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CHEST IMAGING

ORIGINAL ARTICLE

Thoracic manifestations of adult T-cell leukemia/lymphoma on chest CT: difference between clinical subtypes

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PURPOSE
We aimed to evaluate thoracic computed tomography (CT) findings in adult T-cell leukemia/lymphoma (ATL) and their differences among clinical subtypes.

METHODS
Thoracic CT scans of 49 ATL patients were retrospectively reviewed. On CT scans, the presence of lung parenchymal abnormalities (10 patterns), enlarged lymph nodes, pleural and pericardial effusions, and subcutaneous nodules was evaluated by two radiologists in cooperation. According to the Shimoyama criteria, the patients were divided into aggressive ATL group (n=28, acute and lymphoma types) and indolent ATL group (n=21, chronic and smoldering types). Differences in the prevalence of the CT findings between the two groups were examined. In the indolent ATL group, CT scans of 10 patients who eventually underwent transformation to aggressive ATL were also evaluated.

RESULTS
In aggressive ATL, enlarged lymph nodes (68%) was the most frequently observed finding. Several patterns of lung abnormalities were observed, such as ground-glass attenuation (36%), bronchial wall thickening (32%), nodules (29%), and centrilobular opacities (29%). In indolent ATL, enlarged lymph nodules (24%) and bronchiectasis (24%) were relatively frequently detected. Overall, the incidence of abnormal findings was higher in aggressive than in indolent ATL, except for bronchiectasis. Patients with transformation to aggressive ATL frequently demonstrated enlarged lymph nodes (80%).

CONCLUSION
On thoracic CT, enlarged lymph nodes and various lung and airway abnormalities, such as ground-glass attenuation and bronchial wall thickening, were observed in ATL patients, particularly those with aggressive ATL. Bronchiectasis was similarly found in patients with indolent ATL and aggressive ATL.

Adult T-cell leukemia/lymphoma (ATL) is a malignant neoplasm of T-lymphocytes caused by human T-cell lymphotropic virus type 1 (HTLV-1); it is characterized by mono- or oligoclonal integration of proviral deoxyribonucleic acid (DNA) and the presence of abnormal lymphocytes with convoluted nuclei (1–5). The prevalence of HTLV-1 infection varies among countries and/or continents. HTLV-1 has been found to be pandemic in Japan, the Caribbean, South America, and Africa, all of which have high prevalence rates of ATL (1). ATL is usually classified into four clinical subtypes according to the Shimoyama criteria, as acute, lymphoma, chronic, and smoldering types (2, 3). In general, acute and lymphoma types of ATL have a poor prognosis despite recent advances in chemotherapy and stem cell transplantation; therefore, they have been considered to be aggressive types of ATL (3–5). On the other hand, chronic and smoldering types have a relatively better prognosis and can be considered to be a precedent stage of the aggressive types (6). The condition of patients with indolent types of ATL is usually stable; thus, patients with chronic and smoldering ATL are managed with careful monitoring until the disease progresses to the aggressive type, similar to the management of chronic lymphoid leukemia or smoldering myeloma. In a previous study, the 4-year survival rates for acute, lymphoma, chronic, and

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smoldering types of ATL were 5.0%, 5.7%, 26.9%, and 62.8%, respectively (2). Based on these data, the acute and lymphoma types of ATL are generally categorized as aggressive ATL, and the chronic and smoldering types are categorized as indolent ATL.

Patients with ATL often manifest pulmonary complications. Yoshioka et al. (7) reported that ATL patients frequently complained of respiratory symptoms, typically caused by infiltration of leukemic cells in the lungs, even during the period of smoldering or chronic ATL. Although the radiologic findings of these pulmonary manifestations of ATL have rarely been investigated, a few case reports and studies have demonstrated several patterns of abnormal findings on chest CT (8–14). Among them, a study by Okada et al. (8) analyzed the CT findings in multiple ATL patients and concluded that pulmonary ATL involvement frequently caused ground-glass attenuation, centrilobular nodules, thickening of bronchovascular bundles, and consolidation.

Although a recent study has reported various abnormal thoracic findings on chest CT in patients with acute transformation of ATL (13), to our knowledge, no previous study has evaluated thoracic CT findings in participants with ATL and compared the findings between patients with indolent and those with aggressive types of the disease. Considering that these two disease types have very different clinical characteristics, we hypothesized that there are differences in the frequency of abnormal thoracic CT findings in these two groups.

Thus, the aims of this study were (*i*) to evaluate thoracic CT findings in multiple ATL patients, and (*ii*) to investigate differences between the frequency of these findings in patients with aggressive and indolent ATL.

Methods

The Institutional Review Board approved this retrospective study at each institution and waived written informed consent. All CT scans and medical records were anonymized for analysis.

Main points

- In addition to lymphadenopathy, various patterns of pulmonary abnormalities are frequently found on chest CT of ATL patients.
- Some of these ATL findings mimic infectious disease on chest CT, and should therefore be carefully assessed by radiologists.
- Aggressive ATL manifests as abnormal CT findings more frequently than indolent ATL.

Patients

Medical records and chest CT scans of all ATL patients at two institutions (University of the Ryukyus Hospital and Nakagami Hospital) from January 2004 to February 2010 were initially reviewed by two radiologists (S.Y. and T.Y.) with 6 and 12 years of experience in thoracic radiology. HTLV-1 infection was confirmed by positive reactions of serum antibody tests, and ATL was diagnosed by hematologists according to the diagnostic criteria for ATL (2, 3). In brief, the diagnosis of ATL was based on histopathologic or cytologic findings (for example, representative flower cells in peripheral blood samples, and mono-/oligoclonal integration of proviral DNA in the biopsied organs or in lymphocytes from bronchoalveolar lavage). After the exclusion of some patients (n=10) who were diagnosed with lung cancer or concurrent infectious disease, 49 patients were eventually included in this study. The patients were confirmed to be without coexisting infectious disease, collagen vascular disease, heart failure, sarcoidosis, or other lymphoproliferative disorders. These 49 patients (26 males and 23 females; mean age, 66 years; age range, 34–85 years) underwent chest CT at the time of diagnosis without any therapeutic interventions, such as chemotherapy or stem cell transplantation.

The subtypes of ATL were classified according to the Shimoyama criteria (2, 3). Further, based on the classifications proposed by the International Consensus Meeting for ATL (3), we classified acute and lymphoma types as aggressive ATL (n=28), and chronic and smoldering types as indolent ATL (n=21). Patients with indolent ATL had frequent follow-up CT scans, and 10 patients underwent transformation to the aggressive type during the follow-up period.

CT protocols

At University of the Ryukyus Hospital (n=28), patients were scanned with either of four scanners: LightSpeed QXi, LightSpeed VCT (GE Healthcare) Aquilion 64, or Aquilion ONE (Canon Medical Systems). Tube voltage was fixed as 120 kVp, and tube currents varied based on the patient's body habitus or automatic exposure control (AEC). Rotation time was 0.5 seconds. Section thickness for regular images was 5 mm (n=22) or 7.5 mm (n=6), and additional thin-section images (1–2.5 mm) were created for 22 subjects. The matrix size was 512×512 pixels. Reconstruction kernels were selected for lung and mediastinal views, such as FC51 or lung kernels for the lung, and FC86 or standard kernels for the mediastinum.

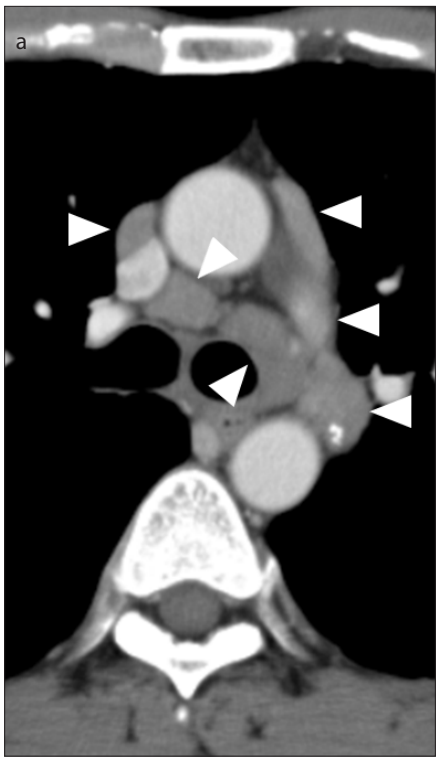
At Nakagami Hospital (n=21), patients were scanned with a 64-detector CT scanner (Aquilion 64). The tube voltage was 120 kVp, and the tube current was regulated by AEC. Rotation time was 0.5 seconds, and the matrix size was 512×512 pixels. Images were contiguously reconstructed with a 5 mm or 7 mm slice thickness, using FC53 (for the lung) and FC13 (for the mediastinum) kernels.

All indolent patients who progressed to aggressive transformation (n=10) were diagnosed and underwent chest CT. The scanning and reconstruction parameters of the follow-up scans, such as tube currents, slice thicknesses, and reconstruction kernels, were similar to those used for the initial scans obtained at the hospital.

Image analysis

Two radiologists (S.Y. and T.Y.) interpreted chest CT scans in cooperation. They were aware that all patients were diagnosed with ATL but did not know the clinical ATL type of each patient. All CT scans were displayed as digital images on computer monitors by a picture archiving and communication system (PACS). For analysis of the lung parenchyma, a lung window was applied (window level of -600 Hounsfield Unit [HU]; window width of 1500 HU). For interpretation of the mediastinum, images were set for a mediastinal window (window level of 40 HU; window width of 350 HU).

According to the previous CT studies for ATL patients and HTLV-1 carriers (8, 15, 16), CT scans were assessed with regard to each of the following patterns: centrilobular opacities, nodule (not centrilobular, <3 cm in diameter), ground-glass attenuation, consolidation, bronchiectasis, thickening of bronchovascular bundles, bronchial wall thickening, interlobular septal thickening, honeycombing, crazy-paving appearance, enlarged lymph nodes (≥1 cm in diameter of the short axis, subclassified into mediastinal, hilar, supraclavicular, and axillary nodes), pleural effusion, pericardial effusion, and subcutaneous nodules. When interpreting CT images, the observers followed an established guideline for the terms of thoracic imaging (17).



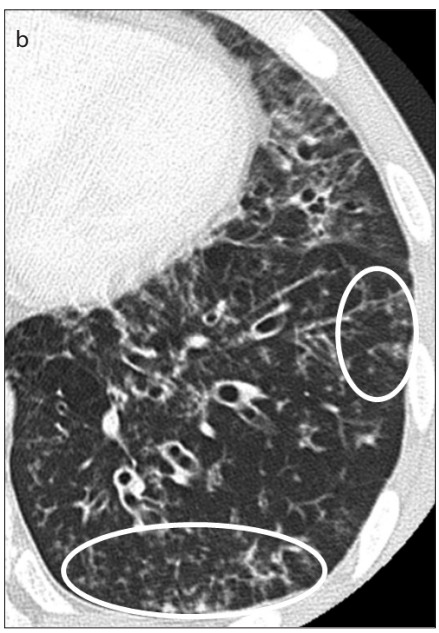


Figure 1. a, b. A 50-year-old man with acute ATL. A contrast-enhanced chest CT image reveals multiple mediastinal lymphadenopathies (**a,** *arrowheads)*. Bronchiectasis, bronchial wall thickening, and multiple centrilobular opacities *(ovoid circles)* are observed in the left lung (**b**).

Table 1. Thoracic CT findings in patients with aggressive and indolent ATL

CT findings	Total (n=49) n (%)	Aggressive ATL (n=28) n (%)	Indolent ATL (n=21) n (%)	*P* *
Centrilobular opacities	10 (20)	8 (29)	2 (10)	0.102
Pulmonary nodules	10 (20)	8 (29)	2 (10)	0.102
Ground-glass attenuation	12 (24)	10 (36)	2 (10)	0.034
Consolidation	5 (10)	4 (14)	1 (5)	0.275
Bronchiectasis	11 (22)	6 (21)	5 (24)	0.843
Thickening of bronchovascular bundles	4 (8)	4 (14)	0	0.007
Bronchial wall thickening	10 (20)	9 (32)	1 (5)	0.002
Interlobular septal thickening	7 (14)	7 (25)	0	0.013
Honeycombing	0	0	0	-
Crazy-paving appearance	0	0	0	-
Enlarged lymph nodes (overall)	24 (49)	19 (68)	5 (24)	0.002
Supraclavicular	13 (27)	13 (46)	0	< 0.001
Axillary	18 (37)	16 (57)	2 (10)	< 0.001
Mediastinal	17 (35)	15 (54)	2 (10)	0.001
Hilar	10(20)	9 (32)	1 (5)	0.018
Pleural effusion	8 (16)	8 (29)	0	0.007
Pericardial effusion	5 (10)	4 (14)	1 (5)	0.275
Subcutaneous nodules	0	0	0	-

CT, computed tomography; ATL, adult T-cell leukemia/lymphoma.
*Comparisons between aggressive and indolent ATL groups were estimated.

Statistical analysis

Comparisons between the frequency of the CT findings in patients with aggressive versus indolent types of ATL were made by the chi-square test. Statistical analyses were performed by using JMP 8.0 software (SAS Institute). A *P* value of less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the results of CT findings observed in patients with aggressive and indolent ATL. In the aggressive ATL group (n=28, 13 females and 15 males, mean age 62 years), 19 patients (68%) showed enlarged lymph nodes (Fig. 1), which was the most frequent abnormal finding in the aggressive group. Among the four locations for lymphadenopathy, axillary lymphadenopathy was the most frequently observed (n=16, 57%). Ground-glass attenuation (n=10, 36%) was the most frequent finding in lung parenchyma, which was followed by bronchial wall thickening (n=9, 32%), centrilobular opacities (n=8, 29%), lung nodules (n=8, 29%), and interlobular septal thickening (n=7, 25%) (Figs. 1–4). Among the patients with lung nodules (n=8), large nodules >10 mm were observed in 2 patients. Bronchiectasis was also observed in 6 patients (21%). Consolidation and thickening of bronchovascular bundles were seen in 4 patients each (14%). Honeycombing and the crazy-paving appearance were not detected. Pleural effusion (n=8, 29%) and pericardial effusion (n=4, 14%) were also seen in the aggressive ATL group.

In the indolent ATL group (n=21, 9 females and 12 males, mean age 66 years), bronchiectasis and enlarged lymph nodes were the most frequent CT findings (n=5, 24%). Centrilobular opacities, lung nodules, and ground-glass attenuation were observed in 2 patients each (10%). Identified lung nodules were <1 cm in diameter. Consolidation and bronchial wall thickening were also seen in a single patient each. Thickening of bronchovascular bundles, interlobular septal thickening, honeycombing, and the crazy-paving appearance were not seen in indolent patients.

Table 2. Thoracic CT findings in aggressive transformation of indolent ATL (n=10)

CT findings	n (%)
Centrilobular nodules	1 (10)
Nodules	2 (20)
Ground-glass attenuation	1 (10)
Consolidation	1 (10)
Bronchiectasis	0
Thickening of bronchovascular bundles	1 (10)
Bronchial wall thickening	0
Interlobular septal thickening	0
Honeycombing	0
Crazy-paving appearance	0
Enlarged lymph nodes (overall)	8 (80)
Supraclavicular	4 (40)
Axillary	4 (40)
Mediastinum	4 (40)
Hilar	1 (10)
Pleural effusion	2 (20)
Pericardial effusion	1 (10)
Subcutaneous nodules	1 (10)

CT, computed tomography; ATL, adult T-cell leukemia/lymphoma.

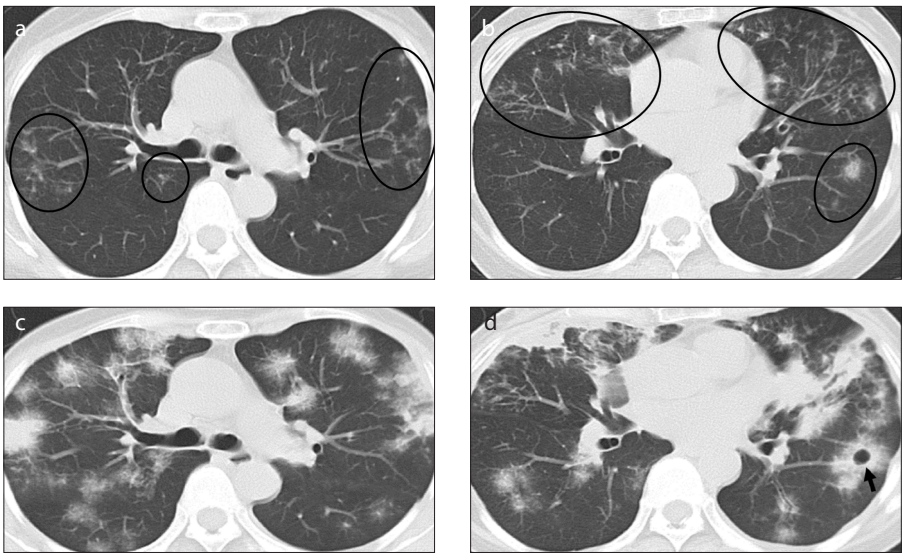


Figure 2. a–d. A 54-year-old woman with acute ATL. Initial chest CT images **(a, b)** show centrilobular opacities and pulmonary nodules in both lungs. Slight bronchiectasis and bronchial wall thickening are also seen **(a, b,** *ovoid circles*). Since mycobacterial infection was initially suspected, no workup for ATL was performed. Follow-up CT images **(c, d)** (without any treatment, three months after the initial scan) demonstrate multiple consolidations accompanied by ground-glass attenuation, which also forms a cavity in the left lower lobe **(d,** *arrow)*. ATL was eventually confirmed by transbronchial lung biopsy.

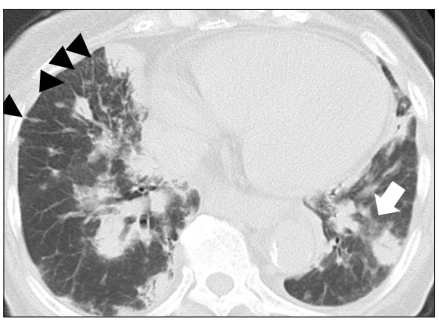


Figure 3. A 79-year-old woman with acute ATL. Chest CT demonstrates multiple consolidations and nodules. Interlobular septal thickening *(arrowheads)* and partial ground-glass attenuation *(arrow)* are also shown in the lung. The patient was diagnosed with ATL by sputum cytology.

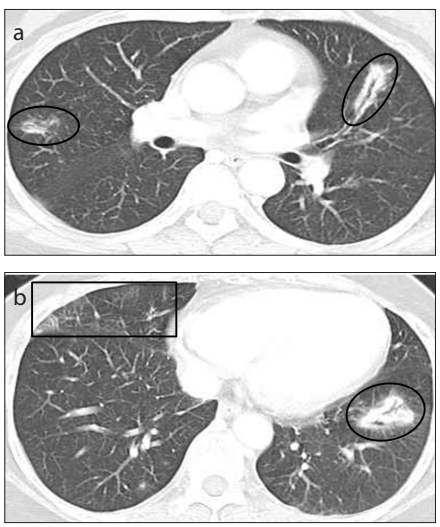


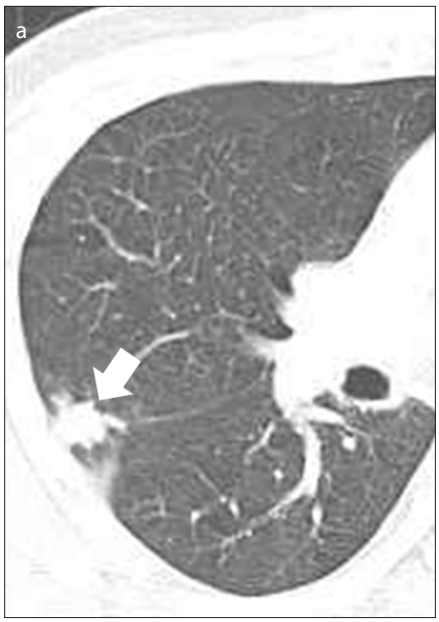
Figure 4. a, b. A 49-year-old woman with acute ATL. Chest CT image **(a)** shows thickening of the bronchovascular bundles in both lungs *(ovoid circles)*, which also forms a localized consolidation in the left lower lobe. Mild ground-glass attenuation and interlobular septal thickening are observed in the right middle lobe **(b,** *rectangle)*. These abnormal shadows disappeared after chemotherapy.

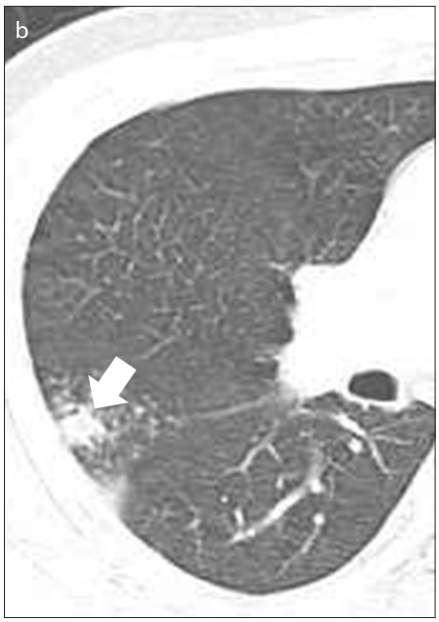
While a pericardial effusion was observed in a single patient (5%), no patient demonstrated pleural effusion in this group.

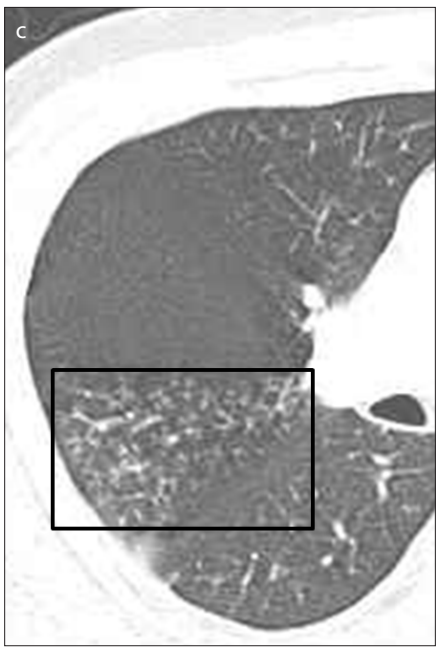
Significant differences between the frequencies of the following findings were observed in the aggressive and indolent ATL groups, and all of the findings were observed more commonly in the aggressive ATL than in the indolent group: enlarged lymph nodes, ground-glass attenuation, thickening of bronchovascular bundles, bronchial wall thickening, interlobular septal thickening, and pleural effusion (Table 1). In particular, while the indolent ATL group demonstrated a single enlarged lymph node or multiple small lymph nodes in one patient each, the aggressive ATL group showed enlarged lymph nodes in many patients; and 9 of 28 aggressive ATL patients demonstrated ≥5 enlarged lymph nodes.

Although the following differences were not significant, 3 patterns of abnormal lung findings (centrilobular opacities, nodule, and consolidation) and pericardial effusion were also more frequently observed in the aggressive ATL group than in the indolent group. By contrast, bronchiectasis was slightly more frequently observed in the indolent group than in the aggressive group, although the difference in frequency was not statistically significant.

Ten patients in the indolent group (4 females and 6 males, mean age 65 years), who underwent transformation to aggressive ATL, manifested various abnormal findings on chest CT (Table 2). Among these patients, enlarged lymph nodes was the most frequently observed finding (n=8, 80%), followed by lung nodules (n=2, 20%) and pleural effusion (n=2, 20%). Centrilobular nodules (Fig. 5), ground-glass attenuation, consolidation, thickening of bronchovascular bundles, subcutaneous nodules (Fig. 6), and pericardial effusion (Fig. 7) were also seen in a single patient each.







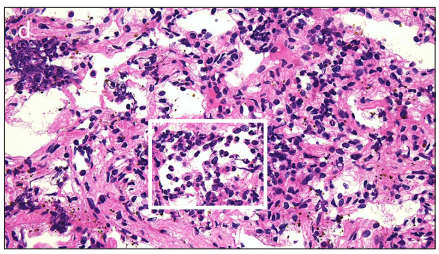


Figure 5. a–d. A 42-year-old man with aggressive transformation of chronic ATL. CT images **(a–c)** show a peripheral lung nodule *(arrows)* and multiple centrilobular nodules *(rectangle)*. ATL infiltration of the lung was diagnosed by transbronchial lung biopsy, which demonstrated that ATL cells infiltrated both the alveolar space *(rectangle)* and interstitium (**d,** H-E staining, ×400).

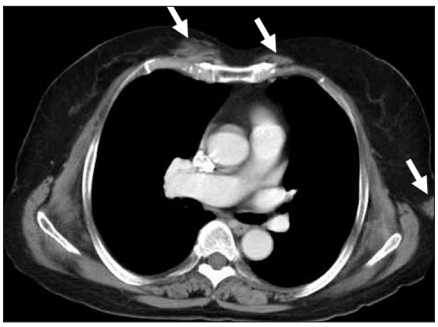


Figure 6. A 67-year-old woman with aggressive transformation of chronic ATL. Multiple subcutaneous masses without clear margins are demonstrated *(arrows)*. Infiltration of ATL was proven by percutaneous biopsy.

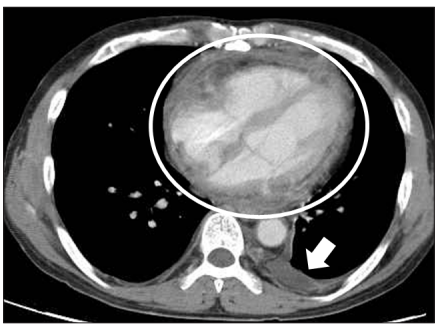


Figure 7. A 49-year-old man with aggressive transformation of smoldering ATL.
CT image shows left pleural effusion *(arrow)*, pericardial effusion and pericardial thickening *(ovoid circle)*. ATL was confirmed by cytological examination of the left pleural effusion. After chemotherapy, these findings improved.

Discussion

In this study in ATL patients, lymphadenopathy was the most frequent abnormal finding on chest CT, and various patterns of pulmonary lesions were also observed. Further, the abnormalities, except for bronchiectasis, were more commonly observed in ATL patients with aggressive disease than in patients with indolent disease. These observations suggest that ATL patients manifest various findings on chest CT, both internal and external to the lungs, in particular when the patient progresses to aggressive ATL.

Although to the best of our knowledge, this study is the first to demonstrate differences between the frequencies of abnormalities on chest CT in patients with aggressive versus indolent ATL, a previous study has already reported several CT findings in many ATL patients (8). In that study, it was reported that ATL patients frequently (69%) manifested various abnormalities on chest CT, and that the most common CT finding was ground-glass attenuation in the lung parenchyma, followed by lymphadenopathy. In contrast, in our current study, the most common CT finding was lymphadenopathy, and various pulmonary findings were less common than lymphadenopathy. The difference between the previous and current studies may be partially caused by the difference between ATL clinical subtypes. In our study, it was clearly demonstrated that patients in the aggressive ATL group more frequently manifested enlarged lymph nodes than those in the indolent group, regardless of its diagnosis at the initial assessment or following transformation from the indolent type. In other words, the aspect of lymphoproliferative disease in ATL was clearly demonstrated in our patient cohort, in comparison with the patients in the previous study. Although the clinical subtypes were not described in the previous study (8), we currently believe that the major thoracic manifestation of ATL would be lymphadenopathy, particularly in aggressive ATL. This would also be concordant with the previous study that analyzed patients with acute transformation to aggressive ATL (13).

In the current study, it was also confirmed that various patterns of abnormal pulmonary findings appeared on chest CT, which generally were more frequent in the aggressive ATL group. This observation is basically concordant with previous studies that evaluated thoracic CT findings in patients with ATL only (8) or with various leukemic disorders, including ATL (11, 12). Similar to these previous studies, no prominent pulmonary findings were clearly determined in our study, and almost all abnormal pulmonary findings were neither specific for ATL nor lymphoma. Further, some patients with aggressive ATL in our study manifested multiple centrilobular nodules on their initial CT, which mimicked bronchiolitis or mycobacterial infections and were later proved to be ATL infiltration. Similar multiple small nodules found on CT have been reported in a patient with another T-cell lymphoma, which also mimicked bronchiolar disorders (18). These observations suggest that ATL could manifest as various patterns of pulmonary manifestations on chest CT; therefore, radiologists and physicians must be aware that pulmonary ATL infiltration should always be taken into consideration when abnormal pulmonary findings appear on chest CT in ATL patients.

These various pulmonary findings on chest CT in patients with ATL reflect various patterns of ATL infiltration in the lung. Okada et al. (8) reported that infiltration of ATL cells into the pulmonary interstitium results in interlobular septal thickening, and ATL cells that infiltrate the walls of respiratory bronchioles extend into the adjacent peribronchiolar interstitium, which leads to multiple centrilobular nodules on CT. Hanaka et al. (14) also reported that diffuse infiltration of ALT cells into the pulmonary interstitium results in ground-glass attenuation on chest CT. These various patterns of ATL infiltration in the lung lead to various patterns of abnormal findings on chest CT. Although very limited numbers of pathologic specimens were obtained from our study cohort by transbronchial lung biopsy or skin biopsy, the histopathologic findings also included different infiltration patterns of ATL cells, as follows: pulmonary nodule/mass formation by aggregations of ATL cells in the alveolar spaces, ATL cell infiltration along peripheral bronchioles, and subcutaneous infiltrations of ATL cells in the chest wall. These pathologic observations were basically concordant with a previous study report that discussed the correlation between CT and histopathologic observations (8).

Since various pulmonary findings on chest CT are observed in patients with ATL, it is difficult to determine some specific findings that strongly suggest the presence of ATL on routine chest CT. However, there are some interesting CT findings that are rarely observed in patients with pulmonary infections: for example, we found patients with multiple masses/consolidations forming a cavity with smooth margins (Fig. 2) and uneven thickening of bronchovascular bundles (Fig. 4). Also, many cases in this study demonstrated interlobular septal thickening. Although these findings are not always specific for ATL or lymphoma, by combining with extrapulmonary findings, such as lymphadenopathy and subcutaneous masses, some cases were diagnosed with ATL at the relatively early stage of the disease in our institutions, based on the opinion of the radiologists. It is currently unclear whether early detection of the aggressive ATL leads to better prognosis; however, a careful interpretation by radiologists who are familiar with the imaging characteristics of the disease may result in early therapeutic interventions to the patients.

It is of interest that bronchiectasis was almost equally detected in both indolent and aggressive ATL groups. Although it is very difficult to exclude preceding or coexisting bronchial infection from these ATL patients, it could be considered that bronchiectasis in ATL patients is caused by HTLV-1 itself, similar to bronchiectasis in HTLV-1 carriers who have not yet developed ATL (13, 15). In the previous studies that targeted HTLV-1 carriers, bronchiectasis was frequently observed on their chest CT scans and was considered to be one of the major manifestations of HTLV-1-associated bronchopulmonary disorders (15, 16). Although the true prevalence of bronchiectasis in ATL should be analyzed in a much larger number of patients, we currently suspect that bronchiectasis in ATL might suggest a long history of HTLV-1 infection and would indicate disease relevance between HTLV-1 infection (carrier) and ATL.

Our study had several limitations. First, this study was retrospective, and we had a relatively small number of patients. Ideally, a prospective study enrolling ATL patients who are confirmed by a systemic screening method not to have coexisting diseases such as pulmonary infection, collagen vascular disease, or heart failure, should be performed to validate the observations in our study. Second, CT scanners and settings were different between patients, which might have resulted in inconsistencies between subtle pulmonary findings. Moreover, because relatively old CT images were analyzed, the scans of some evaluated patients showed images of 5 mm thickness only. Small abnormalities on CT affected by partial volume artifacts, such as tiny parenchymal abnormalities and relatively small lymph nodes, might not have been correctly identified on 5 mm thick images. Also, a more detailed analysis of the location or distribution of thoracic lesions was not performed in the current study. Third, CT findings were not always compared with the pathologic findings. Since obtaining histologic samples by lung biopsy or bronchoalveolar lavage was frequently difficult because of hypoxia or thrombocytopenia, we cannot deny that an unexpected coexisting disease might have exaggerated the pulmonary CT findings. Thus, many observations in this study were based on the assumption that abnormal findings on chest CT were caused by ATL only; however, we could not verify this because of the very limited number of histopathologic examinations.

In conclusion, lymphadenopathy and various patterns of pulmonary findings, including ground-glass attenuation, centrilobular opacities, pulmonary nodules, and bronchial abnormalities, were observed on the chest CT images of ATL patients. Patients with aggressive ATL showed these abnormal findings, particularly lymphadenopathy, interlobular septal thickening, and pleural effusion, more frequently than those with indolent ATL.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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