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T-cell and NK-cell lymphomas in the lung

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ABSTRACT

While the lung is frequently involved by systemic lymphoma, primary pulmonary lymphoma accounts for less than 1% of all extranodal ymphomas. In particular, T-cell lymphoma is very rare in the lung, as a primary or secondary lesion. Patients with pulmonary T-cell lymphoma usually present with cough, dyspnea, pain, fever, recurrent infections, and hemoptysis. Typical radiologic features include pulmonary nodules, consolidation, solid pulmonary opacities, cystic changes, hilar adenopathy, and pleural effusions. Patients with these clinical and radiologic findings are frequently presumed to have pneumonia and initially treated with empirical antibiotics. Therefore, CT-guided needle biopsy, bronchoscopic examination, or even wedge biopsy should be considered when clinical symptoms show deterioration despite adequate antibiotic therapy. Precise pathologic diagnosis and molecular characterization are recommended in all cases, following the World Health Organization (WHO) classification. Principles of treatment typically vary with the different histologic types of T-cell lymphoma.

Introduction

While the lung is frequently involved by systemic lymphoma, primary pulmonary lymphoma accounts for less than 1% of all extranodal lymphomas. In particular, T-cell lymphoma is very rare in the lung, as a primary or secondary lesion. Patients with pulmonary T-cell lymphoma usually present with cough, dyspnea, pain, fever, recurrent infections, and hemoptysis. Typical radiologic features include pulmonary nodules, consolidation, solid pulmonary opacities, cystic changes, hilar adenopathy, and pleural effusions. Patients with these clinical and radiologic findings are frequently presumed to have pneumonia and initially treated with empirical antibiotics. Therefore, CT-guided needle biopsy, bronchoscopic examination, or even wedge biopsy should be considered when clinical symptoms show deterioration despite adequate antibiotic therapy. In this review, we discuss the major clinicopathologic features of pulmonary T-cell and NK-cell lymphomas, which have been summarized in Table 1. Precise pathologic diagnosis and molecular characterization are recommended in all cases, following the World Health Organization (WHO) classification. Principles of treatment typically vary with the different histologic types of T-cell lymphoma.

Peripheral T-cell lymphoma, not-otherwise-specified (PTCL-NOS)

PTCL-NOS is a subgroup of non-Hodgkin lymphoma (NHL) from post-thymic cells (mature peripheral T-cells), which accounts for ~35% of all T-cell NHLs in the North America[1,2]. PTCL-NOS includes the cases that do not fit any specific subtype in the current WHO classification. The patients are usually adults, mostly greater than 60 years of age, and present with stage III or IV disease at diagnosis. The overall clinical course is aggressive with an unfavorable prognosis despite aggressive chemotherapy.

Clinical features

Pulmonary involvement by PTCL-NOS accounts for 2% to 8% of all PTCL-NOS cases and usually represents a systemic involvement of lung[1]. Primary pulmonary PTCL-NOS is rare and defined as lymphomas primarily affecting the lung parenchyma, bronchi, and/or trachea, without extrapulmonary extension within three months after diagnosis[3]. Patients often present with symptoms of fever, coughing and dyspnea.

Although the chest imaging findings of PTCL-NOS are not specific, the results from these studies can help triage and trigger further examinations as well as targeted biopsies. The early lung infiltration by

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Table 1
Characteristics of pulmonary T-cell and NK-cell lymphomas.

Lymphoma Type	Major Morphologic Features	Immunophenotype and Genetics
Peripheral T-cell lymphoma, NOS	Nodular or diffuse infiltrate; polymorphous to monomorphic, medium to large cells; pleomorphic nuclei with hyperchromatic or vesicular nuclei; prominent nucleoli	Positive: CD2, CD3, CD4, BF1 Weak or negative: CD5, CD7 Negative: CD8, CD56, cytotoxic markers, EBER-ISH CD30 variably positive in ~50% cases
Extranodal NK/T-cell lymphoma, nasal-type	Angiocentric invasion; coagulative necrosis; broad spectrum of cytology with typically medium-sized to large cells, some appear blastoid; mixed inflammatory background and capillary proliferation	Positive: CD2, cCD3, CD56, cytotoxic markers Negative: sCD3, CD4, CD5, CD7, CD8, CD16, CD57 EBER-ISH positive Germline *TCR* configuration
Anaplastic large cell lymphoma	Nodular or scattered nodular pattern, intraluminal polypoid mass, or intra-alveolar spread; large pleomorphic cells with characteristic hallmark cells, giant multinucleated wreath cells and Reed-Sternberg–like cells	Positive: CD2, CD4, CD5, CD30, CD43, CD25, EMA, clusterin, cytotoxic markers, EMA Negative: CD3, CD8, CD15 Some cases with null phenotype *NPM1-ALK* or *TPM3-ALK* in ALK+ cases *DUSP22* or *TP63* rearrangements in ALK-negative cases
Adult T-cell lymphoma/leukemia	Micronodular, nodular, and cystic patterns; variable cytologic features; mostly medium to large cells; prominent nuclear pleomorphism with convoluted or multilobed contours	Positive: CD2, CD3, CD4, CD5, CD25 Negative: CD7, CD8, ALK, cytotoxic markers CD30 positive in a subset of cases EBER-ISH negative HTLV-1 positive
Mycosis fungoides/ Sezary syndrome	Patchy or nodular infiltration; small to medium-sized tumor cells; high nucleus to cytoplasm ratio; cerebriform nuclei	Positive: CD2, CD3, CD4, CD5, BF1 CD8 positive in rare subtypes Partial CD30 expression Negative: CD7, CD56 EBER-ISH negative
Angioimmunoblastic T-cell Lymphoma	Patchy or nodular infiltrate; medium-sized to large tumor cells with moderate amount of clear to pale cytoplasm and distinct cell membranes; mixed inflammatory background and capillary proliferation	Positive: CD2, CD3, CD4, CD5, PD1, CD10, BCL6, CXCL13, CD57 CD21- or CD23-positive dendritic meshworks EBER-ISH negative in tumor cells but positive in scattered immunoblasts Mutations in *TET2, DNMT3A* and *IDH2*

PTCL-NOS may present with crazy paving pattern on computed tomography (CT) studies. With disease progression, different infiltrative patterns may appear, including nodules, masses, ground-glass opacities, consolidation, and cavitation as well as hilar/mediastinal lymphadenopathy[4–6].

In many cases, the clinical presentations and radiological findings closely resemble pneumonia[3,7], and therefore the patients may initially be managed as such. Subsequent biopsies for tissue diagnosis are needed to avoid further delay in diagnosis in patients who have failed antimicrobial treatments. Transbronchial biopsy or CT-guided needle core biopsy is often utilized in the initial approach. However, surgical procedures, including open lung biopsy and video-assisted thoracoscopic surgery (VATS), are necessary in some cases for a definitive diagnosis since small needle core biopsy or bronchoscopy may not provide enough diagnostic tissue. The first line therapy of pulmonary PTCL-NOS is cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP)-based chemotherapy, but the prognosis is poor.

Morphologic features

In the lung biopsies, the tumor cells of PTCL-NOS show a nodular involvement with distortion of pulmonary structure or a diffuse infiltration within interlobular septa, pleura, and alveolar walls (Figs. 1A and 1B). Perivascular involvement is frequently noted. The cytomorphology is very broad, from polymorphous to monomorphic. In most cases, the lymphoma consists of medium and/or large cells, which have pleomorphic nuclei with hyperchromatic or vesicular nuclei and prominent nucleoli (Fig. 1C). The cytoplasm is moderate to abundant and usually clear. Frequent mitotic figures and apoptotic bodies are present. Some cases contain scattered to abundant anaplastic cells or occasional Reed-Sternberg-like cells, and rare cases have a predominance of small- to medium-sized neoplastic cells.

The background contains a mixed inflammatory infiltration, including abundant small reactive lymphocytes, frequent eosinophils, plasma cells, and a variable number of epithelioid histiocytes singly or in small clusters (Fig. 1C). In areas of necrosis or obstruction, secondary inflammation and infection can be prominent with abundant acute and inflammatory cells.

Immunophenotype and genetics

Pulmonary PTCL-NOS expresses multiple T-cell associated markers, of which CD3 and CD2 (Fig. 1D) are the most commonly expressed. Most cases demonstrate the immunophenotype of CD4+ and CD8- (Fig. 1E), however, cases of CD4 and CD8 double-positive, double-negative, or CD8+ can be seen. CD5 and CD7 are frequently down-regulated or aberrantly absent (Fig. 1F). Most cases of pulmonary PTCL-NOS arise from alpha/beta T-cells and rare cases show gamma/delta T-cell deviation, which are identified by the immunostaining for T-cell receptor beta (beta F1) and T-cell receptor delta, respectively. Expression of CD56 and cytotoxic markers (TIA1, granzyme B, and perforin) is rarely detected, usually in cases with gamma/delta T-cell derivation. CD30 is expressed in >25% of the lymphoma cells in ~50% of PTCL-NOS. However, in contrast to anaplastic large cell lymphoma (ALCL), the expression of CD30 in PTCL-NOS is usually variable and in <75% of cells.

Differential diagnosis

Primary or secondary pulmonary involvement by “extranodal NK/T-cell lymphoma, nasal type (ENKTL)” has significant overlaps with PTCL-NOS. Morphologically, ENKTL shows a marked angioinvasion with extensive necrosis. The lymphoma cells express CD2, CD3, CD56 and cytotoxic markers; particularly, EBV infection is detected in nearly all cases. Lymphomatoid granulomatosis (LYG) can be confused with pulmonary PTCL-NOS due to the abundance of T-cells, especially in grade 1 and grade 2 lesions (Fig. 2A). LYG demonstrates a characteristic angiocentric and angiodestructive infiltrative pattern, and the

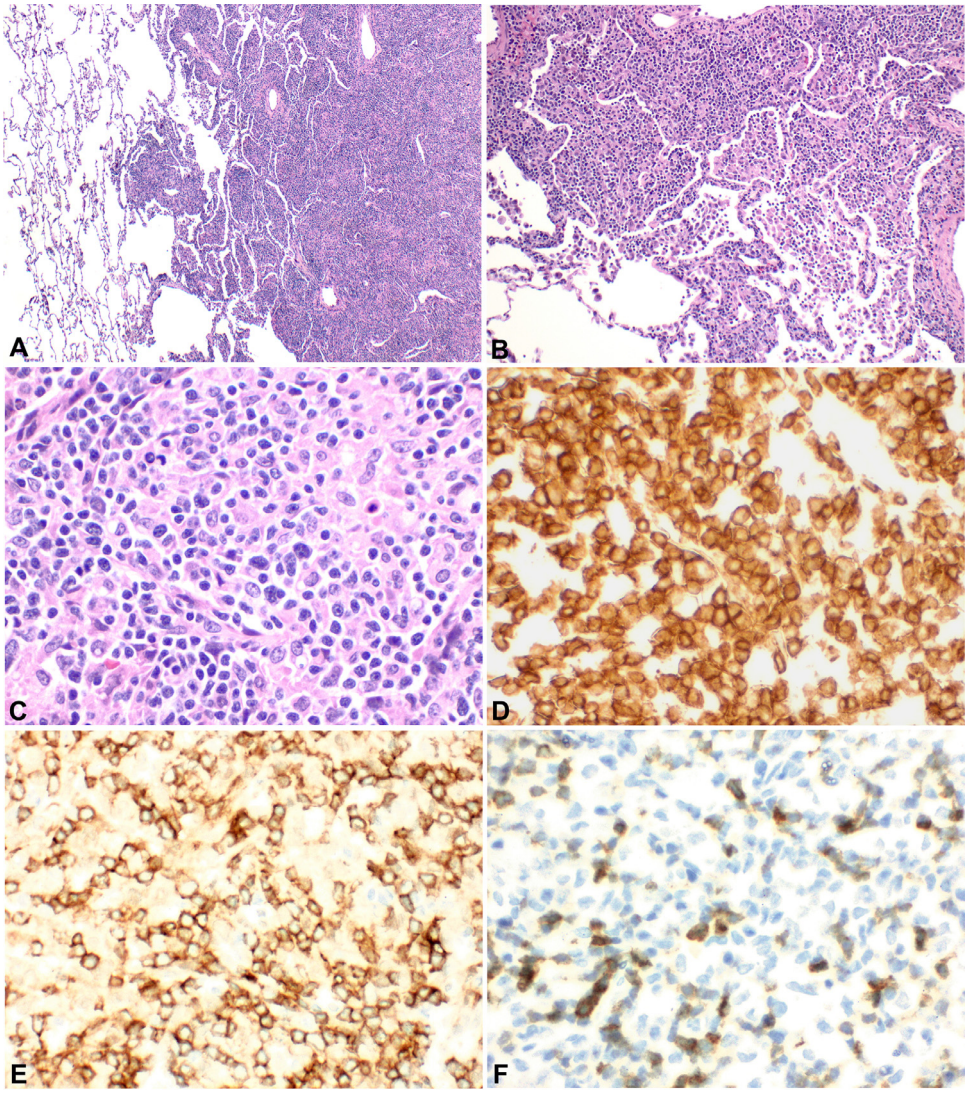

Fig. 1. Peripheral T-cell lymphoma, not-otherwise-specified (PTCL-NOS). (**A**) The lymphoma forms a nodular infiltration in the lung parenchyma (H&E, 20 ×). (**B**) In the periphery of the tumor, there is a mixed reaction of lymphocytes and histiocytes (H&E, 100 ×). (**C**) Loose clusters of medium to large tumor cells in a background of small reactive lymphocytes, plasma cells, and histiocytes (H&E, 400 ×). The lymphoma cells are positive for CD3 (**D**) and CD4 (**E**) with aberrant loss of CD5 expression (**F**) (400 ×).

neoplastic cells are of B-cell lineage albeit variable in number (Fig. 2B). Detection of EBV infection in the large atypical B-cells is helpful in establishing the diagnosis (Fig. 2C).

Pulmonary PTCL-NOS with high CD30 expression must be separated from ALK-negative ALCL, since PTCL-NOS carries a worse prognosis. ALK-negative ALCL displays a more pleomorphic cytology and contains hallmark cells with kidney- or horseshoe-shaped nuclei. CD30 expression in ALCL is strong and uniform, and expression of EMA and cytotoxic markers also favors ALCL over PTCL-NOS. Loss of pan T-cell markers is more frequently observed with ALK-negative ALCL than in PTCL-NOS. In addition, a small subset of ALK-negative ALCL cases harbors *DUSP22* and *TP63* gene rearrangements, as detected in 30% and 8% of cases, respectively[8].

Extranodal NK/T-cell lymphoma, nasal-type (ENKTL)

Extranodal NK/T-cell lymphoma (ENKTL), nasal type, most commonly involves the upper aerodigestive tract, including the nasal cavity, nasopharynx, paranasal sinuses, and palate. Pulmonary ENKTL usually represents involvement of a systemic disease, and the primary pulmonary case is rare, accounting for 0.5% to 1% of all primary pulmonary malignancies[9,10]

Clinical features

Pulmonary ENKTL presents with nonspecific clinical symptoms and radiologic findings, resembling pneumonia or interstitial pulmonary disease[11–13]. The major initial symptoms include fever and cough. Radiologically, most cases show bilateral nodular lesions and consolidations with bronchial or mediastinal involvement and pleural effusion, and occasionally a single mass lesion is detected[10,14]. Clinical laboratory tests commonly detect pancytopenia and elevated LDH levels. Prognosis of pulmonary ENKTL is very poor with a median overall survival of 2 months in a small case series, despite chemotherapy and aggressive treatment[15].

Morphologic features

Histologically, pulmonary ENKTL infiltrates diffusely with a complete or partial destruction of the pulmonary parenchyma. The tumor cells may be present in alveoli and widen interstitial tissue. The characteristic angiocentric and angioinvasive growth pattern with

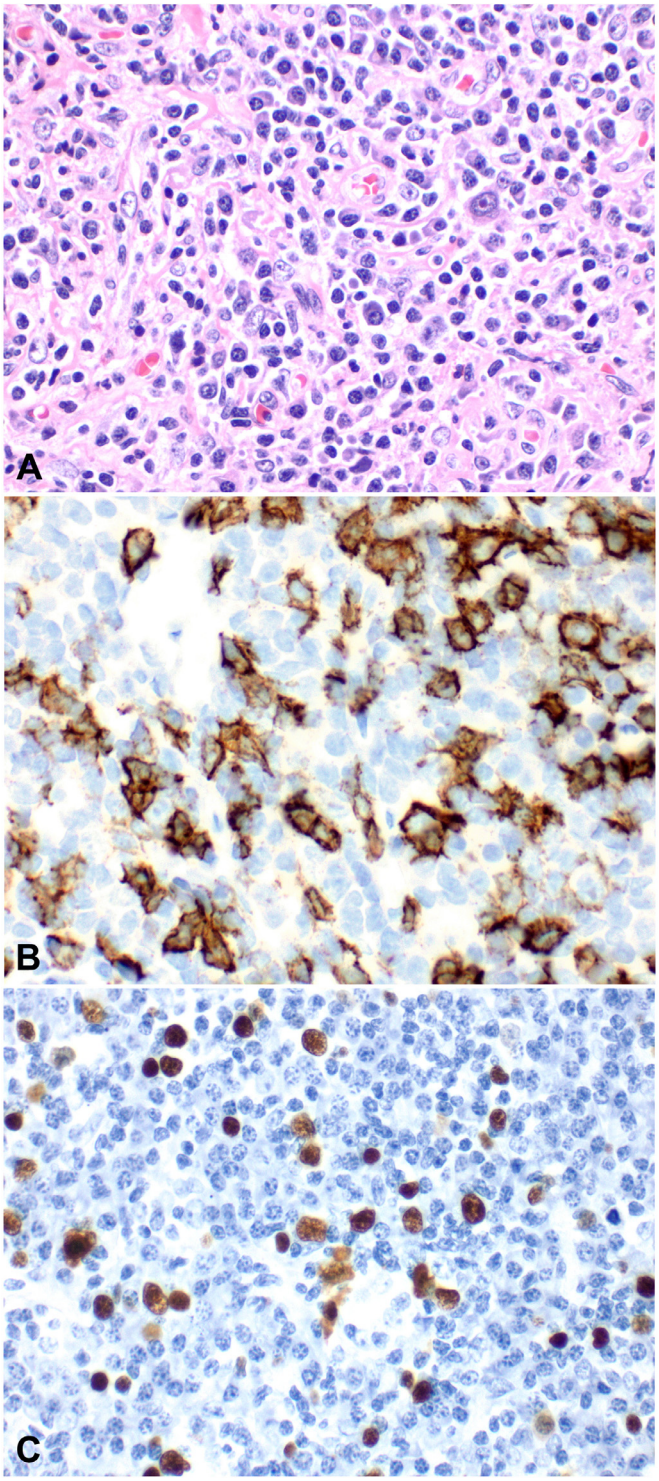

Fig. 2. Lymphomatoid granulomatosis (LYG), grade 2. In this lung biopsy, there are scattered large atypical cells with distinct nucleoli in a background of abundant small lymphocytes, frequent plasma cells, and scattered histiocytes (**A**, H&E). The scattered large cells are positive for CD20 (**B**) and EBER-ISH (**C**). (All 400 ×).

coagulative necrosis is commonly observed (Fig. 3A).

The cytology of lymphoma cells varies among cases or even within the same specimen with a broad spectrum of size. In most cases, the lymphoma is composed of medium-sized to large cells (Fig. 3B), and rare cases show a predominance of small- to medium-sized cells or anaplastic cells. The nuclei are round, irregularly folded, or even elongated. The chromatin is generally granular or condensed but is vesicular in the large cells. Nucleoli are inconspicuous or small but can be prominent in the large tumor cells. The cytoplasm is moderate to abundant in amount and often clear. Frequent mitotic figures and apoptotic cells are easily found.

The background consists of abundant reactive inflammatory cells with mostly lymphocytes and plasma cells (Fig. 3B). Neutrophils are variably present and can be abundant particularly in the areas with necrosis or secondary infection. Similar to the nasal lesions, pulmonary ENKTL often shows a marked proliferation of capillaries with plump endothelial cells.

Immunophenotype and genetics

The tumor cells in pulmonary ENKTL are positive for CD2, cytoplasmic CD3 epsilon, CD56, and cytotoxic markers, TIA1, granzyme B and perforin[16] (Figs. 3C–E). Surface CD3 is negative, and other T-cell and NK-cell associated markers are typically negative, including CD4, CD5, CD7, CD8, CD16, and CD57. The median proliferation index, demonstrated by the Ki67 immunostaining, is approximately 50%. Characteristically, nearly all cases are positive for EBV infection in the tumor cells by EBER-ISH (Fig. 3F). Using PCR assays, most cases of ENKTL have a germline configuration of T-cell receptor (*TCR*) without evidence of clonal rearrangements. However, a small proportion of cases demonstrates clonal *TCR* gene rearrangements, likely representing T-cell differentiation.

Differential diagnosis

Pulmonary ENKTL has abundant inflammatory cells in the background that may obscure the neoplastic cells, and it can mimic an inflammatory process, particularly in the small biopsies with crush artifact. Therefore, careful morphologic assessment is essential to establish an accurate diagnosis in conjunction with essential ancillary studies, particularly EBER-ISH. In patients who had small biopsies not diagnostic of lymphoma, status post anti-infectious or anti-inflammatory treatment, a repeat biopsy or wedge biopsy should be considered for more complete workup.

PTCL-NOS occasionally expresses CD56 and cytotoxic markers. However, in contrast to ENKTL, PTCL-NOS is positive for at least some of the pan-T-cell markers but shows no evidence of EBV infection.

LYG and ENKTL share similar morphologic features including angioinvasion, mixed inflammatory background, and positive EBER-ISH in the tumor cells. In LYG, the lymphoma cells are scattered or in clusters and are of B-cell lineage with expression of CD20 (Figs. 2A–C).

ENKTL must be distinguished from granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis. In GPA, the involved lung parenchyma reveals large areas of necrosis surrounded by palisading histiocytes and scattered multinucleated giant cells (Fig. 4A). The characteristic vasculitis of arteries and veins is present (Fig. 4B). Neutrophils are abundant and frequently form microabscesses (Fig. 4A), whereas lymphocytes and plasma cells are scant. Most patients have elevated serum c-ANCA levels. In contrast to ENKTL, GPA contains no atypical EBV-positive T-cells or NK-cells.

Anaplastic large-cell lymphoma (ALCL)

ALCL often involves lymph nodes and extranodal sites. Pulmonary ALCL is usually part of a systemic process; primary ALCL of the lung is extremely rare, which is difficult to diagnose due to its nonspecific clinical presentations and radiological findings. Approximately 20 cases of primary ALCL of lung have been reported in the English literature by 2019[17–22].

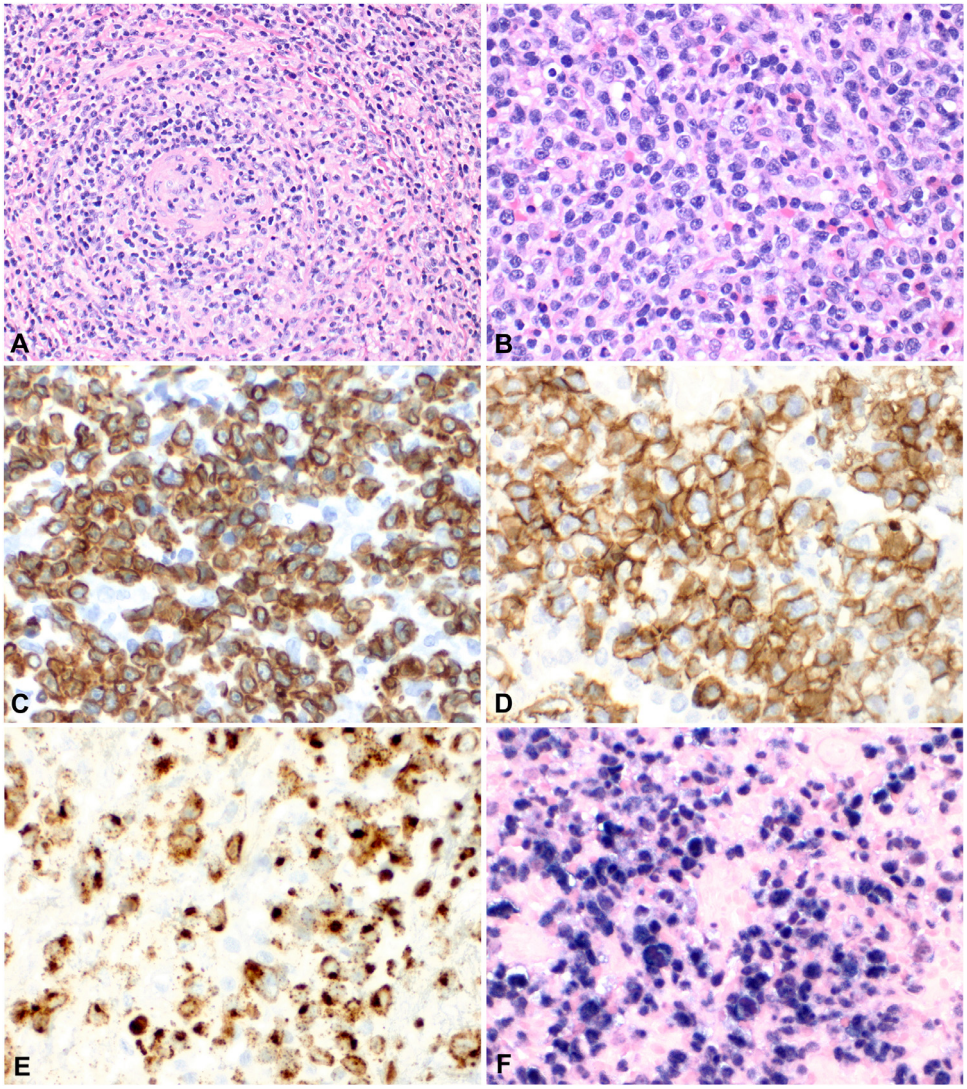

Fig. 3. Extranodal NK/T-cell lymphoma (ENKTL), nasal type, with lung involvement. (**A**) The lymphoma demonstrates an angiocentric infiltrative pattern (H&E, 200 ×). (**B**) Abundant medium to large tumor cells within a background of mixed reactive lymphocytes and eosinophils (H&E, 400 ×). The tumor cells are positive for CD3 (**C**), CD56 (**D**), and granzyme B (**E**) with characteristic infection of EBV by EBER-ISH (**F**) (400 ×).

Clinical features

Patients with pulmonary ALCL usually present with fever, cough, dyspnea, night sweats, and weight loss. Radiologically, the tumor can be unifocal or multifocal with solid or cystic changes[17,23]. One case report showed a large mass with multiple cavities in the lung, mimicking pulmonary abscess[24]. The overall survival is better than that of PTCL-NOS.

Morphologic features

Pulmonary ALCL displays various patterns of infiltration in the parenchyma, with nodular growth pattern (Fig. 5A), scattered nodular pattern with cyst formation, intraluminal polypoid mass formation with occlusion of large airways, and intra-alveolar spread producing a "tumoral pneumonia". The tumor cells are typically large, pleomorphic and have irregular nuclei with vesicular chromatin and prominent nucleoli (Fig. 5B). The cytoplasm is ample and pale, basophilic, or eosinophilic. Scattered hallmark cells, multinucleated giant cells, or even Reed-Sternberg–like cells are present in many cases (Fig. 5B). Rare cases of small-cell variant show a predominant population of small to medium-sized neoplastic cells and only scattered large cells. Lymphoma cells may show vascular invasion. Necrosis is commonly observed and may be extensive in some cases.

ALCL contains variable numbers of reactive inflammatory cells, including lymphocytes, neutrophils, eosinophils and histiocytes. The affected lungs often show obliteration of normal alveolar architecture. Secondary inflammatory changes in the adjacent lung parenchyma are noted in many cases, including acute bronchopneumonia, obstructive pneumonia, organizing pneumonia, and desquamative interstitial pneumonia[23].

Immunophenotype and genetics

ALCL cells are positive for CD30 with a characteristic membranous and Golgi staining pattern (Fig. 5C). For cases with t(2;5) (*NPM1-ALK*) translocation, ALK staining is seen in both cytoplasm and nuclei. However, the most commonly utilized T-cell marker, CD3, is negative in the majority of ALCL cases. Other T-cell markers are mostly positive, including CD2, CD4, CD5, and CD7, although loss of one or more of these markers may occur. CD8 is typically negative, but rare CD8+ cases exist. Most ALCLs are positive for CD43, EMA, CD25, and cytotoxic markers (TIA1, granzyme B, and perforin). EBV infection is not detected in ALCL by EBER-ISH.

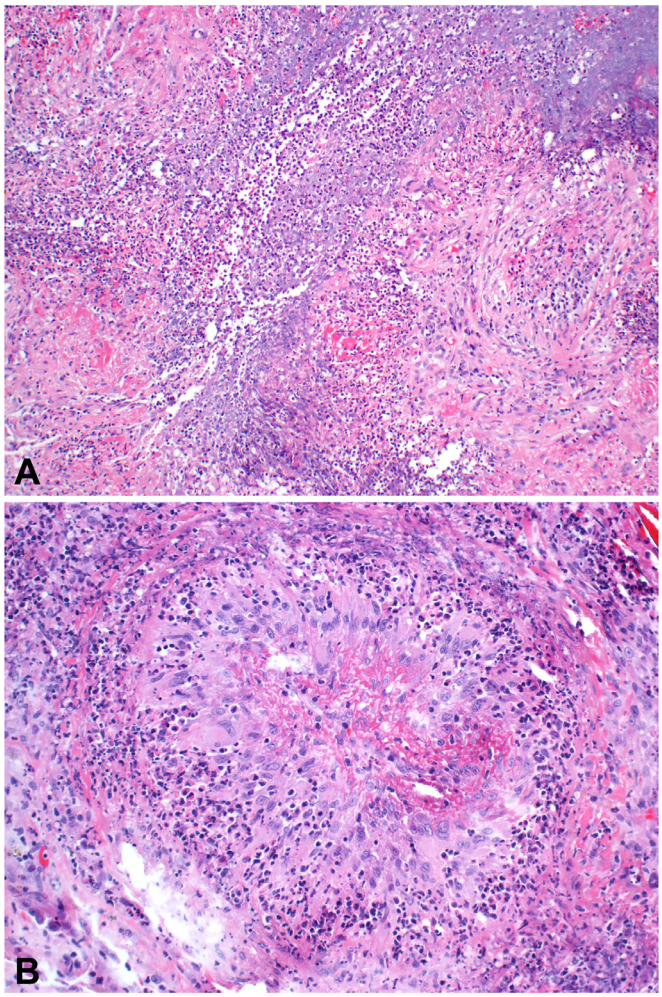

Fig. 4. Granulomatosis with polyangiitis (GPA) in a patient with positive serum c-ANCA. (**A**) The lung parenchyma contains neutrophil-rich necrosis, surrounded by abundant histiocytes and scattered multinucleated giant cells (H&E, 100 ×). (**B**) Characteristic vasculitis of a small artery (H&E, 200 ×).

The vast majority of ALK+ ALCLs harbor either t(2;5)(p23;q35) *NPM1-ALK* or t(1;2)(q25;p23) *TPM3-ALK* rearrangements. In ALK-negative ALCL, *DUSP22* rearrangements occur in about 30% of cases, which are associated with a favorable overall survival rate similar to that of ALK+ ALCL[8]. Rearrangements of *TP63* are detected in ~8% of ALK-negative ALCL cases, and the prognosis is dismal.

Differential diagnosis

Pulmonary ALCL with pleomorphic cytology may mimic poorly differentiated carcinoma of the lung, particularly in the cases with expression of P63 and EMA but lack of CD3 positivity. Moreover, approximately 3% to 5% cases of pulmonary adenocarcinoma express ALK, mostly associated with *EML4-ALK* fusion[25,26]. A rare variant of large B-cell lymphoma expresses ALK (ALK+ LBCL) with a characteristic cytoplasmic dotted pattern[27]. The ALK+ LBCL lacks expression of CD30 and commonly employed B-cell markers, CD20, CD79a and PAX5.

The lymphoma cells in the small-cell variant of ALCL may be weakly positive or even negative for CD30, and only the scattered large tumor cells demonstrate strong expression. Therefore, these cases may potentially be misinterpreted as PTCL-NOS. Conversely, PTCL-NOS may express CD30, usually with a variable staining in a subset of cells. However, it can be difficult to clearly separate ALK-negative ALCL from PTCL-NOS with a high CD30 expression.

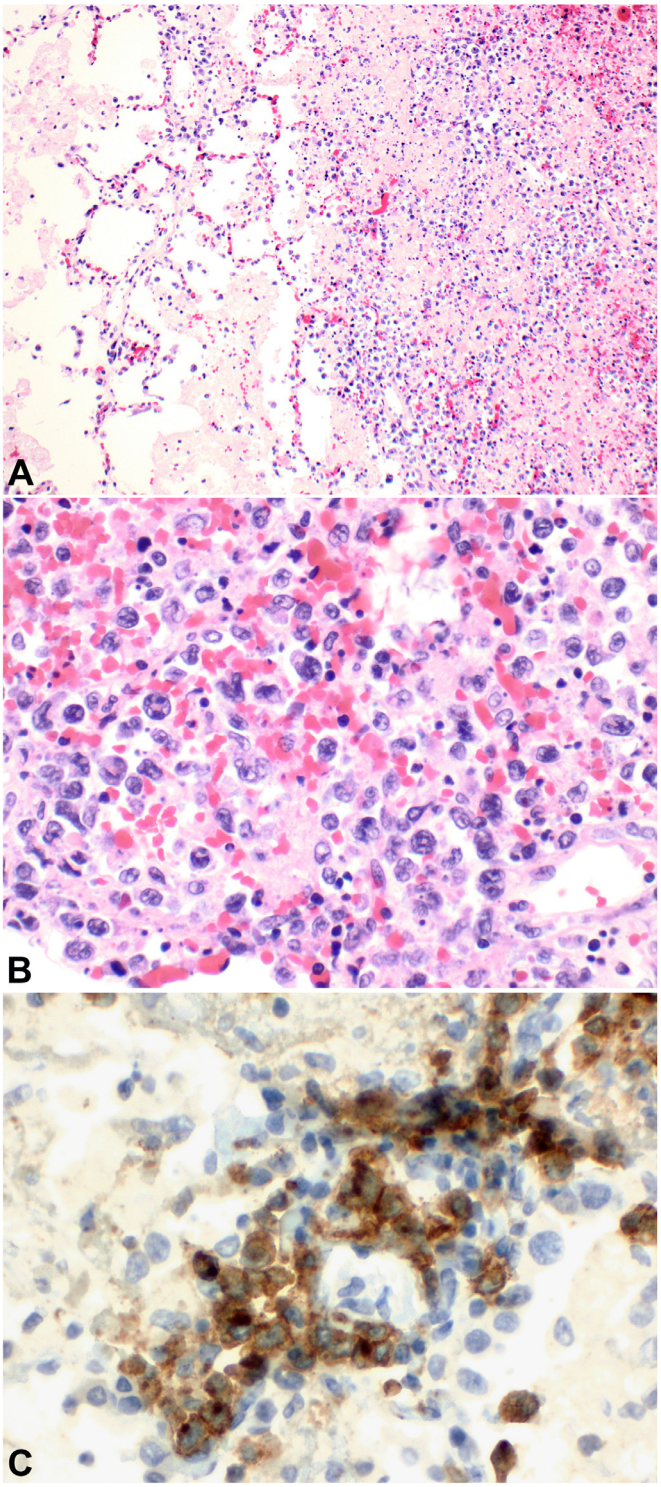

Fig. 5. Pulmonary anaplastic large-cell lymphoma (ALCL). (**A**) In the case, the ALCL reveals patchy involvement with destruction of lung parenchyma and intra-alveolar spread (H&E, 40 ×). (**B**) The large lymphoma cells have pleomorphic nuclei with frequent hallmark cells (H&E, 400 ×). (**C**) CD30 positivity in the tumor cells with characteristic membranous and Golgi staining pattern (400 ×).

Adult T-cell lymphoma/leukemia (ATLL)

ATLL is an aggressive mature T-cell lymphoma associated with

infection of human T-cell lymphotropic virus, type 1 (HTLV-1). ATLL has a high prevalence in several regions, particularly Japan, Caribbean basin, and central Africa.

Clinical features

Nearly all ATLL cases occur in adults, with an average age of 58 years. There are several major clinical variants of ATLL, including acute, lymphomatous, chronic, and smoldering. The acute variant is the most common type with a systemic involvement in the peripheral blood, skin, lymph nodes, and other organs. In the lymphomatous variant, the tumor cells mainly infiltrate the lymph nodes and solid organs without peripheral blood involvement. In both variants, patients present with widely disseminated disease, with characteristic features of hypercalcemia and lytic bone lesions in many patients. In addition, pulmonary manifestations are found in >50% of patients upon initial presentation. The abnormal radiologic findings in the lung include lymphadenopathy, micronodules, ground-glass opacity, multiple lung cysts within localized ground-glass opacity, pleural effusion, thickening of interlobular septum, and bronchiectasis[28,29].

Morphologic features

Patients with ATLL commonly show micronodular, nodular, and cystic changes in the lung; however, some of the lesions are attributed to pulmonary abscess or hemorrhage rather than lymphoma infiltration[29]. There are different patterns of lymphoma infiltration in the lung. The tumor cells may form round nodules or infiltrate into the alveolar wall, alveolar space (Figs. 6A and B), respiratory bronchioles, and bronchovascular bundles. Some cases present with multiple cystic lesions within consolidation; the central cystic space is formed by bronchiectasis and fibrosis, and the consolidation corresponds to a diffuse infiltration of tumor cells.

ATLL cells in the lung exhibit a broad spectrum of cytologic variants, including small, medium, large, and anaplastic (Fig. 6B). In most cases, the lymphoma cells are medium to large, with prominent nuclear pleomorphism. The nuclei are irregular and display characteristic convoluted or multilobed contours. The nuclear chromatin is condensed with distinct nucleoli. However, rare cases are composed mostly of small- to medium-sized tumor cells with irregular nuclei.

Immunophenotype and genetics

The lymphoma cells in ATLL express T-cell markers, CD2, CD3, and CD5, and are mostly positive for CD4 but negative for CD7 and CD8 (Figs. 6C and D). Rare cases are CD4-negative and CD8-positive or double-positive for CD4 and CD8. Characteristically, CD25 is strongly expressed in nearly all cases (Fig. 6E). CD30 may be expressed in a subset of cases, particularly the ones with large cell transformation; however, these cases are negative for ALK and cytotoxic markers.

Differential diagnosis

Pulmonary involvement by ATLL must be distinguished from other causes of pulmonary infiltration, especially infections and interstitial pulmonary diseases. ATLL patients with pulmonary symptoms usually present with systemic leukemic or lymphomatous manifestations, and therefore clinical examinations and careful morphologic assessments are essential for the diagnosis.

Pulmonary ATLL shares similar morphologic and immunophenotypic features to PTCL-NOS and even ALCL. Therefore, in HTLV-1 endemic regions, CD25 immunostain is recommended in the initial workup of T-cell neoplasms. Particularly, for any patients with a suspicion of ATLL, additional studies are necessary to detect active HTLV-1 infection, including serum antigen and molecular assays.

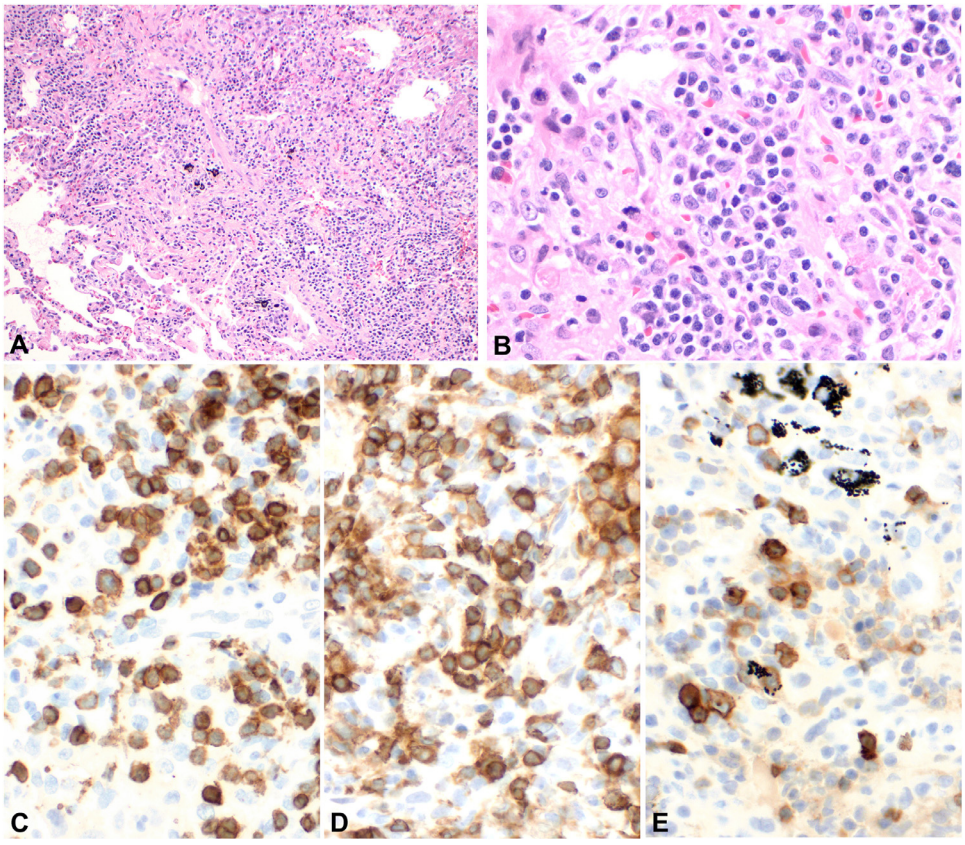

Fig. 6. Pulmonary adult T-cell lymphoma/leukemia (ATLL) in a patient recently diagnosed with ATLL in the blood. There is patchy involvement in the pulmonary parenchyma (**A**, H&E, 100 ×) with infiltration into the alveolar wall (**B**, H&E, 400 ×). (**B**) Scattered atypical medium-sized lymphocytes are identified with a background of abundant small lymphocytes, plasma cells, and histiocytes. (**C**) CD3 highlights scattered medium-sized tumor cells as well as small reactive T-cells (400 ×). (**D**) CD4 is positive in scattered tumor cells and a cluster of alveolar histiocytes with a moderate intensity (right upper corner of the image) (400 ×). (**E**) CD25 expression in the tumor cells (400 ×).

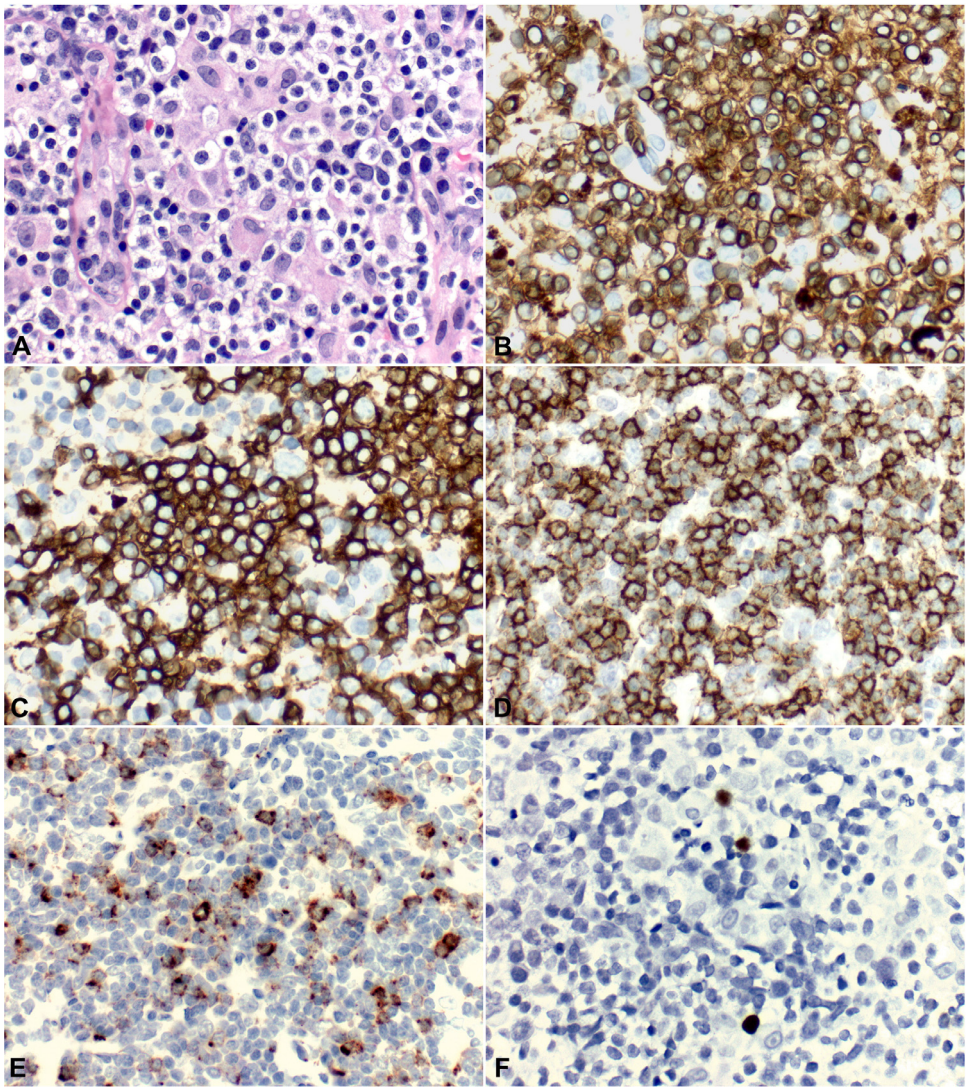

Fig. 7. Pulmonary involvement by angioimmunoblastic T-cell lymphoma (AITL). (**A**) Frequent large lymphoma cells with abundant clear cytoplasm in a background of mixed inflammatory cells and proliferation of high endothelial venules. The tumor cells are positive for CD3 (**B**), PD1 (**C**), CD57 (**D**) and CXCL13 (**E**). Scattered EBV-positive cells are detected by EBER-ISH (**F**). (All 400 ×).

Mycosis fungoides/sezary syndrome (MF/SS)

Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common types of cutaneous T-cell lymphomas (CTCL). MF is characterized by an epidermotropic infiltrate of neoplastic CD4-positive T-cells, whereas SS presents with a systemic disease with lymphadenopathy, erythroderma, and circulating tumor cells in the blood. In the advanced stage, MF can spread to multiple extracutaneous organs, such as lymph nodes, lung, spleen, and liver.

Clinical features

Pulmonary involvement occurs in the advanced stages of MF/SS. It has been reported in ~66% of autopsy cases of advanced stage CTCL[30]. Based on limited case reports, the clinical imaging findings of MF/SS lung involvement include bilateral reticular infiltrates, bilateral and diffuse interstitial opacities, and multiple peribronchovascular nodules[31]. However, pulmonary involvement by MF/SS can resemble pneumonia clinically as well as radiographically.

Morphologic features

In the lung, the MF/SS cells reveal patchy or nodular infiltration in the parenchyma. The tumor cells are usually small to medium-sized, with a high nucleus to cytoplasm ratio. Characteristically, they have highly indented or cerebriform nuclei and a thin rim of clear cytoplasm. With disease progression, there is an increase in large tumor cells, with large cerebriform pleomorphic or blastoid nuclei.

Immunophenotype and genetics

MF/SS cells demonstrate a typical immunophenotype with positive stains for CD2, CD3, CD4, and CD5. CD7 is lost in most cases. CD8 and CD56 are negative. CD30 is usually negative, but partial expression is noted in the cases during disease progression. No evidence of EBV infection is detected in any cases.

Differential diagnosis

Diagnosis of pulmonary involvement by MF/SS is usually not problematic in cases with known clinical history. However, the cases with increased large cells may be confused with PTCL-NOS. While it may be

tempting to use T-cell gene rearrangement studies to determine the relationship between the pulmonary lesion and the skin lesion, clonal heterogeneity of MF has been demonstrated[32]. It's possible that next-generation sequencing technologies may be more helpful in teasing out the clonal relationships, if practically relevant in the future[33].

Angioimmunoblastic T-cell lymphoma (AITL)

AITL is a neoplasm of T-follicular-helper (TFH) cell origin. It accounts for 1% to 2% of NHLs and is the second most common specific subtype of PTCL worldwide[34]. The patients with AITL typically present with advanced stage disease, constitutional symptoms, systemic lymphadenopathy, hepatosplenomegaly, rash, anemia, and polyclonal hypergammaglobulinemia. AITL is usually associated with an aggressive clinical course and a median survival of less than 3 years.

Clinical features

The primary site of AITL presentation is the lymph node. Pulmonary AITL nearly always represents part of a systemic process. Therefore, it is critical to correlate with the clinical history and biopsy findings from lymph nodes and other organs. Pulmonary involvement of AITL shows nonspecific clinical symptoms and radiologic findings, and the patients typically have fever and cough. Other common findings are pleural effusion.

Morphologic features

Diagnosis of AITL is typically based on the excisional biopsy of enlarged lymph nodes, and rarely lung biopsies may be performed in the initial workup or during the course of disease progression or recurrence. In the lung, AITL shows a patchy or nodular infiltrate in the pulmonary parenchyma. The histomorphology is similar to that seen in lymph node specimens with variable numbers of neoplastic T cells in a polymorphous background that includes reactive lymphocytes, eosinophils, plasma cells, epithelioid histocytes, and arborizing high endothelial venules. The neoplastic T cells are medium- to large-sized with clear to pale cytoplasm and distinct cell membranes (Fig. 7A). Epithelioid histiocytes are usually scattered, but they can be abundant, forming clusters or aggregates. The surrounding non-neoplastic lung tissue often has a variable degree of inflammatory reaction secondary to obstruction and infection, which may obscure the tumor morphology.

Immunophenotype and genetics

The lymphoma cells in AITL are positive for pan T-cell markers, including CD2, CD3, and CD5, and the vast majority of cases express CD4 (Fig. 7B). These T-cell antigens do not usually exhibit complete loss, but reduced or variable expression of one or more T-cell antigens can be observed. Characteristically, the neoplastic T-cells express T-follicular-helper (TFH) markers, including PD1, CD10, BCL6, CXCL13, CD57, and ICOS (Figs. 7C–E). Hence, demonstrating at least 2 or 3 of these TFH markers is helpful in the diagnosis of AITL. In addition, scattered EBV-positive cells are nearly always present in the tumor, which are non-neoplastic B-immunoblasts[35] (Fig. 7F). CD21 and CD23 commonly demonstrate expanded and distorted follicular dendritic meshworks, as noted in the nodal cases.

Clonal *TCR* gene rearrangements are detectable in 75% to 90% of AITL cases. Interestingly, 25% to 30% of cases have coexisting clonal *IGH* gene rearrangements[36]. A high incidence of somatic mutations has been detected in the genes involved in epigenetic gene regulation, including *TET2* (47% to 82%), *DNMT3A* (33%), and *IDH2* (20% to 30%)[37,38].

Differential diagnosis

Initial diagnosis of AITL via a pulmonary biopsy is very challenging, even with excisional samples. AITL often contains a proliferation of scattered large B-cells with immunoblastic and centroblastic morphology, which are commonly EBV-positive. Therefore, the lung biopsy may closely resemble lymphomatoid granulomatosis (LYG) or other EBV-positive lymphoproliferative disorders associated with aging, medication and immunosuppression. Moreover, the large B-cells may have Reed-Sternberg–like cytology with expression of CD30 and EBV-positivity, and these cases may be confused with pulmonary involvement by classic Hodgkin lymphoma. It is also very difficult to separate AITL from PTCL-NOS based on the pulmonary biopsy alone. Therefore, an excisional biopsy of lymph node is most likely necessary for a definitive diagnosis if there is a suspicion of AITL clinically.

Pulmonary involvement by other T-cell lymphomas

Rare cases of T-cell lymphoma of gamma/delta T-cell origin have been reported in the lung, including one case of widespread subcutaneous panniculitis-like T-cell lymphoma (PSPTCL)[39,40]. There are usually multiple hypermetabolic lesions in both lungs. The lung biopsy reveals nodular infiltration of monomorphic, medium to large lymphoma cells with round or irregular nuclei, condensed chromatin, and a variable amount of cytoplasm. The tumor cells express CD2, CD3, CD7, CD56, cytotoxic molecules, and TCR gamma/delta, and they are usually negative for CD4, CD5, CD8, CD57, and TCR alpha/beta (beta F1). EBV is not detected by EBER-ISH[39].

It can be very challenging to diagnose early-stage T-cell or NK-cell lymphomas, or partial involvement by such lymphomas, as well as to interpret suboptimal biopsies in this area that may contain limited tissue and/or crush artifact. Moreover, the lymphomatous infiltration can often be obscured by prominent inflammatory reactions in the lung. Therefore, after excluding the possibilities of infection and medical lung disease, special attention should be paid to look for atypical cytologic features and aberrant antigen expression of lymphoid infiltration with the aid of immunostains. CD30 immunostain and EBER-ISH should be considered frequently to rule out subtle or early involvement of ALCL, Hodgkin lymphoma, and EBV+ *T*-cell and B-cell lymphoproliferative disorders. Molecular studies for *TCR* and *IGH* gene rearrangements are helpful in the diagnostic process, but the results must be interpreted with caution and in the context of morphologic and clinical features. For cases with atypical features that are not enough for lymphoma, patients can be closely monitored, and another biopsy may be performed in the lung, adjacent lymph nodes or extrapulmonary sites in the future.

Declaration of Competing Interest

Dr. Xu is on the lymphoma advisory board with Seattle Genetics. Dr. Pan has no relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in article or with a company making a competing product.

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