediated by integrins (leukocyte adhesion receptors) [20, 21], and genes that encode integrins were recently found to be up-regulated by retinoic acid [22]. Conceivably, ATRA increases integrin expression on the leukemic cell surface; this would enhance the cell's adherence to the capillary endothelium and would promote focal endothelial leakage. Methylprednisolone rap-

idly inhibits acute promyelocytic leukemia cell aggregation in a dose-dependent manner, consistent with its prompt clinical effectiveness *in vivo* [23].

Radiologic features may be explained by the proposed hypotheses of pathophysiology of the ATRA syndrome. Most of the patients in our study with ATRA syndrome showed cardiomegaly, widening of the vascular pedicle width, increased pulmonary blood volume, peribronchial cuffing, ground-glass opacity, septal lines, and pleural effusion. These findings are similar to those of congestive heart failure with pulmonary edema, but they could also probably be produced by leukemic lung infiltration and endothelial leakage. Postmortem studies by Frankel et al. [6] reported ex-

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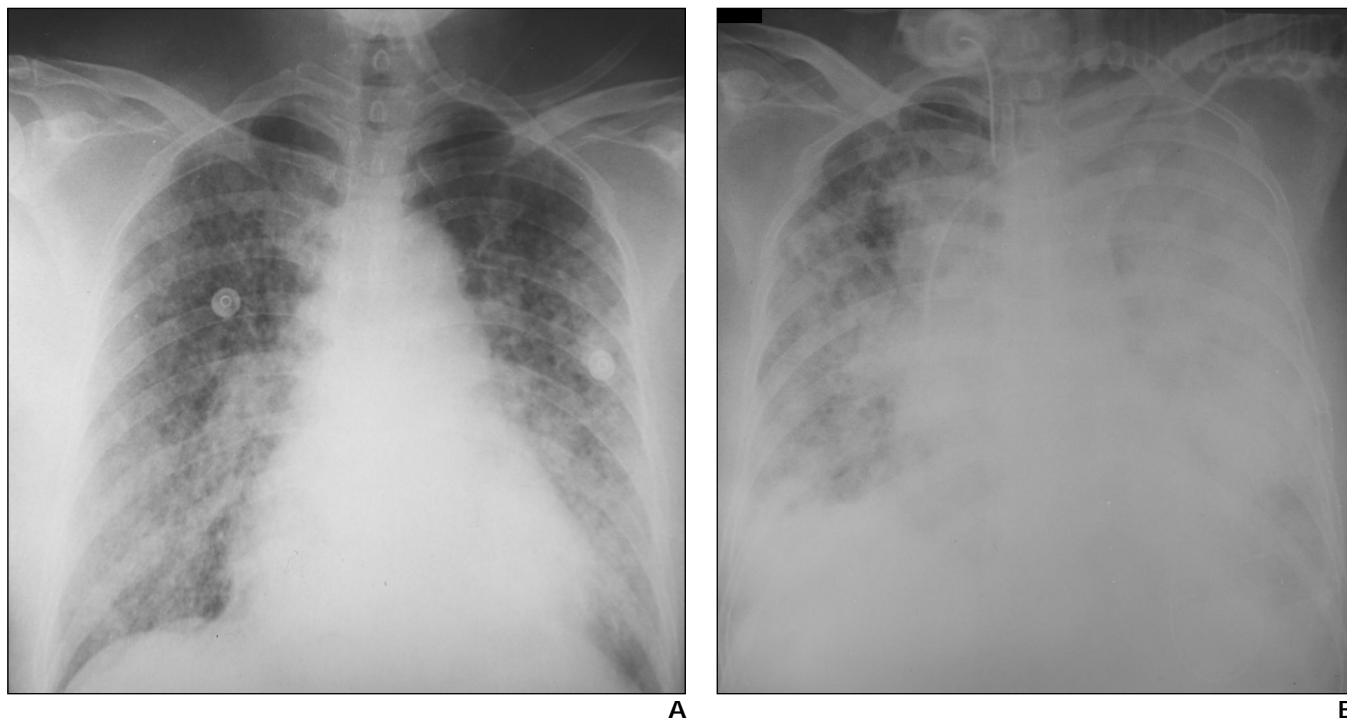


Fig. 3.—57-year-old woman with all-trans-retinoic acid (ATRA) syndrome, progressing into acute respiratory distress syndrome. **A**, Chest radiograph 12 days after ATRA treatment shows increased cardiothoracic ratio and increased vascular pedicle width. Poorly defined nodules and ground-glass opacity are noted in entire lung and are considered to be ATRA syndrome. **B**, Follow-up chest radiograph 42 days after ATRA treatment. Left lung is entirely opacified and coalescent; patchy consolidations are found in right lung, suggesting acute respiratory distress syndrome.

tensive organ infiltration by leukemic cells, involving the lung, pleura, and pericardium. Leukemic cell infiltration to the lung parenchyma through the damaged endothelium may lead to interstitial infiltrates.

At necropsy, Chanarin et al. [24] found a florid fibrinous pericarditis and edematous lung. The heart was enlarged because of a dilated left ventricle with blotchy discoloration throughout the myocardium. Leukemia cells extensively infiltrated the myocardium in the patient described in this study. Such direct infiltration of leukemic cells to the myocardium may lead to heart failure and may induce cardiogenic pulmonary edema and direct endothelial leakage.

If the disease progresses, acute respiratory distress syndrome develops. Diffuse alveolar damage and massive intraalveolar hemorrhage were found in a necropsy patient study by Frankel et al. [6]. Endothelial cell damage, including intraalveolar edema, intraalveolar hemorrhage, and fibrinous exudate, were found by Tallman et al. [7] in a case of fatal retinoic acid syndrome. In our case, the radiographs initially showed ground-glass opacity, poorly defined nodules, consolidation on chest radiography, and patchy zones of consolidation that rapidly

coalesced to form massive air-space consolidation of both lungs on chest radiography, suggesting acute respiratory distress syndrome [25].

Pulmonary hemorrhage developed in three of our study patients while they were being treated with ATRA on the second, seventh, and 16th days in each. Pulmonary hemorrhage appeared as bilateral and poorly defined nodules, ground-glass opacity, and consolidation on conventional radiography. High-resolution CT showed poorly defined centrilobular nodules and ground-glass opacity with or without interlobular septal thickening. Raanani et al. [26] reported two patients with acute promyelocytic leukemia who developed severe ongoing alveolar hemorrhage during treatment with ATRA. They hypothesized that cytokine release by acute promyelocytic leukemia cells and a rapid rise in the leukocyte count induced by ATRA could well have contributed to the development of diffuse alveolar hemorrhage. Nicolls et al. [27] reported the case of a patient with acute promyelocytic leukemia who developed diffuse alveolar hemorrhage 2 weeks after initiation of ATRA treatment. In this patient, an open lung biopsy revealed pulmonary capillaritis, which the authors appropriately suggested repre-

sented one end of the spectrum of alveolar involvement in ATRA syndrome.

Davis et al. [11] reported CT findings in three patients with ATRA syndrome. The most consistent CT findings were small, irregular peripheral nodules in the lung fields and pleural effusions. Two of these patients also showed evidence of reticular and ground-glass opacity as well as anterior mediastinal soft tissue. They also reported the case of a patient with ATRA syndrome who developed pneumothorax. However, none of our study patients experienced either a mediastinal mass or pneumothorax.

The differential diagnosis of ATRA syndrome includes volume overloading pulmonary edema [28], leukemic involvement of the lung [29, 30], and pneumonia. Because the radiologic features of ATRA syndrome are nonspecific, it would be impossible to differentiate one from the other based solely on these features. In an acute promyelocytic leukemia patient receiving ATRA therapy, the ATRA syndrome should be considered when chest radiographs show cardiomegaly, vascular distention, ground-glass opacity, peribronchial cuffing, septal lines, and pleural effusion in the presence of a clinical history including respira-

tory distress, unexplained fever, hypotension, and generalized edema.

Early recognition of ATRA syndrome is important because early intervention with high doses of corticosteroid appeared to abort the progression of this syndrome [9].

Our study has limitations. First, we had no pathologic proof. Second, the study was retrospective and included only a small number of patients.

In summary, chest radiographic features of the ATRA syndrome include increased cardiothoracic ratio, increased vascular pedicle width, ground-glass opacity, peribronchial cuffing, septal lines, and pleural effusion. In addition, chest radiography may show nodules and consolidation. Although the imaging features are not characteristic, in combination with the clinical history, they may aid in early recognition of the ATRA syndrome and thus to its prompt resolution.

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