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Parenchymal lung involvement in adult-onset Still disease

A STROBE-compliant case series and literature review

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Abstract

Parenchymal lung involvement (PLI) in adult-onset Still's disease (AOSD) has seldom, if ever, been studied. We examine here retrospective cohort AOSD cases and present a review of the literature (1971–2014) on AOSD-related PLI cases.

Patients with PLI were identified in 57 AOSD cases. For inclusion, the patients had to fulfill Yamaguchi or Fautrel classification criteria, show respiratory symptoms, and have imaging evidence of pulmonary involvement, and data allowing exclusion of infectious, cardiogenic, toxic, or iatrogenic cause of PLI should be available. This AOSD + PLI group was compared with a control group (non–PLI-complicated AOSD cases from the same cohort).

AOSD + PLI was found in 3 out of the 57 patients with AOSD (5.3%) and the literature mentioned 27 patients. Among these 30 AOSD + PLI cases, 12 presented an acute respiratory distress syndrome (ARDS) and the remaining 18 another PLI. In the latter, a nonspecific interstitial pneumonia computed tomography pattern prevailed in the lower lobes, pulmonary function tests showed a restrictive lung function, the alveolar differential cell count was neutrophilic in half of the cases, and the histological findings were consistent with bronchiolitis and nonspecific interstitial pneumonia. Corticosteroids were fully efficient in all but 3 patients. Ten out of 12 ARDS cases occurred during the first year of the disease course. All ARDS-complicated AOSD cases received corticosteroids with favorable outcomes in 10 (2 deceased). Most PLIs occurred during the systemic onset of AOSD.

PLI may occur in 5% of AOSDs, of which ARDS is the most severe. Very often, corticosteroids are efficient in controlling this complication.

Abbreviations: ACPA = anticitrullinated protein autoantibody, ANA = antinuclear autoantibody, ANCA = antineutrophil cytoplasmic autoantibody, AOSD = adult-onset Still disease, ARDS = acute respiratory distress syndrome, BAL = bronchoalveolar lavage, CRP = C-reactive protein, CT = computed tomography, DLCO = diffusing capacity of the lung for carbon monoxide, ESR = erythrocyte sedimentation rate, HRCT = high-resolution computed tomography, IL = interleukin, PFT = pulmonary function test, PLI = parenchymal lung involvement, reHLH = reactive hemophagocytic lymphohistiocytosis, VC = vital capacity.

Keywords: acute respiratory distress syndrome, adult-onset Still disease, hemophagocytic lymphohistiocytosis, interstitial lung disease

1. Introduction

Adult-onset Still disease (AOSD) is a rare complex auto-inflammatory syndrome of unknown etiology. Its main clinical features are high spiking fever, evanescent salmon-pink rash, polyarthritis, sore throat, and lymphadenopathy.[1] However, the spectrums of clinical manifestations and complications of this entity are very wide.[2,3] The usual laboratory findings are disease-unspecific; they include elevated polymorphonuclear neutrophil count, high C-reactive protein (CRP) level, and high liver enzyme levels.[1,3] The combination of a 5-fold increase in serum ferritin and a glycosylated ferritin level $\leq$20% led to 93% specificity in AOSD diagnosis; nevertheless, in daily practice, this diagnosis remains one of exclusion.[4] According to recent pathophysiological findings, cohort studies, and clinical trials, 2 phenotypes of AOSD may be distinguished: a systemic pattern (monocyclic or polycyclic AOSD) and a chronic articular pattern. Both should be treated with corticosteroids and methotrexate as first disease-modifying antirheumatic drugs. In cases of refractory AOSD, more efficient treatments would be the blockade of interleukin-1 (IL-1) pathway in the systemic pattern and the blockade of IL-6 pathway in the chronic articular pattern.[3,5]

To date, few studies have focused on the visceral complications of AOSD: reactive hemophagocytic lymphohistiocytosis (reHLH)

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is the most frequent life-threatening complication of systemic AOSD, but myocarditis was also mentioned and well defined.[6–8] Besides, no study has focused yet on parenchymal lung involvement (PLI): pleuritis was mentioned in 10% to 50% of the main retrospective AOSD series,[3,9,10] but other pulmonary involvements have been reported only as isolated cases; none of the main AOSD cohorts has reported on PLI.[3]

Here, we study PLI in AOSD by reporting on 3 original cases from a cohort of 57 patients with AOSD and reviewing additional cases from the medical literature.[11]

2. Patients and methods

Cases of AOSD with PLI were identified in a retrospective cohort of 57 patients with AOSD seen in our institution (University Hospitals of Lyon, France) between 1998 and 2010.[11] In addition, we carried out a computer-assisted search for publications on AOSD with PLI in English and French exclusively. The search was made in PubMed (National Library of Medicine, Bethesda, MD), from 1971 (when AOSD was first described) to June 2014, using string [('Adult onset Still disease' or 'Adult onset Still's disease') AND ('lung involvement' or 'pulmonary involvement' or 'interstitial lung disease' or 'acute respiratory distress syndrome' or 'respiratory failure' or 'pneumonitis' or 'pneumonia' or 'lung')]. The reference lists of all retrieved articles were also examined for references not identified in the initial search and duplicate publications were excluded.

Patients were included in the present study whenever they fulfilled the following criteria: confirmed AOSD diagnosis (Yamaguchi or Fautrel classification criteria for AOSD)[12,13]; age >16 years at PLI onset; presence of respiratory symptoms (cough, dyspnea, abnormalities on auscultation, etc.); at least a chest radiography or high-resolution computed tomography (HRCT) showing parenchymal lung infiltrates; and available data that allow excluding infectious causes (sputum culture, bronchoalveolar lavage [BAL] fluid analysis, blood culture, serology, antibiotic treatment failure), cardiogenic causes (brain natriuretic peptide dosage, transthoracic ultrasonography), and toxic or iatrogenic causes (with special attention to methotrexate and tobacco). All other patients were excluded.

The clinical features, laboratory findings, pulmonary function test (PFT) results, BAL results, imaging results, therapeutic strategies, and outcomes were collected and analyzed independently by 2 investigators (AGC and MGV) using a standardized form. In case of mismatch, a third investigator (PS) was asked to complete the form. Finally, AOSD-associated PLI cases in the cohort were reviewed and confirmed by a multidisciplinary team that included interstitial lung disease specialists.

Patients with interstitial lung disease were classified according to the HRCT patterns and the international classification of idiopathic interstitial pneumonias. The latter distinguishes major idiopathic interstitial pneumonias (idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, respiratory bronchiolitis interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia) from rare idiopathic interstitial pneumonias (lymphoid interstitial pneumonia and fibroelastosis) and unclassifiable idiopathic interstitial pneumonias.[14] For "acute respiratory distress syndrome (ARDS)," we adopted Berlin definition.[15]

Bone marrow biopsies were performed in all atypical cases to rule out neoplastic or preneoplastic conditions that share common symptoms with AOSD (especially malignant lymphoma).

Here, AOSD + PLI cases from the cohort together with the cases found in the literature formed the "AOSD + PLI group." This group was compared with a "control group" of 54 patients with AOSD without PLI from the cohort. Between-group differences regarding a list of relevant variables were tested using Fisher exact test for categorical variables or Kruskal–Wallis test for continuous variables. A P value <0.05 was required for statistical significance. The analyses were performed with R software (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/).

According to the current French Legislation (Loi Huriet-Sérusclat 88-1138, December 20, 1988, and its subsequent amendments, text available at http://www.chu-toulouse.fr/IMG/pdf/loihuriet.pdf), an observational study that does not change routine management of patients does not need to be declared or submitted to the opinion of a research ethics board.

3. Results

3.1. Case series

Among the 57 patients with AOSD (27 men and 30 women), the mean follow-up was 8.4 years (median: 6 years), the median age at AOSD diagnosis was 36 years (range: 16–75), and the clinical and laboratory data were comparable with previous literature data.[11] Most of the patients (75%) were followed up in internal medicine or rheumatology departments. The systemic onset of the disease was more prevalent than in previous series and one-third of the patients exhibited a life-threatening complication. In this series, 3 out of 57 patients fulfilled the inclusion criteria for AOSD + PLI (cases 1–3 in Tables 1 and 2). Thus, in this AOSD series, the prevalence of AOSD + PLI was 5.3%.

3.1.1. Case 1. In September 2007, a 47-year-old smoking man was admitted to a general hospital because of a first onset of high spiking fever (40°C), chills, sore throat, headache, and chest pain. Chest radiography and transthoracic ultrasonography performed in the emergency unit yielded arguments for pleuritis and pericarditis. The total-body HRCT showed interstitial and alveolar hyperdensities in the right lower lobe together with atelectasis in the middle lobe. Laboratory data were the following: CRP—382 mg/L; high erythrocyte sedimentation rate (ESR); leukocytes—25,000/mm^3; neutrophils—22,500/mm^3; and procalcitonin—<0.1 ng/mL. Serum ferritin was 473 μg/L (norm: 20–300 μg/L). Liver function tests, lactate dehydrogenase, and β2-microglobulin were in the normal range. Pleural fluid analysis showed a sterile exudate with 60% nonaltered neutrophils. The possibility of an infectious disease was carefully investigated with blood cultures, sputum cultures, tests for *Legionella* and pneumococcal urinary antigens, and serologies; these were sterile or negative. The searches for rheumatoid factors, anticitrullinated protein autoantibodies (ACPAs), antinuclear autoantibodies (ANAs), and antineutrophil cytoplasmic autoantibodies (ANCAs) were negative. A bone marrow aspiration and a bone marrow biopsy revealed a reactive inflammatory pattern without lymphoma infiltrate or hemophagocytosis.

The PFT showed a restrictive lung function. Bronchoscopy was normal and the BAL examination was consistent with a neutrophilic alveolitis (2,000,000 cells/mL, 60% neutrophils). The transbronchial lung biopsy showed a lymphocytic bronchiolitis together with macrophagic alveolitis related to smoking.

After the failure of an empirical antibiotic therapy (amoxicillin and spiramycin), the patient was administered prednisone 1 mg/kg/d, which led to a rapid improvement in clinical,

biological, and radiological symptoms. Then, a progressive decrease of steroid dose was initiated. At 15 mg prednisone/d, the symptoms relapsed (pleuropericarditis, arthralgia, and sore throat). The laboratory data became comparable to those found at the onset of the disease, but glycosylated ferritin was significantly decreased (19%). Thus, the diagnostic criteria for AOSD were fulfilled and the lung involvement was deemed AOSD-linked. Corticosteroid dose was increased and colchicine, intravenous immunoglobulins, and methotrexate were successively given to taper prednisone dosages. The disease relapsed 3 times between 2007 and 2011. Finally, remission was obtained with prednisone 5 mg/d and methotrexate 20 mg/wk. The patient is currently asymptomatic and HRCT and PFT are totally normalized.

3.1.2. Case 2. A 64-year-old man was referred to our center in 2002. He had no particular medical history and was not a smoker. He had suffered, since 1999, from an intermittent biopsy-proven neutrophilic dermatitis considered as an atypical Sweet syndrome. He had during the last few months a transient rash, an intermittent fever (38–39°C), sweats, a 6-kg weight loss, sore throat, dysphonia, cough with mucopurulent sputum, arthralgia, and lymphadenopathy. He has been successfully treated with antibiotics and corticosteroids.

The HRCT showed bilateral confluent hyperdensities consistent with peribronchovascular micronodules, ground-glass hyperdensities, and alveolar condensation, together with 2 excavated lesions in the left lower lobe. This was associated with a mild bilateral pleural effusion and mediastinal lymphadenopathy.

The laboratory data were the following: CRP—158 mg/L; high ESR; procalcitonin—<0.1 ng/mL; hemoglobin—95 g/L; leukocytes—5500/mm^3 (64% neutrophils); platelets—220,000/mm^3; serum ferritin—1432 μg/L; and 29% glycosylated ferritin. As in case 1, serology, blood culture, and BAL culture excluded infection. The bone marrow biopsy revealed a nonspecific inflammatory reaction without hemophagocytosis or malignant lymphoma infiltration. The searches for rheumatoid factors, ACPA, ANCA, and ANA were negative.

The PFT showed the following: vital capacity (VC)—2.71 L (71%); forced expiratory volume in 1 second/VC—78%; and diffusing capacity of the lung for carbon monoxide (DLCO)—85%. Bronchoscopy showed an erosive bronchitis and bronchial biopsies revealed a nongranulomatous ulcerated bronchitis. The BAL content was 486 cells/mm^3 with 95% neutrophils.

An empirical antibiotic therapy (ceftriaxone and spiramycin) was not beneficial. Because AOSD was suspected, a 1 mg/kg/d prednisone treatment was started. This treatment proved highly efficient; all the above-described symptoms regressed. Chest computed tomography (CT) reversed to normal after 2 months of treatment. However, the patient developed a steroid dependence at 15 mg/d prednisone. Colchicine and then hydroxychloroquine was added as steroid-sparing treatment. During the following 3 years, 5 relapses of subacute interstitial lung disease occurred when corticosteroids were tapered below 10 mg/d but resolved with higher dosage. Three years later, the pulmonary functional tests were recovered: VC—2.71 L (71%); forced expiratory volume in 1 second/VC—78%; and DLCO/alveolar volume: 82%. During the following years, the lung involvement did not relapse but the patient developed a chronic reHLH. He was started on intravenous immunoglobulins and azathioprine. Infliximab 5 mg/kg was also introduced in 2007 but did not allow controlling the disease; the patient remained steroid-dependent at 20 mg/d prednisone. In 2011, the patient died from myocardial infarction.

3.1.3. Case 3. In April 2006, a 42-year-old man with a history of heroin abuse and ongoing substitution treatment, cured hepatitis C, and left ulnar osteitis presented with cough and dyspnea. A 5-day treatment with amoxicillin–clavulanate and prednisone was inefficient. Two days later, he exhibited fever (39°C), polyarthralgia, and myalgia. A CT showed bilateral axillary and mediastinal lymphadenopathy together with a right segmental atelectasis. Finally, the progression was favorable after switching for pristinamycin.

In June 2006, the patient was referred to our center after a 7-kg weight loss during the last 2 months, recurrent fever, cough, and New York Heart Association-IV dyspnea. The clinical examination revealed mild edema of the lower limbs, hepatojugular reflux, oligoarthritis of the knees and left wrist, transient nonpruritic rash of the trunk, and cervical lymphadenopathy. The laboratory findings were the following: CRP—250 mg/L; high ESR; leukocytes—19,230/mm^3; neutrophils—17,210/mm^3; fibrinogen—7 g/L; prothrombin time—52%; creatinine—60 μmol/L; elevated transaminases (3 times the normal values); serum ferritin—19,000 μg/L; and glycosylated ferritin—<5%. The bone marrow biopsy was consistent with an inflammatory reactive hyperplasia without hemophagocytosis or lymphomatous infiltrate.

The HRCT showed bilateral pleural and pericardial effusion with mediastinal infracentimetric lymph nodes, parenchymal condensation in the middle lobe and lingula with bronchogram, and passive atelectasis of the lower lobes. The transthoracic ultrasonography confirmed the right-chamber-compressing circumferential pericardial effusion, which was treated by surgical pericardial drainage.

The BAL was hypercellular with 90% neutrophils. The standard cultures and acid-fast bacilli smear and culture were negative. Serology (including HIV testing) and blood cultures ruled out the possibility of infectious disease. The searches for rheumatoid factors, cryoglobulin, ACPA, ANCA, and ANA were negative.

Pleuritis disappeared and atelectasis improved after treatment of the tamponade. Then, another chest CT revealed reticular hyperdensities and septal thickenings. The PFTs could not be performed. Despite a broad-spectrum antibiotic treatment, the patient remained febrile and developed a myocarditis. As the presentation became evocative of complicated AOSD, an intravenous corticosteroid pulse therapy (1 mg/kg/d) was started. The patient became afebrile within 2 days and exhibited a significant clinical improvement, which persisted after shifting to oral corticosteroids.

A control chest HRCT showed regressions of pleural effusion, atelectasis, alveolointerstitial, and lymphadenopathy. After an 18-month follow-up, the outcome was favorable allowing tapering corticosteroids. The patient was then lost to follow-up.

3.2. Literature cases

The literature search identified 41 cases of AOSD + PLI in 37 citations. Fourteen cases were excluded because of the following: insufficient data (n = 4)[16–19]; non-English or non-French language (n = 5)[20–24]; impossibility to rule out an infectious or iatrogenic origin of PLI (n = 3)[25–27]; uncertain AOSD diagnosis (n = 1)[28]; and isolated atelectasis (n = 1).[29] Finally, 27 cases from the literature were kept for analysis (cases 4–30 in Tables 1 and 2). The AOSD + PLI group amounted thus to 30 patients[30–52] (Fig. 1).

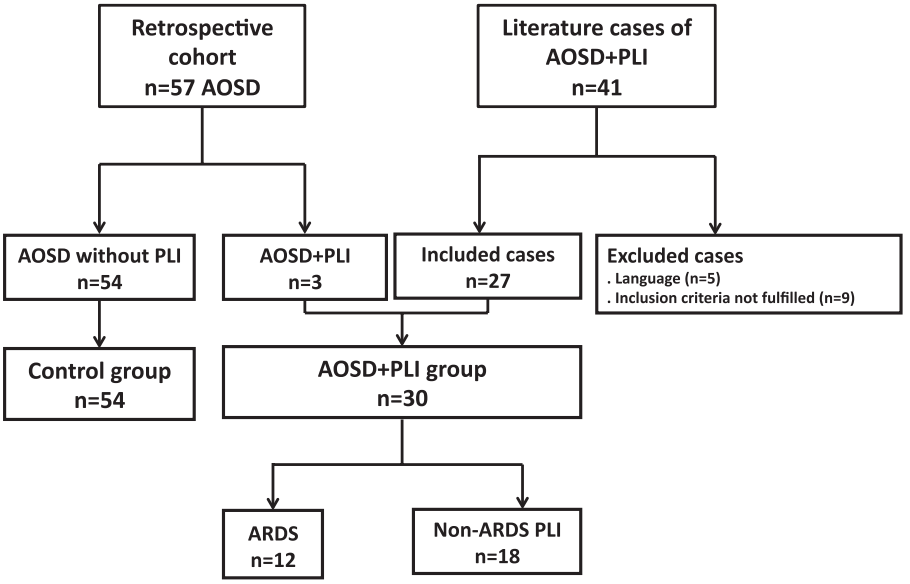

Figure 1. Repartition of patients with AOSD and PLI. AOSD = adult-onset Still disease, ARDS = acute respiratory distress syndrome, PLI = parenchymal lung involvement.

3.3. Description of the AOSD + PLI group

Among the 30 patients with AOSD + PLI, 12 suffered from ARDS. This subgroup is described separately (Fig. 1).

3.3.1. Patients with non-ARDS PLI. Eighteen patients (9 males and 9 females) had AOSD + PLI without ARDS (Table 1). The mean age at AOSD onset in this group was 33.8 years (range: 3–67) and the mean age at PLI onset was 36.6 years (range: 20–67). Respiratory symptoms occurred at onset of AOSD in 9 patients: during the first year of the disease course in 2 patients but later in the remaining 7 (range: 14–204 months). The recurrent respiratory symptoms were cough (13/18, 72%), dyspnea (8/18, 44%), and chest pain (4/18, 22%). Basal crackles (rales) were reported in 5 cases.

The chest x-ray and HRCT revealed unilateral or bilateral interstitial hyperdensities in 13/18 cases (72%) and alveolar hyperdensities in 9/18 cases (50%) with air bronchogram in 6/18 cases (33%). The sites of the lesions were specified in 14 cases: the main site was the lower lobes (11/14), whereas the upper and the middle lobe were less affected (3 and 2/14, respectively). The main HRCT patterns were the following: nonspecific interstitial pneumonia (3 cases), organizing pneumonia (4 cases), and unclassified interstitial lung disease (6 cases). These infiltrates were associated with a pleural effusion in 8 patients and mediastinal lymphadenomegaly in 4 others. Furthermore, 2 patients presented a pneumomediastinum, 2 others atelectasis, 1 excavated nodules, and 1 bronchiectasis.

PFTs were performed in only 7/18 patients. These tests showed a restrictive lung function in 6 cases and an isolated decreased DLCO in 1 case. Patient 8 presented an associated obstructive lung function (Table 1).

BAL analysis results were available in 8/18 patients. The differential cell count profile was mainly neutrophilic (>15% neutrophils in half of the cases, 4/8), lymphocytic, mixed, macrophagic, and hemorrhagic (1 case of each profile).

Six transbronchial lung biopsies and 1 surgical lung biopsy were performed. The histological findings were consistent with bronchitis or bronchiolitis in 2 cases, nonspecific interstitial pneumonia in 2 cases, and organized pneumonia in 3 cases. A nonspecific interstitial fibrosis was found in 3 patients.

All but 1 patient were treated with corticosteroids, 3 received additional intravenous immunoglobulins, and 1 patient was treated with salicylates only. The outcome of the pulmonary involvement was favorable within a few days or weeks in 14/18 cases, whereas 3 patients kept significant PFT abnormalities or dyspnea after 2 years,[30] 4 months,[34] and 10 years.[35] The outcomes of the other cases were not specified. No patient died from respiratory failure.

In 14 cases, the systemic or chronic pattern of the underlying AOSD could be identified. PLI occurred in both patterns but mainly in the former: 11/14 PLIs in systemic AOSD (4 monocyclic AOSD and 7 polycyclic AOSD) versus 3/14 PLIs in chronic articular AOSD.

Finally, in 5 patients, PLI was associated with other well-documented AOSD complications: myocarditis, tamponade, severe systemic inflammation response syndrome, and reHLH (2 cases). In 2 other patients, the association with reHLH was not investigated[33,40] (Table 2).

3.3.2. Patients with ARDS. Among the 12 patients with ARDS, 7 were women (Tables 1 and 2, cases 19–30). The mean age at AOSD onset was 35 years (range: 9–74) and the mean age at ARDS onset was 37.5 years (range: 20–74). ARDS occurred at the onset of the disease in 7 cases, during the first year after diagnosis in 3 other cases, and 10 and 20 years later in the remaining 2 cases. All these patients but 1 (11/12) suffered initially from dyspnea; 5 presented with cough and 5 others with crackles at lung auscultation.

In these 12 cases, imaging findings were consistent with ARDS (bilateral interstitial and alveolar hyperdensities). A pleural effusion was reported in 5 cases and mediastinal lymphadenopathy in 1 case.

According to the worst PaO_2/FiO_2 ratio, 2 patients suffered from mild ARDS ($200 < PaO_2{:}FiO_2 \leq 300$) and 10 from moderate to severe ARDS. The formula of BAL was available in 1 case and was neutrophilic. A lung biopsy was performed in 1 case and was consistent with an organizing pneumonia associated with diffuse alveolar damage.[48]

Table 1

Characteristics of parenchymal lung involvement in AOSD.

Case	First author	Time from AOSD onset (age)	Respiratory symptoms and signs	Imaging data/HRCT pattern	PFT data	Bronchoscopy and BAL findings	Pulmonary histology	Subset of PLI	Specific treatment	Respiratory outcome
1	This series	Initial picture (47)	Chest pain	CXR: pleural effusion; CT: right lower and middle lobe atelectasis, alveolar hyperdensities in right lower lobe	RLF: FEV_1 64%; FVC 68%; FEV_1/VC 80% (DLCO NP)	BAL: 2000/mm^3, 60% PMNs, 25% lymphocytes	TBLB: lymphocytic bronchiolitis	Bronchiolitis, inflammatory atelectasis	Prednisone; IVIG; Colchicine; Methotrexate	Favorable
2	This series	3 yr (64)	Cough	CT: interstitial, ground-glass, and alveolar hyperdensities; excavated nodules in the left lower lobe, pleural effusion, mediastinal lymphadenopathy	RLF: FVC 2.71 L (71%); FEV_1/VC 78%; DLCO 85%	BAL: 486 leukocytes/mm^3, 95% PMNs, sterile	TBLB: nongranulomatous ulcerated bronchitis	Bronchitis and unspecified ILD	Prednisone	Favorable
3	This series	Initial picture (42)	Dyspnea, cough, crackle rales	CT: alveolar hyperdensities, air bronchogram, reticular infiltrates, lymphadenopathy	NA	BAL: 1500 leukocytes/mm^3, 90% PMNs, sterile	NP	Unclassified ILD	Methylprednisolone IVIG	Favorable
4	Corbett[30]	14 mo (21)	Dyspnea, cough, left basal rales	CXR: left lower lobe infiltrate	RLF: FVC 0.94 L, 26.5%; FEV_1 0.92 L, 30%; DLCO 30%	NP	TBLB: nonspecific interstitial inflammation with fibrosis	ILD (possible NSIP)	Prednisone	Persistent severe restrictive defect
5	Cantor[31]	13 yr (34)	Dyspnea, pulmonary rales	CXR: patchy lower lobe infiltrate, small pleural effusion	RLF: FVC 2.01 L, 45%; FEV_1/FVC 83%; FEV_1 1.68, 46%; DLCO 84%	NP	NP	Unclassified ILD	Prednisone	Favorable: symptoms and PFT improvement
6	Van Hoeyweghen[32]	6 mo (36)	Cough	CXR: hilar lymphadenopathy; CT: lower lobes alveolar and interstitial infiltrates	Decreased DLCO: FVC 100%; FEV_1 87%; DLCO 57%	Bronchoscopy: normal; BAL: sterile, 1000 leukocytes/mm^3 (60% neutrophils, 11% lymphocytes, 26% macrophages)	SLB: peribronchial and interstitial fibrosis	ILD (possible NSIP)	Salicylates	Favorable
7	Yoshinaga[33]	17 yr (20)	Dyspnea, tachypnea, basal crackle rales	CXR: bilateral reticular infiltrates in lower lobes; CT: diffuse reticular infiltrates, subpleural honeycombing	RLF: VC 50%; DLCO 25%. PaO_2 67 mm Hg; $PaCO_2$ 37 mm Hg	NP	NP	ILD (UIP or NSIP)	Methylprednisolone; IVIG; Cyclophosphamide	NA
8	Dikensoy[34]	6 yr (21)	Dyspnea, cough, expectoration, cyanosis, subcutaneous crepitation, biphasic ronchi rales	CXR: pneumomediastinum; CT: diffuse bronchiectasis, air trapping signs accentuated on expiratory CT	Obstructive and RLF: FEV_1 0.66 L, 21%; DLCO 51%; KCO 94%; $PaCO_2$ 39.3 mm Hg; PaO_2 37.1 mm Hg; SaO_2 71.5%	NP	NP	Obliterative bronchiolitis	Methylprednisolone, and then prednisone methotrexate	Persistant dyspnea and obstructive lung function
9	Tieulié[35]	Initial picture (45)	Cough	CT: alveolar hyperdensities, air bronchogram, labile interstitial infiltrates in lower lobes	NP	BAL: 150 leukocytes/mm^3, 95% PMNs, sterile	NP	Organizing pneumonia	Prednisone	Favorable, mild persistent RLF
10	Hijikata[36]	1 mo (67)	Cough	CXR: interstitial infiltrate in right apex; CT: alveolar hyperdensity with air bronchogram in right upper lobe	NP	BAL: 4800 leukocytes/mm^3, 78% macrophages, 14% lymphocytes (CD4/CD8 ratio 0.8), 6% PMNs, sterile	TBLB: interstitial inflammatory cell infiltration, cuboidal cell metaplasia, and intraluminal polypoid organization	Organizing pneumonia	Prednisolone (NSAIDs)	Favorable (within 3 wk)
11	Sari[37]	5 yr (28)	Dyspnea, cough	CXR: bilateral alveolar infiltrate; CT: bilateral dense alveolar infiltrate, air bronchogram, mediastinal lymphadenopathy, pleural effusion	NP	BAL: hemorrhagic	NP	Diffuse alveolar hemorrhage	Methylprednisolone	Favorable
12	Nie[38]	Initial picture (39)	Cough, chest pain, tachycardia	CXR: bilateral pleural effusion; CT: bilateral lower lobes interstitial infiltrates	NP	NP	NP	Unclassified ILD	Methylprednisolone	Favorable (within 5 d)
13	Nie[38]	Initial picture (21)	Cough, chest pain, tachycardia	CT: left lower lobe infiltrate, bilateral pleural effusion	NP	NP	NP	Unclassified ILD	Methylprednisolone	Favorable (within 7 d)
14	Sato[39]	Initial picture (32)	NA	CXR: alveolar hyperdensities and air bronchogram in the right upper lobe; CT: ground-glass hyperdensities surrounded nodule in the right apex	NP	Bronchoscopy: normal; BAL: lymphocyte predominant, CD4/CD8 1.15	TBLB: lymphoplasmacytic inflammatory infiltration on bronchial wall, intra-alveolar organization	Organizing pneumonia	Prednisone	Favorable
15	Ibn Yacoub[40]	15 mo (24)	Dyspnea, cough, chest pain	CXR: pleural effusion; CT: atelectasis with contiguous pleural thickening	NP	Bronchoscopy: inflammatory sterile secretions; BAL: NP	NP	Bronchitis and atelectasis	Prednisone	Favorable (within 1 wk)

(*continued*)

Table 1

(continued).

Case	First author	Time from AOSD onset (age)	Respiratory symptoms and signs	Imaging data/HRCT pattern	PFT data	Bronchoscopy and BAL findings	Pulmonary histology	Subset of PLI	Specific treatment	Respiratory outcome
16	Ak[41]	Initial picture (24)	Cough	CXR: right lower and middle lobe infiltrate, small pleural effusion	NP	NP	NP	Unclassified ILD	Prednisone	Favorable
17	Fujii[42]	Initial picture (64)	NA	CT: reticular and ground-glass hyperdensities; In lower lobes, pneumomediastinum, pneumothorax	NP	NP	NP	Unclassified ILD, pneumomediastinum, pneumothorax	Methylprednisolone	Favorable
18	Ghosal[43]	Initial picture (30)	Dyspnea, cough, tachypnea, crackle rales	CXR: patchy infiltrates in left upper lobe; CT: interstitial and alveolar hyperdensities in the left upper lobe, air bronchogram	NP	BAL: sterile	TBLB: interstitial dense lymphoplasmacytic infiltrates with focal organizing pattern	Organizing pneumonia	Methylprednisolone; Prednisone	Favorable
19	Pedersen[44]	Initial picture (40)	Dyspnea	CXR: bilateral interstitial infiltrates	NP	NP	NP	ARDS	Methylprednisolone	Favorable
20	Paccalin[45]	Initial picture (20)	Cough, dyspnea	CXR: bilateral interstitial infiltrates; CT: bibasal alveolar hyperdensities, mediastinal lymphadenopathy	NP	BAL: *Streptococcus pneumoniae* (ventilator-associated pneumonia)	Mediastinal lymphadenopathy biopsy: nonspecific lymphadenitis	ARDS	Methylprednisolone	Favorable
21	Iglesias[46]	20 yr (29)	Dyspnea, tachypnea, scattered cracle, rales	CXR: dense bilateral alveolar infiltrates; CT: bilateral alveolar infiltrates	NP; PaO_2/FiO_2 49 mm Hg (PEEP 10 cm H_2O)	BAL: sterile	NP	ARDS	Methylprednisolone	Favorable
22	Carron[47]	Initial picture (31)	Dyspnea	CXR: diffuse bilateral alveolar and interstitial infiltrates	NP	NP	NP	ARDS	Methylprednisolone	Favorable in 48 h
23	Stoica[48]	2 mo (74)	Dyspnea	CXR: cardiomegaly; CT: bilateral interstitial infiltrates	NP; PaO_2/FiO_2 187 mm Hg	BAL: sterile	TBLB: nongranulomatous inflammatory infiltrate; SLB: extensive diffuse interstitial fibrosis with organizing pneumonitis, no infection	ARDS; Organizing pneumonia	Methylprednisolone; IVIG	Death
24	Suleiman[49]	10 yr (36)	Pleuritic cough; Dyspnea	CXR: pleural effusion; CT: interstitial lung infiltrate	PaO_2/FiO_2 85 mm Hg (PEEP 10 cm H_2O)	Bronchoscopy: normal; BAL: sterile	NP	ARDS	Methylprednisolone; Methotrexate	Favorable (within <1 wk)
25	Hagiyama[50]	1 mo (24)	Dyspnea	CXR and CT: bilateral alveolar infiltrate with air bronchogram	PaO_2/FiO_2 60 mm Hg	NP	NP	ARDS	Methylprednisolone; Prednisone; Cyclophosphamide (700 mg on first day)	Favorable (14 d)
26	Hagiyama[50]	1 mo (20)	Dyspnea	CXR: bilateral diffuse pulmonary infiltrates with air bronchogram	PaO_2/FiO_2 41 mm Hg	NP	NP	ARDS	Methylprednisolone	Favorable (12 d)
27	Biron (2005)	Initial picture 14 d (39)	Dyspnea, tachypnea, cough	CXR: diffuse interstitial infiltrates, mild pleural effusion; CT: alveolar hyperdensities in the lower lobes	PaO_2/FiO_2 220 mm Hg	BAL: normocellular, 30% PMNs, sterile	NP	Mild ARDS	Methylprednisolone; Prednisone	Favorable (within 2 d)
28	Biron (2005)	Initial picture (68)	Dyspnea, cough, chest pain, crackle rales	CXR: pleural effusion; CT: alveolar hyperdensities in the lower lobes	PaO_2/FiO_2 233 mm Hg	Pleural fluid: sterile exudate	NP	Mild ARDS	Methylprednisolone; Prednisone	Favorable (within 3 d)
29	Biron (2005)	Initial picture (43)	Dyspnea, bilateral crackle rales	CXR and CT: pleural effusion, alveolar hyperdensities	NA	BAL: normocellular, sterile	Pericardial biopsy: nonspecific inflammatory infiltrate	ARDS	Methylprednisolone; Prednisone; IVIG	Favorable (within 2 d)
30	Dua[52]	Initial picture (26)	Dyspnea, cough, coarse breath sounds, crackle rales, tachycardia	CXR: bilateral interstitial infiltrates; CT: bilateral pleural effusions, diffuse airspace opacities, interstitial infiltrates	PaO_2/FiO_2 278, and then worsened	Bronchoscopy: normal; BAL: sterile	NP	ARDS	Methylprednisolone; Cyclosporine	Favorable (within 3 d); Then ARDS relapsed 14 d later with reHLH; Death (CMV infection)

AOSD = adult-onset Still disease, ARDS = acute respiratory distress syndrome, BAL = bronchoalveolar lavage, CMV = cytomegalovirus, CT = computed tomography, CXR = chest radiography, DLCO = diffusing capacity of the lung for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity (L, % predicted), HRCT = high-resolution computed tomography, ILD = interstitial lung disease, IVIG = intravenous immunoglobulins, KCO = DLCO/AV, NA = not available, NP = not performed, NSAID = nonsteroidal anti-inflammatory drug, NSIP = nonspecific interstitial pneumonia, PEEP = positive end-expiratory pressure, PFT = pulmonary function test, PLI = parenchymal lung involvement, PMN = polymorphonuclear cell, reHLH = reactive hemophagocytic lymphohistiocytosis, RLF = restrictive lung function, SLB = surgical lung biopsy, TBLB = transbronchial biopsy, UIP = usual interstitial pneumonia, VC = vital capacity.

Table 2

Characteristics of AOSD in patients with lung involvement.

Case	First author	Age at AOSD onset, yr	Sex	Yamaguchi and/or Fautrel criteria	AOSD characteristics at respiratory onset				AOSD outcome	Other complications/ concomitant reHLH
					AOSD clinical symptoms	WBC, mm^{-3}	PMN, mm^{-3}	Serum ferritin, μg/L (GF%)		
1	This series	47	M	Both fulfilled	Fever, polyarthralgia, sore throat, lymphadenopathy, pleurisy, pericarditis	25,000	22,500	473 (19)	Polycyclic	Tamponade
2	This series	61	M	Fautrel fulfilled	Fever, polyarthralgia	5,500	3,430	1,432 (2)	Polycyclic	reHLH
3	This series	42	M	Both fulfilled	Fever, arthralgia, lymphadenopathy	18,000	15,480	19,000 (5)	Monocyclic	Myocarditis
4	Corbett[30]	19	F	Both fulfilled	Fever, polyarthritis, sore throat, rash, pericarditis, pleurisy, abdominal pain, conjunctivitis, ELE	18,000	NA	NA	Polycyclic	Severe SIRS
5	Cantor[31]	21	M	Both fulfilled	Fever, polyarthritis, sore throat, rash, pericarditis, pleurisy, splenomegaly, ELE	26,500	21,000	NA	Polycyclic	No
6	Van Hoeyweghen[32]	35	M	Fautrel fulfilled	Fever, polyarthralgia, sore throat, rash, lymphadenopathy	16,500	NA	NA	Polycyclic	No
7	Yoshinaga[33]	3 (SOJIA in remission from 15 to 20 yr old)	F	Both fulfilled	Fever, polyarthralgia, sore throat, rash, lymphadenopathy, hepatosplenomegaly, pericarditis	24,200	NA	23,000	Polycyclic	Thrombocytopenia (reHLH?)
8	Dikensoy[34]	14 (initial SOJIA)	F	Fautrel fulfilled	Fever, polyarthritis	18,400	NA	NA	Chronic	No
9	Tieulié[35]	45	M	Both fulfilled	Fever, polyarthritis, myalgia, sore throat, splenomegaly	20,100	18,100	NA (57)	Polycyclic (PLI never relapsed)	No
10	Hijikata[36]	67	M	Both fulfilled	Fever, polyarthralgia, sore throat, rash, lymphadenopathy	21,000	18,000	1,893	Monocyclic	No
11	Sari[37]	23	F	Both fulfilled	Fever, polyarthritis, sore throat, rash, lymphadenopathy, hepatosplenomegaly	39,700	35,700	8,651	Chronic (PLI never relapsed)	No
12	Nie[38]	39	F	Both fulfilled	Fever, arthralgia, sore throat	14,710	12,700	13,147	Monocyclic	No
13	Nie[38]	21	M	Both fulfilled	Fever, sore throat, pleurisy	26,900	24,210	33,160	NA	No
14	Sato[39]	32	F	Both fulfilled	Fever, polyarthritis, sore throat, rash, ELE	9,300	8,900	505	NA	No
15	Ibn Yacoub[40]	22	F	Both fulfilled	Fever, polyarthritis, sore throat, rash, lymphadenopathy, weight loss	8,800	NA	490,000	Chronic	Anemia (56 g/L), thrombocytopenia (40 g/L): probable reHLH (not investigated)
16	Ak[41]	24	M	Both fulfilled	Fever, arthralgia, myalgia, rash, hepatosplenomegaly	17,800	17,100	11,840	NA	No
17	Fujii[42]	64	F	Both fulfilled	Fever, polyarthritis, rash, hepatosplenomegaly, ELE	11,900	9,520	5,511	NA	reHLH
18	Ghosal[43]	30	F	Both fulfilled	Fever, polyarthritis, rash, hepatomegaly, ELE	20,000	17,800	11,000	Monocyclic	No
19	Pedersen[44]	40	M	Both fulfilled	Fever, polyarthritis, rash, ELE, jaundice	18,000	NA	NA	Monocyclic?*	Severe SIRS, MOF, DIC (reHLH not investigated)
20	Paccalin[45]	20	F	Both fulfilled	Fever, polyarthralgia, rash, lymphadenopathy, pericarditis, ELE	20,600	16,480	10,100	Monocyclic	Ventilator-associated pneumonia, pneumothorax, intracranial hypertension; No reHLH
21	Iglesias[46]	9 (SOJIA in remission until 29)	F	Both fulfilled	Fever, polyarthralgia, myalgia, rash, hepatomegaly	16,600	NA	26,000	Polycyclic	Severe SIRS, MOF, DIC; No reHLH
22	Carron[47]	31	M	Both fulfilled	Fever, monoarthritis and polyarthralgia, myalgia, sore throat, rash, lymphadenopathy	26,000	NA	1,892	Monocyclic?*	No
23	Stoica[48]	74	F	Both fulfilled	Fever, polyarthralgia, myalgia, sore throat, rash	20,000	17,200	NA	Monocyclic	Severe SIRS; DIC; reHLH not investigated
24	Suleiman[49]	26	F	Both fulfilled	Fever, polyarthralgia, myalgia, sore throat, rash, pleurisy, pericarditis, ascites, ELE	31,000	NA	7,880	Polycyclic	Acute renal failure
25	Hagiyama[50]	24	F	Fautrel fulfilled	Fever, polyarthritis, sore throat, rash, ELE	12,900	12,225	103	Monocyclic?*	Severe SIRS
26	Hagiyama[50]	20	M	Both fulfilled	Fever, rash, lymphadenopathy, ELE	12,200	10,700	14,455	Monocyclic?*	Sever SIRS; Thrombocytopenia (86,000/mm^3); reHLH not investigated
27	Biron (2005)	39	F	Both fulfilled	Fever, polyarthralgia, sore throat, rash, pleurisy, ELE	22,000	19,800	8,590 (11)	Polycyclic (relapse at 6 mo without PLI)	No reHLH
28	Biron (2005)	68	M	Both fulfilled	Fever, polyarthralgia, rash, pleurisy, pericarditis, ELE	28,000	24,600	42,600 (6)	Monocyclic	No reHLH
29	Biron (2005)	43	M	Both fulfilled	Fever, myalgia, sore throat, pleurisy, pericarditis, ELE (hepatitis)	15,600	14,200	21,195 (12)	Polycyclic (relapsed at 6 mo without PLI)	No reHLH
30	Dua[52]	26	F	Both fulfilled	Fever, myalgia, sore throat, rash	20,000	18,400	4,022	NR	Severe SIRS; reHLH; Seizure

AOSD = adult-onset Still disease, DIC = diffuse intravascular coagulation, ELE = elevated liver enzyme, F = female, GF = glycosylated ferritin, M = male, MOF = multiple organ failure, NA = not available, PLI = parenchymal lung involvement, PMN = polymorphonuclear cell, reHLH = reactive hemophagocytic lymphohistiocytosis, SIRS = systemic inflammatory response syndrome, SOJIA = systemic onset of juvenile idiopathic arthritis, WBC = white blood cell count.

* Because these cases are reported ones, follow-up data are unavailable and the monocyclic onset of AOSD is not sure.

Table 3

Comparison between AOSD with and without parenchymal lung involvement.

	AOSD + PLI group	Non-ARDS PLI group	ARDS group	Control group
Clinical data				
N	30	18	12	54
Female patients	16 (53)	9 (50)	7 (58)	30 (56)
Male patients	14 (47)	9 (50)	5 (42)	24 (44)
Age at AOSD onset	34.3 ± 18	33.5 ± 17.8	35 ± 19.4	37.8 ± 15.9
Fever	30 (100)	18 (100)	12 (100)	52 (96)
Arthralgias	14 (47)	8 (44)	6 (50)	51 (94)
Arthritis	12 (40)	9 (50)	3 (25)	24 (44)
Rash	22 (73)	11 (61)	11 (92)	42 (78)
Sore throat	18 (60)	12 (67)	6 (50)*	42 (78)
Lymphadenopathy	10 (33)*	7 (39)	3 (25)	31 (57)
Pleurisy	8 (27)	4 (22)	4 (33)	8 (15)
Pericarditis	8 (27)	5 (28)	3 (25)	9 (17)
Systemic AOSD	18/21 (86)	11/14 (79)	7/7 (100)	40 (74)
Monocyclic AOSD	7/21 (33)	4/14 (29)	3/7	16 (30)
Polycyclic AOSD	11/21 (52)	7/14 (50)	4/7	24 (44)
Chronic AOSD	3/21 (15)	3/14 (21)	0	14 (26)
Other complications	13 (43)	6 (33)	7 (58)*,†	16 (30)
Proven reHLH	3 (10)	2 (11)	1 (8)	8 (15)
Deaths	2 (7)	0 (0)	2 (17)	0 (0)
Laboratory data				
Leukocytes	19,507 ± 7,089*	19,017 ± 7954*	20,241 ± 5,806*	13,607 ± 6,848
Polymorphonuclears	17,050 ± 6,765*	15,651 ± 9,246*	16,701 ± 4,432*	11,668 ± 5,888
Elevated transaminases	13 (43)	5 (28)*	8 (67)	31 (57)
Serum ferritin, μg/L	37,363 ± 101,027*	47,662 ± 133,261*	13,684 ± 13,056*	8,877 ± 20,364

Data are expressed as either n (%) or value ± SD. AOSD = adult-onset Still disease, ARDS = acute respiratory distress syndrome, PLI = parenchymal lung involvement, reHLH = reactive hemophagocytic lymphohistiocytosis, SD = standard deviation, SIRS = systemic inflammatory response syndrome.

* Significant difference versus the control group.

† 7 patients among the 12 in the ARDS group suffered from other AOSD complications: severe SIRS (n = 6), multiple organ failure (n = 2), and diffuse intravascular coagulation (n = 3).

All 12 patients were treated with corticosteroids, 2 received additional intravenous polyvalent immunoglobulins, 1 received cyclophosphamide, and 1 cyclosporine. The outcome of ARDS was quickly favorable in 10 cases (often in <1 week), but 2 patients died: the first from ARDS and the second from an associated reHLH at 12 and 6 weeks from AOSD onset.

Regarding the AOSD pattern, ARDS occurred only in the systemic pattern. The complications associated with AOSD were frequent: 8 out of 12 patients had at least 1. The most common complications were severe systemic inflammation response syndrome (n = 6), multiple organ failure (n = 2), and diffuse intravascular coagulation (n = 2). reHLH was confirmed in only 1 patient with ARDS; however, reHLH was probably underreported because, in cases 19, 23, and 26, the necessary investigations were not carried out.

3.4. Comparison between the AOSD + PLI group and the AOSD control group

The age at AOSD onset was lower in the AOSD + PLI group than in the control group. The distribution of PLI was equivalent between men and women. The frequencies of various AOSD symptoms were the same in the AOSD + PLI group and in the control group, although lymphadenopathy seemed less prevalent in the AOSD + PLI group and sore throat less frequently reported in the ARDS group. As mentioned above, ARDS occurred only during systemic AOSD, whereas other PLIs could also occur during chronic articular AOSD. The occurrence of other complications of AOSD was more frequent in the ARDS group than in the control group (Table 3).

The examination of the laboratory data showed that the leukocyte count, the polymorphonuclear cell count, and the serum ferritin level were higher in the AOSD + PLI group than in the controls (Table 3).

4. Discussion

A PLI may be associated with AOSD; this occurred in nearly 5% of AOSD cases in our series, which is more frequent than in the general population. Two main kinds of PLI may be distinguished during AOSD: 1 with ARDS and another with other PLIs.

ARDS seems to be an early complication of systemic AOSD because it occurred during the first year of the disease in all but 2 cases (83%). It is the leading cause of death in AOSD-related PLI: it was associated with death in 2 patients (17%). Furthermore, ARDS was frequently associated with other organ failures or other systemic complications of AOSD. In most cases, corticosteroids provided favorable outcomes, this treatment being the standard of care in systemic and complicated AOSD.[53] In fact, ARDS has been shown to be caused by an inflammatory injury to the lungs and corticosteroids remain of interest in noninfectious cases.[54,55]

In the light of recent advances in the understanding of the pathophysiology of AOSD, underlying reHLH could be underreported.[3,56,57] Identifying this entity should be a key element in ARDS control in case of corticosteroid failure (the case of the 2 patients who died) because this speeds switching the treatment to cyclosporine, etoposide, or biological agents.[58] Data on the IL-1 receptor antagonist (anakinra) and the humanized anti–IL-6 receptor antibody (tocilizumab) are scarce in life-threatening

complications of AOSD. However, the rapid use of anakinra may be of value in this situation.[59–62] In a recent case series, 2 out of 5 patients with reHLH in AOSD had lung involvement. In agreement with the literature, the present study suggests that treatment with a combination of IL-1 receptor antagonist, a calcineurin inhibitor, and a systemic glucocorticoid may lead to favorable outcomes.[63]

The non-ARDS PLI could occur during systemic AOSD, more rarely during chronic rheumatic AOSD, but at any time during the course of the disease. The clinical features were nonspecific and the basal crackles were reported in one-quarter of cases. Imaging revealed most often lower lobe interstitial and alveolar infiltrates together with pleural effusion. As in connective tissue disease—especially in dermatomyositis—2 cases of pneumomediastinum were reported.

PFTs were not frequently performed. They often showed a persistent restrictive lung function in 3 cases without chronic respiratory failure; this highlights the interest of performing these tests in monitoring the disease and assessing the sequelae. The differential cell count of the BAL had most often a neutrophilic profile, but this is not specific to AOSD + PLI. This finding should raise the concern about a pulmonary infection before starting corticosteroids. Imaging and histological data allow dividing AOSD-related non-ARDS PLI into 2 groups: a predominant airway involvement (bronchiolitis and bronchitis) and a predominant interstitial lung disease (nonspecific interstitial pneumonia, organizing pneumonia, or unclassifiable interstitial pneumonia).

In non-ARDS PLI cases, corticosteroids were often efficient. Only a minority of patients kept pulmonary function sequelae. Thus, the present results do not support the use of methotrexate or intravenous immunoglobulins during the acute phase of non-ARDS PLI.

Comparing the AOSD + PLI group and the control group, the age at AOSD onset was lower in the former, but this finding should be interpreted with caution because some patients with PLI found in the literature presented a first flare of AOSD during childhood, whereas this could not be documented in the retrospective cohort because it included only patients >16 years old.

The present study has the biases inherent to its retrospective design, mainly data missingness (local cases) and publication bias (literature cases). Actually, complicated onset of AOSD could be overrepresented in our AOSD cohort in comparison with previous data (33% vs 5%–11%). This may be the consequence of the following: the high proportion of polycyclic AOSD (44%); the recruitment mainly in internal medicine departments instead of in rheumatology departments as in other series; the recruitment in a university hospital, which often increases the proportion of severe cases; and a longer follow-up period than in previous studies (during a mean period of 8.4 years).[11] Moreover, because these specific PLIs are not frequent in AOSD, the occurrence of respiratory symptoms during the course of the disease should lead to investigate and exclude pulmonary infection, treatment toxicity, or heart failure before starting a steroid treatment.

Finally, other rarer pulmonary complications of AOSD, such as aseptic empyema and diffuse alveolar hemorrhage, have been anecdotally reported.[37,64] In addition, pulmonary hypertension may also be a thoracic complication of AOSD. In fact, pulmonary hypertension is a well-described complication of juvenile onset of Still disease.[65] Its occurrence in the adult seems rare: to the best of our knowledge, only 8 cases have been reported yet.[66–72] In these cases, the right chamber catheterization argued in favor of pulmonary artery hypertension (precapillary) of various severities. These cases were not associated with PLI. Interestingly, recent biological treatments such as anakinra or tocilizumab seemed efficient in controlling this complication.[66,70]

5. Conclusion

A specific PLI may occur in about 5% of AOSD cases. ARDS is the most severe pulmonary manifestation in the systemic pattern of AOSD; its occurrence should orient toward an underlying reHLH because it was responsible for all AOSD + PLI–attributable deaths in this study. Non–ARDS–PLI includes bronchiolitis and nonspecific interstitial lung diseases; its prognosis is favorable. In most of AOSD + PLI cases, prednisone is efficient and the outcome is favorable. In refractory or life-threatening PLI cases, biological treatments such as anakinra or tocilizumab are presumably of interest but this remains to be proven.

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