Pulmonary Manifestations of the Autoimmune Lymphoproliferative Syndrome
A Retrospective Study of a Unique Patient Cohort

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Abstract

Rationale: Patients with autoimmune lymphoproliferative syndrome (ALPS), a disorder of impaired lymphocyte apoptosis, often undergo radiographic chest imaging to evaluate the presence and progression of lymphadenopathy. These images often lead to parenchymal and interstitial lung findings of unclear clinical significance.

Objectives: To characterize the pulmonary findings associated with ALPS and to determine if lung abnormalities present on computed tomographic (CT) imaging of the chest correlate with infection or functional status.

Methods: Patients with lung abnormalities observed on chest CT scans were retrospectively identified from the largest known ALPS cohort. Lung computed tomography findings were characterized and correlated with medical records, bronchoalveolar lavage, biopsy, and lung function.

Measurements and Main Results: CT images of the chest were available for 234 (92%) of 255 of the patients with ALPS. Among patients with a chest CT scan, 18 (8%) had lung abnormalities on at least one CT scan. Fourteen (78%) of those 18 were classified as having ALPS with undetermined genetic defect. Most patients (n = 16 [89%]) with lung lesions were asymptomatic. However, two (11%) of them had associated dyspnea and/or desaturation on room air. Immunosuppressive treatment was administered for lung disease in nine (50%) cases, and all were followed for clinical outcomes.

Conclusions: Patients with ALPS can develop chest radiographic findings with protean manifestations that may mimic pulmonary infection. Management of patients with ALPS with incidental lung lesions identified by CT imaging should be guided by clinical correlation. Symptomatic patients may benefit from chest CT imaging and lesion biopsy to exclude infection and guide administration of immunosuppressive therapy.

Keywords: pulmonary function; imaging; natural history

The autoimmune lymphoproliferative syndrome (ALPS) is a disorder of impaired lymphocyte apoptosis associated with defects in the CD95 signaling cascade (1, 2). Lymphadenopathy, splenomegaly, and autoimmune cytopenias are typical in the clinical presentation of ALPS and are caused by unregulated lymphocyte proliferation. Lymphoproliferation in ALPS is not directly related to the development of infection or malignancy, though patients are at increased risk for B-cell lymphomas (3, 4). ALPS typically presents in early childhood, and patients may experience fatigue, pallor, icterus associated with hemolytic anemia, or bruising and hemorrhages due to thrombocytopenia. Lung manifestations of ALPS have not previously been well described.

Criteria for the diagnosis of ALPS were created by consensus in 1999 and revised in 2010 by a group of international investigators. The diagnostic criteria are summarized in Table 1 (2). The immunophenotypical hallmark of ALPS is the expansion of "double-negative" T-cell receptor $\alpha\beta^+$ T lymphocytes that lack both CD4 and CD8 markers such that they compose more than 1.5% of all circulating lymphocytes. The exact pathophysiological role for double-negative T-cell receptor $\alpha\beta^+$ T lymphocytes in the development of ALPS is unknown, but because their presence is seldom seen in other hematological disorders, they are thought to be pathognomonic for ALPS (5).

Genetic diagnostic techniques have allowed for ALPS to be divided into multiple subclassifications based on the identification of specific defects in the apoptotic pathway. ALPS-FAS involves either homozygous or heterozygous germline mutations in the *FAS* gene; ALPS-sFAS involves somatic mutations to *FAS*; ALPS-FASLG involves mutations to the FAS ligand; and ALPS-CASP10 involves germline mutations to the gene encoding for *caspase* 10. Autoimmune lymphoproliferative syndrome with undetermined genetic defect (ALPS-U) is a term used to categorize patients who fulfill the diagnostic criteria for ALPS but have an as yet undetermined genetic mutation. Mutations in the *FAS* gene associated with defects in lymphocyte apoptosis are the most commonly recognized causes of ALPS, and most published experience related to ALPS stems from the natural history studies of these patients (4). While ALPS is rare, its true prevalence is

unknown because many cases are likely undiagnosed due to variable phenotypic expression (6).

Despite the extensive underlying lymphoproliferative abnormalities and perturbations of the immune system, the clinical course of ALPS is typically relatively benign. With the exception of patients who undergo splenectomy, serious infectious consequences of ALPS-associated immunosuppression are surprisingly uncommon (4, 7, 8). A significant number of patients with ALPS do not require intervention for the asymptomatic lymphadenopathy and splenomegaly seen in this population. In fact, both of these conditions often appear to improve with age (9). Despite this, patients with ALPS are regularly followed for evidence of disease progression (including development of lymphoma) and often undergo serial radiography. During such routine monitoring, abnormal radiographic results with unclear clinical significance can be encountered.

In this article, we report lung manifestations based on routine and clinically indicated computed tomographic (CT) scans of the chest in the largest known cohort of patients with ALPS. We also report the histopathological findings associated with CT scan findings and the associated

pulmonary signs, symptoms, and clinical courses. Most of the patients with ALPS with lung lesions described here do not have a *FAS* mutation to account for their symptoms.

Methods

Subjects
Patients with chest CT scan abnormalities were identified from a database of patients with ALPS enrolled in a natural history protocol approved by an institutional review board of the National Institutes of Health (www.clinicaltrials.gov identifier NCT00001350). The ALPS cohort at the National Institutes of Health is the largest collection of patients assembled for study of this disease. Of 839 patients followed in the cohort, 584 are either healthy relatives of patients with confirmed ALPS or have an unclassified disease with ALPS-like features.

Patients in the ALPS cohort were followed at regular intervals (one or two visits yearly and as needed for evaluation of clinical change) that included clinical and laboratory evaluations. In addition, CT scans of the neck, chest, abdomen, and pelvis were obtained approximately every 2 years to monitor for the development of splenomegaly, mediastinal

Table 1. 2009 Revised diagnostic criteria for autoimmune lymphoproliferative syndrome

A diagnosis of ALPS is based on the presence of both required criteria and at least one primary accessory criterion. A probable case of ALPS is suspected in the presence of both required criteria and one secondary accessory criterion.

Required criteria
1. More than 6 mo of nonmalignant, noninfectious lymphadenopathy and/or splenomegaly
2. Elevated $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ double-negative cells ($\geqslant$1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes)

Accessory criteria
Primary
1. Evidence of defective lymphocyte apoptosis
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or *CASP10* genes
Secondary
1. sFASL levels >200 pg/ml *or*
   a. Plasma IL-10 levels >20 pg/ml *or*
   b. Vitamin B_{12} levels >1,500 ng/L *or*
   c. Plasma IL-18 levels >500 pg/ml
2. Typical immunohistological findings as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias in the presence of elevated IgG levels
4. Family history of nonmalignant and/or noninfectious lymphoproliferation with or without accompanying autoimmunity

Definition of abbreviations: ALPS = autoimmune lymphoproliferative syndrome; sFASL = soluble FAS ligand; TCR = T-cell receptor.
Adapted by permission from Reference 31.

lymphadenopathy, and evidence of lymphoma. CT scans were also obtained for clinical indication at the discretion of care providers. CT examinations were acquired with the following scanners, based on availability: SOMATOM Definition Flash (Siemens Healthcare, Malvern, PA), Brilliance 16 (Philips Healthcare, Bothell, WA), Aquilion One (Toshiba America Medical Systems, Tustin, CA), Siemens Definition (Siemens Healthcare USA, Malvern, PA), or LightSpeed (GE Healthcare, Chicago, IL). We conducted a retrospective review of the data available from January 1, 1993, to December 31, 2013, of the 234 patients with clinical data and a confirmed diagnosis of ALPS.

Data Extraction

Demographic and clinical information were collected by chart review. Clinical information, including documentation of bronchoalveolar lavage (BAL), lung biopsy, culture (blood, sputum, and/or lavage) and sensitivity, respiratory symptoms, 6-minute walk tests (6MWTs), and pulmonary function tests (PFTs) performed for clinical indications, was reviewed. Lung function was assessed and categorized as obstructive, restrictive, mixed, or no significant abnormality according to the American Thoracic Society/European Respiratory Society recommendations (10, 11). Respiratory manifestations were captured and categorized according to chart documentation. Patient management was ascertained as immunosuppression, antibiotics, or observation. Outcome was assessed as improved, unchanged, or worsened. Findings were retrospectively reviewed in multidisciplinary sessions with radiology, pathology, pulmonology, and infectious disease physicians.

Chest Imaging

Abnormal CT images from patients with ALPS were identified for further study. A radiologist (L.R.F.) reviewed all abnormal scans in a random fashion and rated each scan with a subjective severity scale of 0–3 (0 = not present, 1 = mild, 2 = moderate, 3 = severe) (12) for the following characteristics: ground-glass opacities, tree-in-bud nodules, larger nodules (3–10 mm and not in tree-in-bud distribution), consolidation, septal and nonseptal lines, cavitation, cysts, bronchiectasis, and overall disease. The radiologist was blinded to identifying information, including patient

information and scan date. Additionally, five randomly selected scans were inserted into the reviewer's queue and repeated for internal validation.

Statistical Analysis

Baseline characteristics between subjects with ALPS with pulmonary abnormalities and those without pulmonary abnormalities on CT scans were compared using Fisher's exact test (for discrete variables) and Wilcoxon's rank-sum test (for continuous variables). Among the subjects with pulmonary abnormalities, results of baseline PFTs and computed tomography were summarized. Spearman's correlations were estimated to evaluate the relationship between chest CT scan patterns and the percent predicted diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) corrected for Hb. A Bonferroni correction was applied to account for multiplicity.

To explore the clinical course, the proportion of patients managed with antibiotics, immunosuppression, or observation, as well as the proportion of patients whose clinical status improved, did not change, or worsened, was determined. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.1.2 software.

Results

Clinical data, including CT images of the chest, were available for 234 (92%) of 255 of the patients with ALPS. Approximately 8% (n = 18) of patients in our cohort had at least one chest CT examination with abnormal lung findings that necessitated further clinical evaluation. The time from onset of ALPS-defining symptoms to first abnormal chest CT examination ranged from 1 to 37 years, with an average of 12.7 years.

Characteristics of Patients with Abnormal Chest Imaging

Table 2 shows the characteristics of each of the 18 patients with ALPS with abnormal chest computed tomography findings. Four were female, and 14 were male. Fourteen carried a diagnosis of ALPS-U, three patients had ALPS-FAS, and one had ALPS-FASLG. Notably, 78% of patients with lung lesions had ALPS-U, compared with only 14% of patients without lung lesions (Table 3). Sixteen of the 18 patients

with lung lesions were asymptomatic; 2 (11%) had associated dyspnea and/or desaturation on room air. All 18 were nonsmokers.

Of the 18 patients with radiographic lung lesions, 12 patients had pathology results from pulmonary specimens. Specimens were collected when (1) $D_{L_{CO}}$ was low, (2) there was concern about progressive pulmonary deterioration, or (3) there was concern about infection in the setting of immunosuppressive administration. Eight patients contributed multiple biopsy and/or BAL specimens. Histopathology revealed five patients with lymphocytic infiltrates, three with pneumonitis, three with chronic inflammation, two with organizing pneumonia, two with follicular bronchiolitis, and two with granulomatous changes. Multiple findings were possible for each biopsy. An example of corresponding chest computed tomography and histopathology findings is shown in Figure 1.

None of the patients demonstrated concurrent infection on initial workup or during follow-up. Evaluations included bacterial, fungal, and mycobacterial cultures; viral polymerase chain reaction of BAL fluid; and cytopathology. None of the patients were treated with antibiotics. Immunosuppressive medications, including corticosteroids, mycophenolate mofetil, and azathioprine, were safely used to manage nine (50%) of the patients during the study period. An example of pre- and post-treatment findings is shown in Figure 2. Improvement in computed tomography findings and symptoms was not always permanent; waxing and waning of lesions was observed.

Fifteen of the 18 patients had PFTs ordered for clinical indications. PFTs were not consistently coordinated with CT scanning; seven patients had their PFTs performed on the same day as a CT scan, whereas six patients had their testing performed more than 1 year after a chest CT scan. All 15 patients who underwent testing had available spirometry, and 14 had lung volumes; 6 showed a restrictive pattern, 2 had obstructive patterns, and 7 had no significant abnormality. Of the 15 patients with $D_{L_{CO}}$, 12 (67%) had abnormal values. Eleven patients contributed 6MWT data, and four of those manifested significant oxyhemoglobin desaturation (>3% decline) with exertion (13). Baseline pulmonary

Table 2. Patient characteristics

Patient	Sex	ALPS Subtype	Age at First Abnormal CT (yr)	D_{CO} Corrected for Hb* (% predicted)	Lung Physiology	Lung CT Patterns	Pathology Findings	Presenting Symptoms	Treatment for Pulmonary Disease	Outcome (yr of follow-up)
1	M	ALPS-U	21	96	Obstructive†	Bronchiectasis, cyst, nodules not TIB, septal lines	NA	Asymptomatic	Continued on same dose of MMF	No change (18)
2	M	ALPS-U	14	59	No significant abnormality	Bronchiectasis, consolidation, GGO, nodules not TIB, septal lines, TIB	Interstitial lymphoplasmacytic infiltrate‡ (TTB)	Asymptomatic	None	No change (12)
3	M	ALPS-U	11	58	Restrictive	Bronchiectasis, GGO, nodules not TIB, septal lines, TIB	NA	Asymptomatic	None	No change (27)
4	M	ALPS-U	17	68	Restrictive	Bronchiectasis, cyst, GGO, nodules not TIB, septal lines, TIB	Patchy lymphocytic infiltrate‡ (TBB, BAL)	Asymptomatic	Continued on same dose of MMF, given pulse dose steroids	CT-based improvement (27)
5	F	ALPS-U	10	61	Restrictive	Bronchiectasis, consolidation, GGO, nodules not TIB, septal lines, TIB	Organizing pneumonia with BOOP-like changes‡ (TBB)	Asymptomatic	Prednisone, azathioprine, MMF	Persistent diffusion defect, 6MWT and CT-based improvement (6)
6	M	ALPS-U	15	57	Restrictive†	Bronchiectasis, cavitation, consolidation, GGO, nodules not TIB, septal lines, TIB	Follicular bronchiolitis‡ (TBB)	Asymptomatic	Continued on same dose of MMF and methotrexate, given pulse dose steroids	No change in symptoms, progressive decline in D_{CO} (24)
7	F	ALPS-U	7	NA	NA	GGO, TIB, nodules not TIB	Follicular bronchiolitis, pneumonitis characterized by inflammation and lymphocytes in bronchioles, BOOP-like changes, EBER-negative‡ (TTB)	Asymptomatic	None	Pulmonary outcome unknown; patient deceased (4)
8	F	ALPS-FAS	39	72	No significant abnormality	Bronchiectasis, consolidation, cyst, GGO, nodules not TIB, septal lines, TIB	Granulomatous and chronic inflammation (TTB)	Asymptomatic	None	No change (53)
9	M	ALPS-FAS	36	NA	NA	Cyst, GGO	NA	Asymptomatic	None	No change (47)
10	M	ALPS-U	14	70	No significant abnormality	GGO, TIB, nodules not TIB, bronchiectasis	NA	Asymptomatic	Continued on same dose of MMF	No change (16)
11	M	ALPS-U/STAT3 GOF mutation	22	50	Restrictive	Bronchiectasis, consolidation, GGO, nodules not TIB, septal lines, TIB	Dense fibrous scar tissue, minimal chronic inflammation (TTB)	Asymptomatic	Continued on same dose of MMF	No change in symptoms, D_{CO} improved (21)
12	M	ALPS-U	14	62	No significant abnormality	GGO, TIB, nodules not TIB, bronchiectasis	NA	Asymptomatic	Continued on same dose of sirolimus	No change in symptoms, CT-based improvement (3)
13	M	ALPS-U	30	60	No significant abnormality	Bronchiectasis, consolidation, GGO, nodules not TIB, septal lines, TIB	Mild chronic inflammation of bronchial wall, mild chronic interstitial pneumonitis (TBB)	Asymptomatic	None	No change (8)

(Continued)

Table 2. (*Continued*)

Patient	Sex	ALPS Subtype	Age at First Abnormal CT (yr)	D_{CO} Corrected for Hb* (% predicted)	Lung Physiology	Lung CT Patterns	Pathology Findings	Presenting Symptoms	Treatment for Pulmonary Disease	Outcome (yr of follow-up)
14	F	ALPS-U	12	103	Obstructive	Bronchiectasis, consolidation, GGO, nodules not TIB, septal lines, TIB	Patchy lymphocytic infiltrate, no evidence of double-negative T cells‡ (TBB, BAL)	DOE	MMF increased	D_{CO} improved (15)
15	M	ALPS-U	6	NA	NA	GGO, TIB, septal lines	Focally necrotizing granulomatous pneumonitis, interstitial lymphocytic infiltrate, small necrotizing granulomas (TBB)	Asymptomatic	None	NA (4)
16	M	ALPS-FAS	22	77	No significant abnormality	Nodules not TIB	NA	Asymptomatic	None	NA (22)
17	M	ALPS-U	13	41	Restrictive†	GGO, nodules not TIB, septal lines, TIB	Patchy T-cell–predominant lymphocytic infiltrate‡ (TBB, BAL)	Dyspnea, desaturation on room air	MMF, prednisone	D_{CO} and symptoms wax and wane (14)
18	M	ALPS-FASLG	16	64	No significant abnormality	Bronchiectasis, GGO, nodules not TIB, septal lines, TIB	Nondiagnostic‡ (TBB, BAL)	Asymptomatic	None	No change in symptoms, progressive decline in D_{CO} (24)

Definition of abbreviations: ALPS-U = autoimmune lymphoproliferative syndrome with undetermined genetic defect; BAL = bronchoalveolar lavage; BOOP = bronchiolitis obliterans organizing pneumonia; CT = computed tomographic scan; D_{CO} = diffusing capacity of the lung for carbon monoxide; DOE = dyspnea on exertion; EBER = Epstein-Barr virus–encoded small RNA; GGO = ground-glass opacity; GOF = gain of function; MMF = mycophenolate mofetil; 6MWT = 6-minute walk test; NA = not available; STAT3 = signal transducer and activator of transcription 3; TBB = transbronchial biopsy; TIB = tree-in-bud pattern; TTB = transthoracic biopsy.
One patient was reclassified from ALPS-U to STAT3 gain-of-function mutation.
*First D_{CO} measurement was obtained after CT abnormalities were detected.
†Exertional dyspnea greater than 3% in 6-minute walk test.
‡Pathology reviewed at the National Institutes of Health.

function and 6MWT data are summarized in Table 4. Three asymptomatic patients had no PFTs done.

Chest CT Image Findings

A total of 60 chest CT scans were obtained on the 18 patients with interstitial lung lesions. The following patterns were seen in these patients: ground-glass opacities (n = 16), larger nodules (n = 16), tree-in-bud nodules (n = 15), bronchiectasis (n = 14), septal thickening (n = 13), consolidation (n = 7), cysts (n = 4), and cavitation (n = 1). The average overall severity score was 1.65 (range, 0–3). Data summarizing the presence or absence of each pattern, along with distribution of severity scores, are shown in Table 5. Most scans demonstrated multiple patterns. When all patterns were considered, six patients had a maximum severity of 1, six had a maximum severity of 2, and six had a maximum severity of 3. Repeat scoring of five randomly selected scans revealed acceptable internal consistency: 64% (29 of 45) of scored features remained unchanged, with the severity of the remaining 36% (16 of 45) increasing or decreasing by only 1 unit.

Among patients with lung lesions, no correlation was found between the degree of abnormality of lesion characteristics visualized by chest computed tomography and pulmonary function status. Spearman's correlations were all nonsignificant.

Discussion

In this retrospective evaluation of a large cohort of patients with ALPS, we characterized the pulmonary manifestations in patients with ALPS with chest CT scan abnormalities. Most patients had no pulmonary symptoms. Those with evidence of symptomatic progression improved while on immunosuppressive therapy. Ground-glass opacities and larger nodules were the most common computed tomography findings, followed by tree-in-bud nodules, then bronchiectasis and septal thickening. Despite presenting with computed tomography findings that can be suggestive of infection, none of the 18 patients with ALPS with chest computed tomography changes had clinical evidence including systemic symptoms to support active infection, even while receiving immunosuppressive medications. Our data show that the disease

Table 3. Demographics of patients with confirmed autoimmune lymphoproliferative syndrome

Patient Characteristics	All Patients with ALPS (n = 234)	Patients with ALPS without Lung Lesions (n = 216)	Patients with ALPS with Lung Lesions (n = 18)	P Value
Sex				0.3069
Male	151 (64.5%)	137 (63.4%)	14 (77.8%)	
Female	83 (35.5%)	79 (36.6%)	4 (22.2%)	
Median age at presentation, yr (range)	14 (1–63)	13 (1–63)	14 (6–39)	
ALPS subclass				0.0000
ALPS-U	45 (19.2%)	31 (14.4%)	14 (77.8%)	
ALPS-FAS	163 (69.6%)	160 (74.1%)	3 (16.7%)	
ALPS-FASLG	1 (0.4%)	0 (0.0%)	1 (5.6%)	
ALPS-sFAS	19 (8.1%)	19 (8.8%)	0 (0.0%)	
ALPS-CASP10	6 (2.6%)	6 (2.8%)	0 (0.0%)	

Definition of abbreviations: ALPS = autoimmune lymphoproliferative syndrome; ALPS-CASP10 = ALPS with mutations in *caspase* 10; ALPS-FAS = ALPS with homozygous or heterozygous mutations in *FAS*; ALPS-FASLG = ALPS with mutations in the FAS ligand; ALPS-sFAS = ALPS with somatic mutations in *FAS*; ALPS-U = autoimmune lymphoproliferative syndrome with undetermined genetic defect.
Data are presented as count (percent) or median (range).

course of ALPS is variable. Observed lymphoid infiltrates are likely a nonspecific host response and reflect lymphoproliferation due to an overactive immune system.

Our findings do not necessarily mirror what has previously been reported in ALPS, as previous descriptions have been focused on ALPS-FAS (4). The ALPS-U subtype showed a disproportionate predominance among those with lung lesions. It is likely that ALPS-U includes as yet unidentified genetic diseases associated with lung lesions. To this point, one patient classified as ALPS-U during this study period was subsequently found to have a signal transducer and activator of transcription 3 (*STAT3*) gain-of-function (GOF) mutation. The patients in the recently described early-onset lymphoproliferation and autoimmunity associated with *STAT3* GOF mutations had a predominance of autoimmune cytopenias, lymphadenopathy, and hepatosplenomegaly similar to patients with ALPS, but also with striking liver disease with nodular regenerative hyperplasia and arthritis. Four of the 13 patients had lung manifestations ranging from nodules to lymphocytic interstitial pneumonitis. However, there was also a predominance of severe or recurring pulmonary and extrapulmonary infections not seen in the patients we describe here (14).

Other recently described ALPS-like disorders of immune regulation associated with lung manifestations result from mutations in the phosphatidylinositol-3-OH kinase (*PIK3CD*), cytotoxic T-lymphocyte antigen 4 (*CTLA4*), and LPS-responsive and beige-like anchor (*LRBA*) genes. GOF mutations in *PIK3CD* encoding for PI3K110δ or in-frame deletions of *PIK3R1* leading to GOF in PI3K110δ were manifested clinically by recurring sinopulmonary infections, lymphadenopathy, cytopenias, cytomegalovirus and/or Epstein-Barr viremia, and predisposition to lymphoma
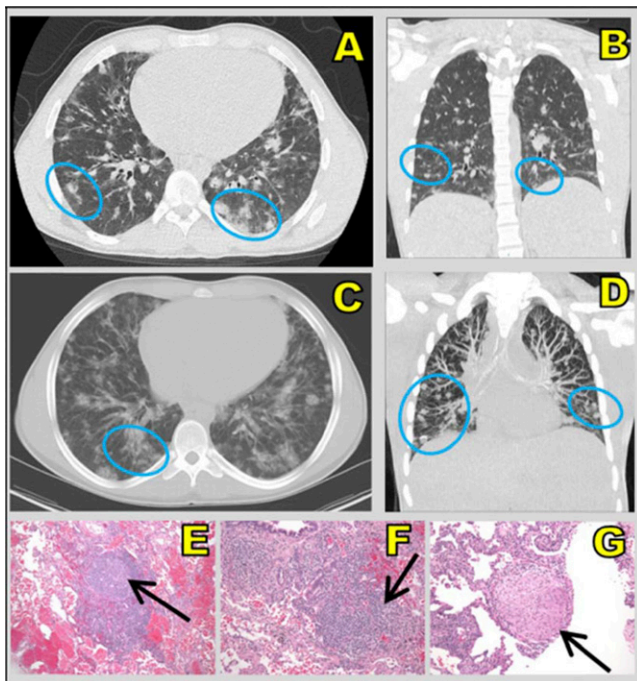

Figure 1. (*A* and *C*) Axial and (*B* and *D*) coronal computed tomographic scans show ill-defined, diffuse ground-glass nodules (*blue ovals*), which are common in fungal infection, in the lower lobes. Right lung biopsy (hematoxylin and eosin stain; original magnification, ×10) shows (*E*) a nodular lymphoid infiltrate with a prominent "naked" reactive germinal center, (*F*) a peribronchial lymphocytic infiltrate, and (*G*) a nonnecrotizing granuloma composed of epithelioid and rare multinucleated giant cells (*black arrows*) associated with interstitial lymphocytic infiltrate. This patient (patient 6 from Table 2) denied pulmonary symptoms and is an active hockey player.
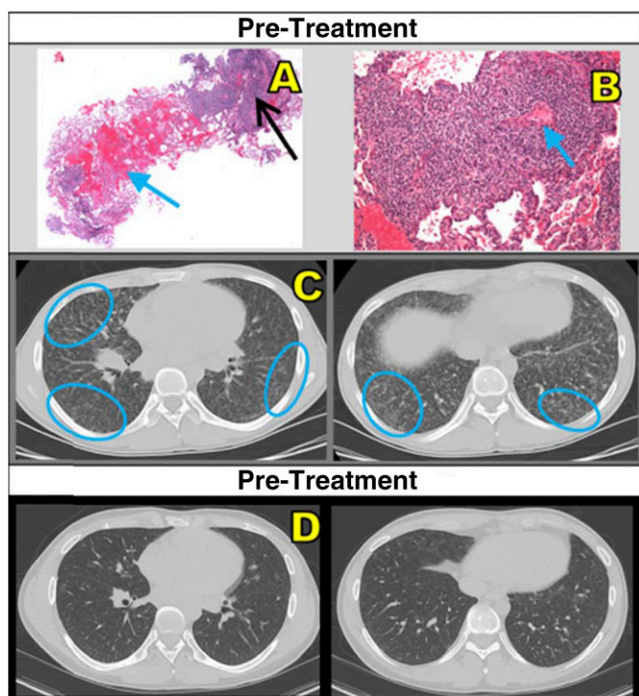
Figure 2. (A) Core lung biopsy (hematoxylin and eosin stain; original magnification, ×2) shows intraalveolar hemorrhage (blue arrow) and patchy peribronchial/perivascular lymphocytic infiltrate (black arrow). (B) Dense lymphocytic infiltrate and interstitial widening, sparing blood vessels (blue arrow) (original magnification, ×10). (C) Pretreatment computed tomographic scans show miliary-like, small, ill-defined, diffuse micronodular ground-glass nodules (blue ovals) in right middle and bilateral lower lobes. (D) This patient (patient 4 from Table 2) showed interval improvement after treatment with mycophenolate mofetil and high-dose methylprednisolone.

(15–17). Nodular lymphoid hyperplasia of mucosal surfaces including the airways, bronchiectasis, atelectasis, and consolidation related to airway narrowing and recurring infection are also seen in this disease. In a lesser number of patients, alveolitis features and lymphocytic infiltrates have been recognized.

Patients with *CTLA4* deficiency have presented with autoimmune cytopenias; organomegaly; hypogammaglobulinemia; endocrinopathies; and lymphocytic infiltration of the gut, brain, and lungs. Recurring respiratory tract infections and granulomatous lymphocytic interstitial lung disease have been reported in a majority of patients, while bronchiectasis has been less common (18, 19). Finally, patients with *LRBA* deficiency, which leads to defective and diminished CTLA-4 expression, typically have evidence of immune dysregulation, organomegaly, and hypogammaglobulinemia, with about one-half presenting with lung involvement. The latter included persistent lymphocytic infiltrates, bronchiectasis, and granulomatous inflammation; about one-third were diagnosed with granulomatous lymphocytic interstitial lung disease. Recurring infections were seen in 15 (71%) of 22 patients, including 10 with upper and 9 with lower respiratory tract infections (20).

Among patients with ALPS with lung lesions, computed tomography–based lesion classification did not correlate with functional status. Decisions as to whether it is appropriate to observe a patient, administer antibiotics, or administer immunosuppression must take into consideration the patient's other ALPS manifestations, such as cytopenias, clinical status, and progression of symptoms or lung function abnormalities. In many cases, treatment administered for other disease aspects (e.g., pulse doses of corticosteroids and mycophenolate mofetil for cytopenias) resulted in improvement of radiographic abnormalities.

Imaging can influence management needed to address pulmonary symptoms in addition to describing the extent or progression of lung lesions over time (21); computed tomography findings in combination with pathology results were essential in ruling out infection and thus in guiding administration of immunosuppressive therapy in our cohort. However, the need for treatment (pulse dose prednisone followed by steroid-sparing measures) was ultimately determined by clinical status and symptoms. While all patients with suspected lymphoproliferative disorders of uncertain etiology should undergo baseline imaging to determine distribution and

Table 4. Summary of baseline pulmonary function test results of patients with lung lesions and autoimmune lymphoproliferative syndrome

	Number of Patients Tested	Mean Values	95% CI
FEV_1, L/s	15	2.94	(2.17–3.71)
Percent predicted		84.87	(74.77–94.96)
FVC, L/s	15	3.51	(2.52–4.50)
Percent predicted		86.73	(75.69–97.77)
FEV_1/FVC ratio	15	0.86	(0.81–0.91)
Total lung capacity, L	14	4.96	(3.72–6.19)
Percent predicted		89.14	(82.61–95.68)
Residual volume, L	14	1.29	(0.91–1.67)
Percent predicted		102.07	(79.79–124.35)
$D_{L_{CO}}$-corrected Hb	15	23.06	(18.01–28.12)
Percent predicted		69.77	(60.32–79.22)
6-minute walk distance, m	11	539.82	(486.32–593.32)
Prewalk saturation, %	11	98	(96.35–99.65)
Postwalk saturation, %	11	95	(90.67–99.33)

Definition of abbreviations: CI = confidence interval; $D_{L_{CO}}$ = diffusing capacity of the lung for carbon monoxide.

Table 5. Severity scores for chest computed tomography findings

Pattern	Presence on Any Scan (n = 18 patients)	Highest Severity Score (n = 18 patients)			
		0	1	2	3
Bronchiectasis	14 (77.8)	4 (22.2)	11 (61.1)	3 (16.7)	0 (0.0)
Cavitation	1 (5.6)	17 (94.4)	1 (5.6)	0 (0.0)	0 (0.0)
Consolidation	7 (38.9)	11 (61.1)	2 (11.1)	4 (22.2)	1 (5.6)
Cyst	4 (22.2)	14 (77.8)	3 (16.7)	1 (5.6)	0 (0.0)
Ground-glass opacity	16 (88.9)	2 (11.1)	7 (38.9)	7 (38.9)	2 (11.1)
Larger nodules	16 (88.9)	2 (11.1)	7 (38.9)	4 (22.2)	5 (27.8)
Septal thickening	13 (72.2)	5 (27.8)	9 (50.0)	3 (16.7)	1 (5.6)
Tree-in-bud nodules	15 (83.3)	3 (16.7)	8 (44.4)	6 (33.3)	1 (5.6)

Sixty scans were available for the 18 patients with lung lesions; each patient could have multiple scans. The first column shows how many patients manifested a particular pattern on any one of their computed tomographic scans. The severity score columns show the highest severity score for each pattern for each patient across all of their scans. Severity was rated on a scale of 0–3 for each pattern on each chest computed tomographic scan. If all scans for a patient had a severity of 0 for a particular pattern, that pattern was considered absent. If any scan had had a nonzero score for a pattern, that pattern was considered present.

extent of lung involvement, routine and repeated chest CT scans are unlikely to affect management in the absence of signs or symptoms.

Radiographic findings seen in patients with ALPS are also seen in other disorders of the immune system. Common variable immune deficiency (CVID), also characterized by lymphoproliferation and autoimmune cytopenias, can be associated with chronic pulmonary disease (22–24). Patients with CVID may have similar, asymptomatic chest radiographic findings. In their study of adult patients with CVID, Maarschalk-Ellerbroek and colleagues found that almost all patients screened with chest computed tomography displayed previously unknown evidence of pulmonary abnormalities (25). Although those authors found that a diverse number of abnormal chest computed tomography findings correlated with specific T- and B-cell profiles, the computed tomography findings did not correlate with PFT results. van de Ven and colleagues also reported that abnormal immune function may contribute to development of radiographic changes in the pediatric CVID population. In that study, patients with CVID with a history of chronic structural airway disease and radiographic evidence of interstitial and/or parenchymal lung disease had distinct immunological profiles despite having no differences in PFT results (26). While an aberrant immune response may provide a plausible explanation for CT scan abnormalities in patients with CVID (27), a similar rationale could also be applied to explain the presence of

chest computed tomography changes in patients with ALPS.

Some patients with ALPS can have varying degrees of hypogammaglobulinemia similar to those of CVID patients or following exposure to rituximab, an anti-CD20 monoclonal antibody (28). Five of our 18 patients with ALPS and lung lesions had IgG levels lower than 5 g/L, a required criterion for CVID, at one or more time points. While such IgG levels are consistent with a possible diagnosis of CVID (29), evaluation of complete CVID criteria was not possible, owing to data limitations. It should also be noted that 16 of our 18 patients received intravenous immunoglobulin and 6 received rituximab during the study period. Prospective collection of such data may provide insight to the link between ALPS and CVID or point toward one of the recently described genetically defined immune regulation disorders. Research suggesting that patients with CVID and patients with ALPS may share characteristic B-cell abnormalities provides further evidence that CVID and ALPS may have immunological overlap and may represent different aspects of a similar pathological entity (30).

Limitations

This study was limited intrinsically by the small sample size of the ALPS population with CT scans. Although our institution has the largest ALPS cohort, ALPS remains an orphan disease. Furthermore, this was a retrospective rather than a prospective study. *A priori* standardization of CT scan

frequency and technique, a standardized procedure to rule out suspected infections, and blinded CT scan interpretation criteria could produce more robust results. Evolving ALPS disease classification also engenders uncertainties; with recognition of new ALPS-related immune disorder groups as additional genetic data becomes available, some patients may be reclassified and thus impact the correlations.

Last, PFT data were not available for all patients with ALPS, because routine PFTs were not part of the ALPS natural history cohort protocol; PFTs were collected per clinical indication, and thus their presence in the database is correlated with symptoms. For instance, 9 of the 12 patients with follow-up $D_{L_{CO}}$ values manifested a subsequent decrease. It may have been that these patients had a clinical decline that precipitated $D_{L_{CO}}$ evaluation or that the change reflected progression of their lung pathology related to ALPS. Thus, PFT comparisons cannot be made between patients with and without lung lesions or between patients with and without symptoms, owing to inherent bias. Standardized prospective collection of PFT data in all patients would have facilitated this evaluation.

Conclusions

Patients with ALPS can develop protean chest radiographic findings, which may overlap with those seen in pulmonary infection. Lung lesions are likely a manifestation of the overall aberrant lymphoproliferation rather than of

specific pulmonary disease. Most patients with radiographic abnormalities were classified as ALPS-U, were asymptomatic (89%), and had decreased diffusing capacity. The possibility of other genetically defined immune dysregulation disorders with similar lung manifestations should be considered. Management of patients with ALPS with incidental lung lesions identified by computed tomography

should be guided by clinical status. Symptomatic patients or those with declining lung function may benefit from chest computed tomography and lesion biopsy to rule out infection and guide administration of immunosuppressive therapy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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