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## Pulmonary Manifestations of Untreated Adult T-cell Leukemia on Chest Radiography

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### 成人 T 細胞白血病 (ATL) の胸部単純 X 線所見

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成人 T 細胞白血病 (ATL) 患者34例の治療前の胸部単純 X 線写真における異常所見について検討を加えた。有所見率は71% (24例) と高く、なかでも肺野病変は reticulonodular pattern (8例), acinar pattern (4例) および, reticuloliner pattern (2例) に分類することができたが、この

うち reticuloliner pattern を呈した2例は生検で ATL 細胞の浸潤と診断された。その他に胸水 (24%), 肺門もしくは縦隔リンパ節腫大 (21%), 骨病変 (3%) 等が認められた。これらの結果から ATL 患者の胸部単純 X 線写真の読影には十分な注意が必要と思われた。

### Introduction

ATL is caused by the human T-cell leukemia virus (HTLV-I) and is observed in fluminating form in the southwestern regions of Japan. ATL has received increasing attension since it was first reported in 1977<sup>1)</sup>; especially beause of its peculiar clinical manifestations and its resemblance to the effect of HTLV-III in the aquired immunodeficiency syndrome (AIDS). Patients with ATL reportedly have a higher incidence of respiratory complications as compared to those afflicted with other hematologic disorders<sup>2)</sup>; however, there have been no reports of the exact incidence of each of the various radiographic abnormalities seen at their initial presentations. We reviewed the chest radiographic findings at the times of the initial diagnoses of ATL patients to clarify the role of chest radiography in estimating the clinical status of those patients.

### Subjects and Methods

Between October 1983 and March 1987, 34 consecutive proven but yet untreated ATL patients admitted to Saga Medical School Hospital. The chest radiographs of these patients made at their first hospital admissions were reviewed. The diagnoses of ATL were based on their hematologic findings and anti-adult T-cell leukemia-associated antigen antibodies (anti-ATLA antibodies) in sera. The radiographs

Table 1 Clinical Manifestations at Initial ATL Presentation (34 patients)

Clinical Manifestations	Patients (No.)
Palpable Lymphadenopathy	20(59%)
Skin Lesions	15(15%)
Hypercalcemia (>11mg/dl)	8(24%)
Leukocytosis (>8000/mm <sup>3</sup> )	5(15%)
Fever	5(15%)
Dyspnea	5(15%)

Table 2 Radiographic Manifestations in 34 ATL Patients

Radiographic Findings	No. of patients
Pleural Effusions	8(24%)
Bilateral	3
Unilateral	5
Lymphadenopathy	7(21%)
Mediastinal	4
Hilar	6
Pulmonary changes	14(41%)
Reticulonodular Pattern	8
Reticulolinear Pattern	2
Acinar Pattern	4
Bone Lesions	1( 3%)
Normal	10(29%)

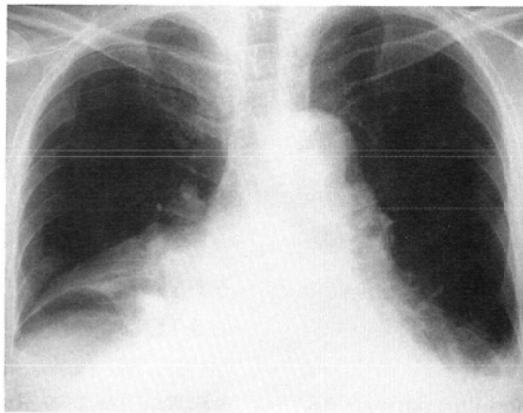


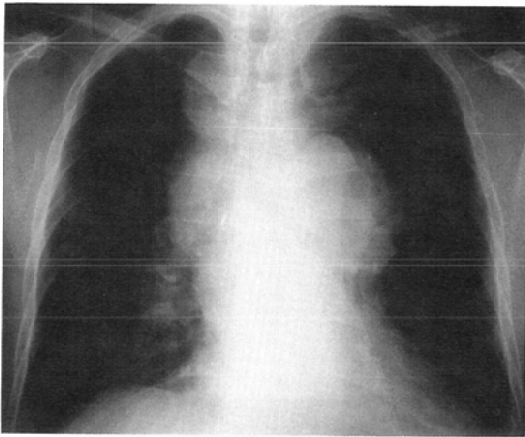
Fig. 1 Bilateral pleural effusion in a 70-year-old man with ATL.

were carefully reviewed for the presence of mediastinal or hilar lymphadenopathy, pulmonary and pleural abnormalities, and bone lesions. Chest radiography was supplemented with other modalities when they were available, including tomography of the chest and computed tomography. Pulmonary findings at autopsy were not included in this review because of the long intervals between the times of initial clinical presentation and diagnosis and autopsy. Histopathological verification of the pulmonary disease was obtained by biopsy and/or bronchoalveolar lavage at the initial clinical presentations of five patients. Regression of radiographic abnormalities following chemotherapy was a criterion for the diagnosis of malignant cell involvement. The frequency of chest radiographic abnormalities was correlated with the three major clinical manifestations listed on Table 1; palpable lymphadenopathy, skin lesions and hypercalcemia (serum calcium levels more than 11 mg per dℓ).

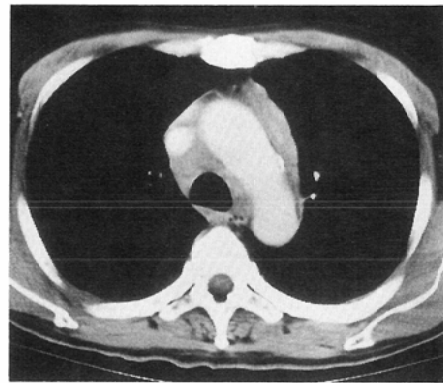
### Results

Review of the initial chest radiographs revealed that 24 of the 34 patients (71%) had one or more of the above thoracic abnormalities; five patients had multiple abnormalities (Table 2). Eleven of these patients were considered to have leukemic cell infiltrations which corresponded to the abnormalities on chest radiography in view of the histopathological proof and/or response to chemotherapy.

Pleural effusions were observed in 8 patients (24%) (Fig. 1); 6 of them were accompanied by hilar lymphadenopathy, inflammatory disease, or hypoproteinemia. Mediastinal and/or hilar lymphadenopathy was observed in 8 patients (21%) (Fig. 2), all of which was assumed due to leukemic cell infiltration, based on positive superficial lymph node biopsies. The lung abnormalities observed in 14 patients (41%) were classified as reticulonodular, reticulolinear and acinar. The reticulonodular pattern was observed in 8 patients (Fig. 3), three of whom were clinically diagnosed as diffuse panbronchiolitis; and 5 as bronchiectasis and/or chronic bronchitis. The reticulolinear pattern was observed in two patients who were diagnosed as leukemic cell infiltration on bronchoalveolar lavage (Fig. 4), and they responded to chemotherapy. The acinar pattern was observed in 4 patients, all of whom were considered from their clinical courses to have bacterial infections. Osteolytic lesions developed in the ribs and the clavicles of one

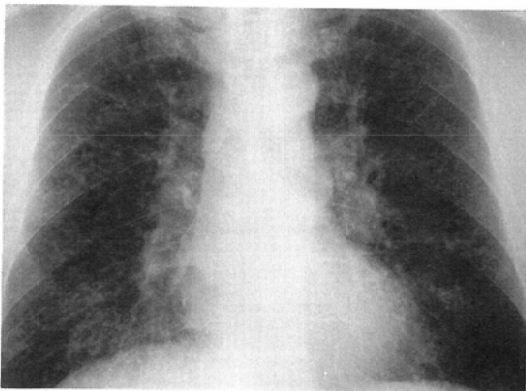


2A

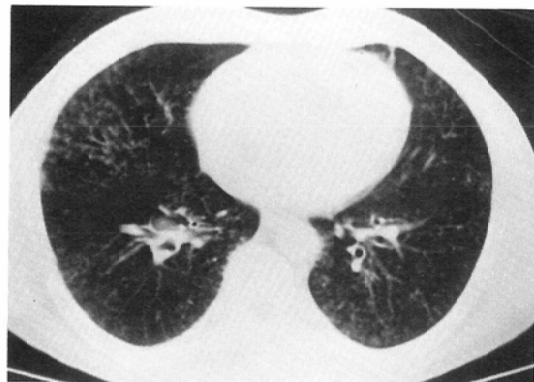


2B

Fig. 2A, B Chest radiography (A) and CT (B) of a 68-yr-old man show mediastinal and hilar lymphadenopathy.

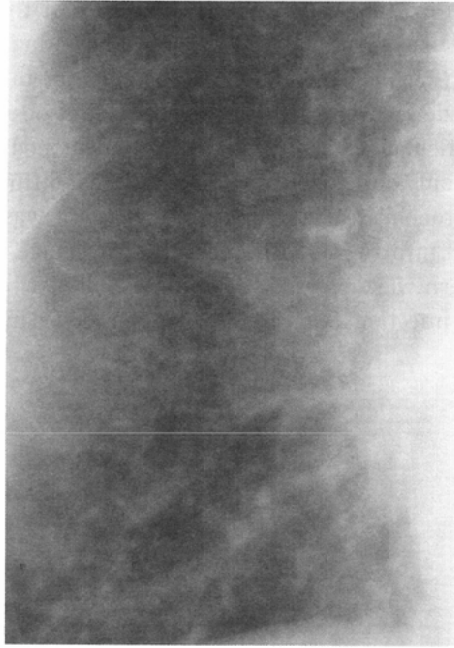


3A

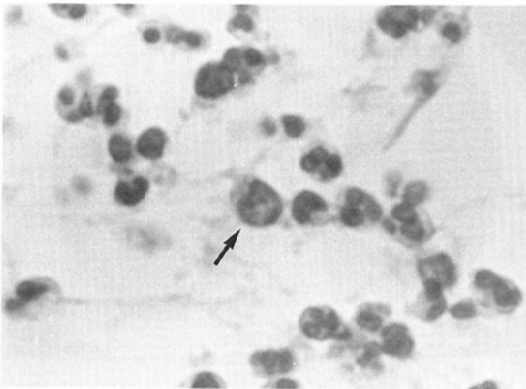


3B

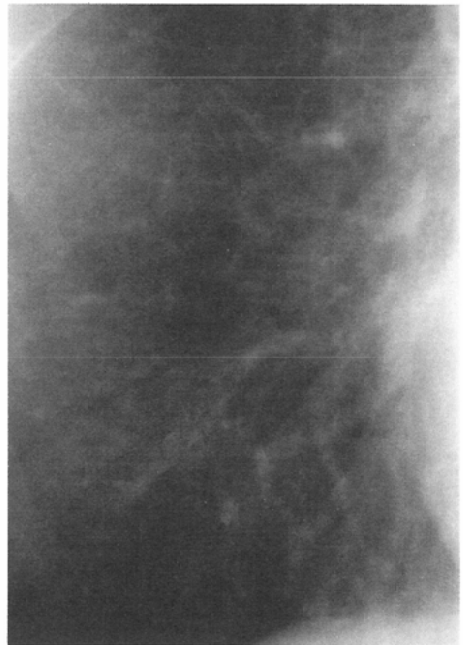
Fig. 3A, B Chest radiography (A) of a 45-yr-old man shows diffuse reticulonodular pattern with bronchiectatic change. CT scan of lung base (B) demonstrates micronodules in perivascular distribution. This was diagnosed as diffuse pan-bronchiolitis on transbronchial lung biopsy.



4A



4B



4C

Fig. 4A, B, C Magnified view of the chest radiograph (A) of a 75-yr-old man at the initial presentation demonstrates diffuse reticulolinear pattern. Leukemic cell infiltration was proved on bronchoalveolar lavage (B; black arrows). The diffuse lung disease regressed after chemotherapy (C).

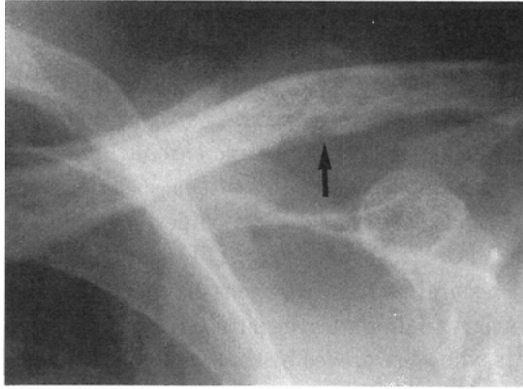


Fig. 5 Chest radiography of a 50-yr-old woman shows multiple osteolytic changes in the left clavicle and the scapular (black arrows). Leukemic cell infiltration was proved at autopsy.

Table 3 Correlations between Radiographic Findings and Clinical Manifestations

Radiographic Findings	Palpable Lymphadenopathy		Hypercalcemia		Skin Lesions	
	(+)	(-)	(+)	(-)	(+)	(-)
Pleural Effusions	7	1	3	5	3	5
Lymphadenopathy	7	0	5	2	2	5
Pulmonary changes	7	6	3	3	7	7
Bone Lesions	0	1	1	1	0	1
Normal	4	6	1	1	4	6
Totals	20	14	8	26	15	19

patient (Fig 5) and proved to be leukemic cell infiltrations at autopsy. Patients with palpable lymphadenopathy had a higher prevalence of pleural effusions and mediastinal and/or hilar lymphadenopathy than did those without palpable lymphadenopathy. The same tendency was observed in correlation with hypercalcemia. However, no significant difference was observed in the frequency of radiographic abnormalities in the patients with or without skin lesions (Table 3).

### Discussion

The prevalence of intrathoracic abnormalities in leukemia patients detected by chest radiography was reportedly 49 to 95 percents<sup>3)-5)</sup>, but in the present study, based on initial chest radiography, this was observed to be 71% no less than previously reported, based on autopsy findings. The rates of adenopathy and pleural effusions were similar to those of patients with untreated non-Hodgkin's lymphoma as reported by Filly et al.<sup>6)</sup>. Reticulonodular, reticulolinear and acinar patterns were recognized in the lungs. A characteristic of the lung changes in the present series was the predominance of the reticulonodular pattern, which accounted for 24% of all subjects, and for 57% of patients having lung abnormalities. This type of pulmonary change was attributed to chronic lung disease, such as diffuse panbronchiolitis and/or bronchiectasis. Furthermore, diffuse panbronchiolitis heralded the onset of ATL 6 months prior to the initial clinical presentation of ATL in two patients in the present series. These results support the

hypothesis of a relationship between ATL and chronic lung disease as reported by Yoshioka et al.<sup>2)</sup>. Some reports have suggested a relationship between chronic lung diseases and "smoldering ATL"<sup>7)</sup>. Smoldering ATL is characterized by the presence of a few abnormal cells (0.5~3.0%) in the peripheral blood over a relatively long period. This has been observed in patients with fungus infections of the skin, chronic lymphadenitis, chronic renal failure, strongyloidiasis and chronic lung diseases including bronchiectasis, chronic bronchitis and diffuse panbronchiolitis<sup>28)</sup>. Due to its association with the immune deficiency state, to some extent, smoldering ATL has been considered a borderline condition between the healthy carrier state of HTLV-1 and definite ATL. We surmise that ATL may be a cause of chronic lung diseases in endemic areas in Japan. These respiratory tract infections may reflect T-cell insufficiency in ATL patients.

Another interesting pulmonary finding was the diffuse fine reticulolinar pattern which developed in both lung fields of two patients who were proved by biopsies to have ATL cell infiltrations. Though their numbers are few, this pattern may represent a finding characteristic of leukemic cell infiltrations in patients with ATL. When correlated with the other clinical manifestations previously described, skin lesions did not relate significantly to the intrathoracic abnormalities. Hypercalcemia was observed in 8 patients. Pleural effusions and lymphadenopathy developed more frequently among those with hypercalcemia, and osteolytic lesions developed in one. Although the pathophysiology of hypercalcemia in patients with ATL has not yet been clarified, Kinoshita et al. reported that serum calcium levels paralleled to the courses of the disease<sup>9)</sup>. The presence of thoracic abnormalities in patients with hypercalcemia may therefore reflect progression of the disease. Skeletal involvement in ATL has also been reported, though its incidence is relatively low<sup>10)11)</sup>. One of our patients presented with lytic bone lesions in the ribs, clavicles, scapulae, and both ilia. Biopsy of the right ilium revealed ATL cell infiltration. In patients with palpable lymphadenopathy, pleural effusions and intrathoracic lymphadenopathy developed with high frequency, and we assume that palpable lymphadenopathy reflects extension of the disease as well.

On follow up study, 12 of 21 deaths (57%) of our patients with ATL were due to pulmonary complications, including pneumonia or pulmonary hemorrhages. However, only four of 8 patients (50%) with initial pulmonary lesions died of pulmonary complications; remainder died of complications such as gastrointestinal hemorrhage, renal failure and cerebrovascular disease. We were unable to establish a close correlation between initial pulmonary changes and causes of death in patients with ATL.

This study revealed a relatively high prevalence of a variety of intrathoracic manifestations in ATL patients even at the times of their initial clinical presentations. This underscores the importance of initial chest radiography for staging the disease. Since the radiographic abnormalities of the chest observed in ATL patients are not specific as to disease, transbronchial biopsy or bronchoalveolar lavage should be performed to clarify the causes of the radiographic abnormalities. HTLV-1 infections must be borne in mind, in the evaluation of intractable chronic pulmonary diseases, especially in regions where ATL is endemic.

### Acknowledgement

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