



Published in final edited form as:

Ann Rheum Dis. 2019 December ; 78(12): 1722–1731. doi:10.1136/annrheumdis-2019-216040.

Emergent high fatality lung disease in systemic juvenile arthritis

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Abstract

Objective—To investigate the characteristics and risk factors of a novel parenchymal lung disease (LD), increasingly detected in systemic juvenile idiopathic arthritis (sJIA).

Methods—In a multicentre retrospective study, 61 cases were investigated using physician-reported clinical information and centralised analyses of radiological, pathological and genetic data.

Results—LD was associated with distinctive features, including acute erythematous clubbing and a high frequency of anaphylactic reactions to the interleukin (IL)-6 inhibitor, tocilizumab. Serum ferritin elevation and/or significant lymphopaenia preceded LD detection. The most prevalent chest CT pattern was septal thickening, involving the periphery of multiple lobes ± ground-glass opacities. The predominant pathology (23 of 36) was pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia (PAP/ELP), with atypical features including regional involvement and concomitant vascular changes. Apparent severe delayed drug hypersensitivity occurred in some cases. The 5-year survival was 42%. Whole exome sequencing (20 of 61) did not identify a novel monogenic defect or likely causal PAP-related or macrophage activation syndrome

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Patient and public involvement statement Patients were not involved in the research process of this study. Results will be shared via CARRA patient communication mechanisms.

Patient consent for publication Not required.

Ethics approval Ethics approval was obtained through the Stanford University School of Medicine institutional review board.

Contributing case reporters obtained approval per local institutional review board requirements. Institutional review board permission was obtained at each institution according to local requirements.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

(MAS)-related mutations. Trisomy 21 and young sJIA onset increased LD risk. Exposure to IL-1 and IL-6 inhibitors (46 of 61) was associated with multiple LD features. By several indicators, severity of sJIA was comparable in drug-exposed subjects and published sJIA cohorts. MAS at sJIA onset was increased in the drug-exposed, but was not associated with LD features.

Conclusions—A rare, life-threatening lung disease in sJIA is defined by a constellation of unusual clinical characteristics. The pathology, a PAP/ELP variant, suggests macrophage dysfunction. Inhibitor exposure may promote LD, independent of sJIA severity, in a small subset of treated patients. Treatment/prevention strategies are needed.

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a chronic, inflammatory disease of childhood, observed worldwide, with an incidence of 0.4–0.9/100 000 in North America and Europe.¹ A similar disease occurs in adults (adult-onset Still's disease (AOSD); incidence: 0.2–0.4/100 000).² sJIA is characterised by a combination of arthritis, which can be destructive, and systemic inflammation, including daily fever spikes, evanescent macular rash and serositis. A life-threatening complication (mortality rate: 8%–17% in sJIA)³ is overt macrophage activation syndrome (MAS). MAS is a form of secondary haemophagocytic lymphohistiocytosis (HLH) that manifests as a cytokine storm with very high serum ferritin and, in severe cases, organ failure. Therapies that antagonise cytokines interleukin (IL)-1 and IL-6 were introduced into management of sJIA ~15 years ago. This approach is rapidly effective in >65% of patients, implicating these inflammatory mediators as key drivers of sJIA.^{4–6}

The usual pulmonary complications of sJIA are pleuritis and pleural effusion.¹⁷ Scattered case reports of other lung diseases (LDs) in sJIA have appeared.^{8–12} However, in the last decade, paediatric rheumatologists have increasingly detected cases with types of LDs rarely seen in sJIA previously. Kimura *et al*¹³ described 25 cases that occurred before February 2011; diagnoses included pulmonary arterial hypertension (64%), interstitial LD (28%) and pulmonary alveolar proteinosis (PAP) (20%). sJIA course was considered severe, with MAS in 80%.

Here, we performed a multicentre, retrospective study of 61 cases with centralised analyses of radiographic, pathological and genetic data to provide current characterisation of LD in sJIA or sJIA-like disease, search for early indicators and investigate risk factors.

METHODS

Case definition and comparators

We used an operational sJIA case definition, developed by expert consensus as a modification of the International League of Associations for Rheumatology sJIA classification criteria.¹⁴ Cases failing to meet the case definition but managed clinically like sJIA were classified as sJIA-like. We identified 61 patients with sJIA or sJIA-like disease and parenchymal LD through the Childhood Arthritis and Rheumatology Research Alliance (CARRA) network and the international paediatric rheumatology listserv (administered by McMaster University, Ontario). Inclusion required verification of sJIA or sJIA-like illness,

data at LD diagnosis, and parenchymal LD by chest CT and/or lung tissue, available for expert review. Comparator data were from physician-classified patients with sJIA without known LD enrolled in the CARRA registry (CR)¹⁵ between 2015 and 2018, or in the PharmaChild pharmacovigilance registry.¹⁶ See online supplementary figures S1A–B and S2 and online supplementary information for additional details.

Data collection

Data included demographics, medical history, and clinical features at sJIA onset, at LD diagnosis and at defined time points (visits) before and after LD diagnosis. RegiSCAR score for drug-related eosinophilic systemic syndrome (DReSS) was calculated from clinical data.¹⁷ Online supplementary information includes details and definitions (online supplementary table S1).

Data analysis

Centralised analyses were performed for chest CT scans from 58 of 61 subjects, histopathology from 36 of 61 subjects and whole exome sequence (WES) data from 20 subjects. R V.3.5.1 program was used for all statistical analyses. Additional methods are in online supplementary information.

RESULTS

Disease characterisation: features unusual for sJIA

The cohort included 45 cases of sJIA and 16 cases of sJIA-like disease; demographics (table 1) and findings prior to or associated with LD did not differ systematically between these two groups (online supplementary tables S2–S4). Demographics of the LD cohort are mostly similar to subjects with sJIA in the CR, with the notable exceptions of significantly lower median age at sJIA onset and significantly higher prevalence of trisomy 21 (T21) (table 1). These findings are discussed further in the Candidate risk factors for parenchymal LD section.

Clinical features prior to LD and associated with LD are summarised in online supplementary tables S2 and S3, respectively. At LD diagnosis, respiratory signs and symptoms were typically absent or subtle, although hypoxia was reported in 43% and clinical pulmonary hypertension (PH) in 30%. Strikingly, 61% of patients developed acute clubbing, sometimes as the first indicator of LD. In over half of these, digital erythema occurred (figure 1A–C). Other atypical features were pruritic, non-evanescent rashes in 56% (figure 1D–F), eosinophilia in 37%, and unexplained, severe abdominal pain in 16% (likely underestimated as this was not directly queried). Anaphylaxis to tocilizumab was unusually common, occurring in 38% of those exposed (14 of 37; see online supplementary table S3, footnote 6), compared with 0.6% (1 of 159) in the CR and 0.9% (1 of 110) in the tocilizumab trial in sJIA.⁵ Overall, the LD cohort manifested clinical features that are unusual for sJIA¹⁸ or pulmonary disease.

Candidate early indicators of LD in sJIA: ferritin and lymphopaenia

The median time to LD diagnosis after sJIA onset was 1.6 years (IQR 0.8–3.3 years), excluding 6 of 61 cases with LD at systemic disease onset. To identify candidate early signs of LD, we analysed laboratory values commonly followed in sJIA. We matched cases to sJIA controls from the CR (1:1) for factors including laboratory test timing relative to sJIA onset, overall drug exposure, sex and sJIA onset age (online supplementary figure S3). We then assessed serum ferritin as an indicator of inflammation. The mean serum ferritin level in cases 1 year prior to LD diagnosis was not distinguishable from that of propensity-matched patients with sJIA in the CR. However, the level rose substantially within the 12 months before LD diagnosis in the cohort (figure 1G, online supplementary figure S4).

Another finding that preceded LD detection was significant lymphopaenia (absolute lymphocyte count <60% of age-adjusted, lower limit of normal).¹⁹ This degree of lymphopaenia, without concurrent MAS, was documented between the 6-month and 1-month visit prior to LD diagnosis in 42% of cases (excluding those with LD at sJIA onset; online supplementary table S3). We were unable to compare this with CR controls due to lack of information. However, this degree of lymphopaenia is not a known feature of active sJIA.¹⁸ Increased ferritin and lymphopaenia before LD diagnosis suggest a possibly extended incubation phase associated with smouldering inflammation and/or delayed recognition of LD.

Radiological features

As a step towards determining the nature of the LD, chest CT scans from 58 of 61 patients, most obtained at diagnosis, were systematically reviewed (RPG). Most exhibited one or more of five patterns (figure 2A–E). Pattern A (septal thickening involving the periphery of multiple lobes, most marked in the lower lung zones, parahilar/paramediastinal and/or anterior upper lobes with or without adjacent ground-glass opacities) was the most frequently observed (60%). Crazy-paving (figure 2B), peripheral consolidation (figure 2C), peribronchovascular consolidation (figure 2D) and predominantly ground-glass opacities (figure 3E) were seen in 21%, 22%, 16% and 12%, respectively. Among those with contrast-enhanced CTs, 11 of 30 (37%) displayed hyperenhancing lymph nodes (figure 2F), a peculiar finding, previously reported in unusual conditions.^{20,21} Findings like pattern A have been observed with connective tissue disease-associated interstitial LD or interstitial pneumonia with autoimmune features.²² However, unlike these disorders, radiological signs of fibrosis (honeycombing, traction bronchiectasis) were uncommon in our cohort. Overall, the observed CT findings are unexpected in sJIA; the more typical finding of pleural effusion^{17,18} was rare at LD diagnosis (online supplementary table S4).

Histopathology and related genetics

Biopsy or autopsy tissues of 36 of 61 patients were available for centralised analysis (GD). Multicompartment disease (some combination of alveolar, airway, pleural, vascular alterations) was observed in all cases. Using their primary pattern of injury, three subgroups were defined: spectrum of PAP/endogenous lipoid pneumonia (ELP), vasculopathy and other (online supplementary table S4). The pathology typically associated with pattern A on CT is non-specific interstitial pneumonia (NSIP).^{22,23} Surprisingly, in 21 patients with CT

pattern A who had histology, only 1 had NSIP. Instead, the predominant pathology (64% of cases reviewed) was PAP/ELP (figure 2G), which was patchy and often accompanied by associated vascular changes (figure 2G, right). PAP/ELP is very rare in rheumatic disease,²⁴ and the CT pattern typically associated with PAP is crazy-paving (pattern B).²⁵

To identify other histological features associated with PAP/ELP-like pathology in our cases, we generated a heat map (online supplementary figure S5A). Not surprisingly, type II alveolar cell hyperplasia was highly associated with PAP/ELP.^{26,27} The next associated finding was lymphoplasmacytic inflammation (71% of PAP/ELP cases). Third, 55% had mild to moderate pulmonary arterial wall thickening. Hypertensive vascular changes are not typically associated with inherited PAP/ELP, suggesting a secondary disease process.^{26–28} Electron microscopy (EM) (available in nine PAP/ELP cases) demonstrated well-formed lamellar bodies within type II alveolar epithelial cells. Variable accumulation of macrophages containing lamellar debris, lipid and cholesterol clefts was observed (figure 2H). The EM findings are more characteristic of macrophage overloading or dysfunction than of genetic disorders in surfactant metabolism.^{29,30} When we examined 13 PAP/ELP cases (6 with EM analysis) for genes causing hereditary PAP (*SFTPA1*, *SFTPB*, *SFTPC*, *ABCA3*, *NKX2-1*, *CSF2RA*, *CSFR2B*, *MARS*),^{26,28,31–35} 6 were heterozygous for protein-changing mutations, but none was de novo in trio analyses (online supplementary table S5A). One (*SFTPC* p.R167Q) causes PAP with low penetrance³¹; the others are not known to cause PAP in heterozygotes. While these rare variants (maximum allele frequency <5%) might contribute to LD in these children, they are not likely the full explanation.^{32,36,37}

Vascular abnormalities were the predominant finding in 4 of 36 biopsies (online supplementary figure S5B–D, table S4). Consistent with chest CT findings, interstitial fibrosis was generally mild, with advanced fibrosis/remodelling in only 4 of 36 samples, including 2 autopsies (online supplementary figure S5D).

Candidate risk factors for parenchymal LD

Other genetic factors—No evidence for a shared monogenic explanation for LD was found in WES of the 20 cases analysed (not shown). We also assessed the frequency of HLH/MAS-related gene variants (*PRF1*, *LYST*, *STX11*, *STXBP2*, *UNC13D*, *NRLC4*). Rare protein-altering variants, all heterozygous and none de novo, were found (online supplementary table S5B). Concordance between these variants and MAS (at sJIA onset or ever during disease course to data close) was not observed. The frequency of such variants (55%) is higher than reported for sJIA with MAS (36%)³⁸ and could contribute to propensity for inflammation.

Early-onset sJIA—Compared with control subjects with sJIA in the CR, the LD cohort's median age at sJIA onset was substantially younger (table 1; 2.3 years (1.1–5.0) vs 5.2 years (2.8–9.8), $p = 1 \times 10^{-7}$; online supplementary figure S6A). The CR cohort showed the full age of onset range of published sJIA cohorts, whereas the LD cohort was similar to a subgroup with younger onset age in sJIA cohorts^{39,40} (online supplementary figure S6B). Within LD cases, early onset of sJIA/sJIA-like disease was tightly correlated with PAP/ELP-like pathology (Wilcoxon test, $p = 2.3 \times 10^{-4}$; if cut-off for age at sJIA onset <5 years, OR=15,

Fisher's $p = 0.001$, compared with older children in the cohort). Of cases, 91% (21 of 23) with PAP/ELP had sJIA onset at <5 years (online supplementary figure S6C).

Trisomy 21—In the LD cohort, T21 prevalence (table 1) was strikingly higher (10%) than in sJIA registry cohorts (0.2%; 1 of 471 in the CR and 2 of 914 in PharmaChild, these being similar to the frequency (0.14%) in live births).⁴¹ There were suggestions of more aggressive LD in these children, all of whom developed LD on anti-IL-1/IL-6. Four of six children with T21 were hypoxic (OR=7.8, Fisher's $p = 0.08$, compared with the proportion of non-T21 with hypoxia). Two of five with T21 showed advanced interstitial fibrosis/remodelling (OR=8.4, Fisher's $p = 0.09$), and two of four children with advanced fibrosis had T21. Five of six (83%) had viral or fungal lung infection at LD diagnosis, compared with 16 of 55 (29%) of non-T21 (OR=12, Fisher's $p=0.02$)

Pre-exposure to cytokine inhibitors—Compared with previously described patients with sJIA,¹⁸ the LD cohort demonstrated rare clinical, radiological and pathological findings. During the time period of the series, the annual number of cases in the LD cohort increased dramatically, although some bias of ascertainment is possible due to increased awareness of this disease (figure 3A). PAP/ELP pathology increased among biopsied cases (figure 3B). The proportion of cases exposed to IL-1/IL-6 inhibitors increased in the cohort (figure 3C) and in all reported LD cases in sJIA (online supplementary figure S7A). These three trends coincided with increased use of IL-1/IL-6 inhibitors for sJIA.⁴² This prompted us to ask whether, compared with the CR sJIA cohort, the LD cohort was enriched for cases with exposure to IL-1/IL-6 inhibitors prior to LD. We matched the LD cases and CR controls for a number of potential confounders (online supplementary figure S7B). We found no difference in overall exposure to IL-1/IL-6 inhibitors; the exposure level in the CR controls was already high (online supplementary figure 7C; 46 of 53, 87%). Interestingly, among specific drug exposures, we found there was a moderate increase in anakinra exposure (OR=2.2 (0.94–5.5), $p = 0.07$). We next asked whether exposure to these inhibitors was related to the prevalence of unusual features. The frequencies of acute clubbing, digital erythema, unexplained abdominal pain, peripheral eosinophilia, CT pattern A or D, hyperenhancing lymph nodes and PAP/ELP pathology, but not PH, were substantially higher ($p < 0.1$; false discovery rate <20%) in pre-exposed versus non-pre-exposed subjects (figure 4A–B). These associations were not specific to one inhibitor. The median time from IL-1/IL-6 inhibitor to LD diagnosis was 1.2 years (IQR 0.7–2.0 years, $n=46$).

Severe or refractory sJIA—A possible bias in the associations with pre-exposure is increased severity of sJIA and related treatment, that is, channel bias. We assessed five clinical features associated with sJIA severity, as there is no validated sJIA severity index. For increased severity, we assessed MAS at sJIA onset, need for calcineurin inhibitors and persistent arthritis; for reduced severity, we assessed 'ever off' steroids and positive treatment response. The small sample of non-exposed subjects prevented us from performing a full analysis within our cohort. We compared the pre-exposed LD subgroup with published cohorts (figure 4C–F; online supplementary table S6). In Russo and Katsicas,⁴³ the proportion of children with early-onset sJIA (<1.5 years) with MAS at sJIA onset was 10× higher than the proportion of children with later sJIA onset (>1.5 years) (32% vs 3%).

This difference was interpreted to indicate more severe inflammation in early-onset sJIA. Among pre-exposed subjects with early-onset sJIA LD, the proportion with MAS at onset (27%) was comparable with early-onset subjects in Russo and Katsicas.⁴³ For pre-exposed children with later-onset sJIA LD, a significantly higher proportion had MAS at onset versus the comparable group in Russo and Katsicas⁴³ (26% vs 3%; OR=12.75, p = 0.0004) and versus another sJIA cohort, Behrens *et al*⁴⁴ (OR=4.83, p = 0.003). These observations raised the possibility that LD was associated with MAS at onset, resulting in increased inhibitor use. However, there was no association in the LD cohort between MAS at onset and any of the unusual features of LD (figure 4G).

The pre-exposed LD cohort was generally similar to published cohorts for frequency of treatment-responsive disease (lack of calcineurin inhibitor, a period of systemic quiescence or substantially reduced steroid treatment; Figure 4C–F). One exception was that a lower proportion of the LD subgroup treated with inhibitors for \geq 6 months were ever off steroids, perhaps reflecting more severe disease; nonetheless, this proportion was >50% (figure 4F). In addition, at data close, 58% of the pre-exposed (18 of 31) reported inactive sJIA (on medication) despite continuing LD in 94% (17 of 18). These observations argue that refractory sJIA is not required for LD development or persistence.

Survival

The period of follow-up after LD diagnosis was variable (median 1.7 years; IQR 0.75–3 years). Survival was drastically lower in the LD cohort (mortality: 159/1000 person-years; figure 5) than in a UK cohort of patients with sJIA who required biologic agents (mortality: 3.9/1000 person-years).⁴⁵ The predominant cause of death in our cohort was reported as diffuse LD (12 of 22 deaths), with MAS in 5 of 12 (online supplementary table S7). Among 75 categorical variables (online supplementary table S2–S5), male sex, hypoxia at initial LD evaluation, predominantly neutrophilic bronchoalveolar lavage (BAL) (\geq 40% neutrophils, over 10 times the normal),^{46,47} but not PH, appeared to associate with shortened survival (online supplementary figure S8A–D). These associations were not significant after adjusting for multiple tests. However, BAL neutrophilia (\geq 50%) has been linked to fatality,^{48,49} and 100% in our series (12 of 12) with this feature were deceased by data close.

DISCUSSION

LD in sJIA was characterised by young age at sJIA onset and unusual clinical features, including acute erythematous clubbing, atypical rash and anaphylaxis to tocilizumab; severe tocilizumab reaction in sJIA with pulmonary disease was also noted in the data from the PharmaChild registry.⁵⁰ The most prevalent finding on chest CT was peripheral septal thickening \pm ground-glass opacities. Crazy-paving, consolidation and hyperenhancing lymph nodes were also observed. On tissue diagnosis, this group showed primarily PAP/ELP-like pathology. Compared with PAP/ELP in other settings, the LD pathology was distinctive for its patchiness and associated vascular changes.

The proportion of LD cases with PAP/ELP-like tissue diagnosis has increased since 2010, coinciding with increasing use of IL-1/IL-6 inhibitors.⁴⁰ Pre-exposure to these inhibitors was characteristic of the predominant phenotypic subtype in our series. It is possible that this

association is confounded by concomitant reduction in steroids with inhibitor use or by treatment of severe inflammation; our data do not conclusively rule out these possibilities. However, severe disease has been observed since the initial description of sJIA in 1897,⁵¹ whereas the LD with associated features described here appears to be new and increasing in frequency. Among biopsied cases, PAP/ELP was found in 80% with pre-exposure (includes one with mostly pleural sample and limited PAP foci) vs 36% not pre-exposed (OR=7 (95% CI 1.45 to 33.7), Fisher's $p = 0.015$; online supplementary figure S5E) and was independent of PAP/ELP association with young age (online supplementary figure S9). Thus, IL-1/IL-6 inhibitor exposure may promote development of PAP/ELP-like disease and may qualitatively influence LD-associated features in a subset of patients with sJIA, among the substantially larger group of patients who derive striking benefit from these inhibitors.

Autopsy RNA sequencing data from the Genotype-Tissue Expression project show the lung is a major physiological producer of IL-1 and IL-6 in adults (online supplementary figure S10),⁵² and cytokine profiling suggests that circulating IL-1RA levels (reflecting the IL-1 activity) in young (<4 years) healthy children are 2× higher than in older healthy children.⁵³ In addition, NF κ B, a key transcription factor downstream of IL-1, stimulates angiogenesis and alveolarisation in the postnatal, developing lung.⁵⁴ These observations raise the possibility of a physiological role of IL-1/IL-6 in the lung, particularly in early childhood. The striking enhancement of LD risk by early age of sJIA onset suggests developmental vulnerabilities that may interact with the inhibitors.

A specific relationship between reduced IL-1 and PAP development is described in mice. IL-1 $\alpha^{-/-}$ mice (but not IL-1 $\beta^{-/-}$ mice) challenged with inhaled silicone, an inflammasome (NLRP3) activator,⁵⁵ develop PAP-like LD.⁵⁶ In the lung, IL-1 regulates granulocyte-macrophage colony-stimulating factor (GM-CSF) levels^{57,58} and macrophage function^{56,57}; disruption of either can lead to surfactant accumulation and PAP^{59,60} These findings imply a link between reduced IL-1 and PAP, but also suggest that additional triggers may be required for disease development, in line with the rarity of severe parenchymal LD among the overall population of patients with sJIA treated with IL-1/IL-6 inhibitors. The association of PAP and paediatric haematological malignancies, especially myeloid leukaemia, can be ascribed in some cases to dysregulation of the GM-CSF/GM-CSF receptor axis and consequent macrophage dysfunction.⁶¹

We found an outsized risk of LD in children with T21 and sJIA. T21 carries increased susceptibility to adverse drug reactions⁶² and to viral pneumonia.⁶³ Another contributing factor may be underlying type 1 interferonopathy, recently described in T21.⁶⁴ An association of T21 and PAP in the context of haematological malignancy also has been reported.⁶⁵

Drug hypersensitivity reactions can occur in children treated with biologic drugs for rheumatic disease.⁶⁶ A subset of LD cases met the criteria for DReSS (online supplementary tables S1 and S8), a delayed form of severe drug-related hypersensitivity with organ involvement that can include lung.^{17,67,68} DReSS findings included dramatic eosinophilia, often despite concurrent steroids, together with extensive, persistent rash, frequently involving the face, which is uncommon in sJIA.¹⁸ Altered drug metabolism in childhood

may increase risk of hypersensitivity reactions.⁶⁹ Another consideration is drug-induced interstitial lung disease (DiILD), previously reported in children with rheumatic disease on biologics.⁷⁰ DiILD has overlapping chest CT findings with LD in sJIA.⁷¹ No pathological findings are pathognomonic of DiILD,^{71,72} but PAP has been described.²⁴ Drug cessation is indicated when DReSS or DiILD is recognised.⁶⁸

Infection may exacerbate LD, trigger its detection or be causally linked. Pathogens identified at initial lung evaluation (online supplementary table S3) included rhinovirus (a cause of severe lower respiratory infection in young children⁷³), herpes viruses and pneumocystis, all of which require IL-1 for optimal host defence.^{55,74,75} Pneumocystis pneumonia (PCP) is a recognised cause of PAP²⁵ and is associated with high mortality in immunocompromised individuals.⁷⁶ PCP risk is also elevated in DReSS.⁷⁷ At least four of our cases had PCP; these were diagnosed by PCR of BAL, the preferred test in non-HIV immunosuppressed patients.⁷⁶ It seems prudent to consider prophylaxis for patients with sJIA with lymphopaenia or steroid use (consistent with recommendations⁷⁸) or T21.

LD in sJIA has been associated with MAS.^{13,79} In 23 out of 61 cases in our series, LD detection occurred with concurrent MAS. Out of these 23, 19 had their first MAS episode at or after LD diagnosis, suggesting that LD may trigger systemic inflammation. Consistent with this possibility, 4 of 11 cases with MAS co-occurred with initial detection of LD during three treatment trials of the inhibitors (n=331 subjects in total).⁴⁻⁶

PH with a range of severity was observed with or without pre-exposure to inhibitors and with or without PAP/ELP pathology. Out of 20 subjects, 2 lacked substantial parenchymal LD at PH detection. Together, these observations argue that PH in this LD cohort has heterogeneous biology.

Persistent arthritis (figure 4F) was less frequent in the pre-exposed LD cohort than in the sJIA cohort in the CARRA legacy registry (2010–2013),⁴² and of comparable frequency to children treated with IL-1 inhibition as first-line sJIA therapy. Inhibitor therapy may attenuate arthritis when given early or the LD cohort may be enriched for children with systemic inflammation-predominant disease.^{18,80}

Over 50 additional LD cases in sJIA have been reported to us since closing this series. The Food and Drug Administration (FDA) adverse event website (FDA Adverse Event Reporting System) shows 39 adults (rheumatoid arthritis (23), AOSD (11), other (5)) developing alveolar disease or PH on IL-1/IL-6 inhibitors and 4 DReSS cases (second quarter, 2019). An apparent discrepancy between adverse event reports and the frequency of sJIA-LD reported here may reflect its underdiagnosis or under-reporting.⁸¹

The association between cytokine inhibition and sJIA-LD and related mechanistic hypotheses demand further investigation. We acknowledge the limitations of retrospective data, use of historical/published data for controls, possible biases as mentioned and false discovery issues associated with multiple hypothesis testing in a large data set. With these limitations, one cannot assign causality to cytokine inhibition in LD in sJIA. Likewise, it is premature to make treatment recommendations solely on the basis of our findings. Therapeutic decision making for patients with sJIA-associated LD is challenging, and

currently individualised management is appropriate. However, in children with risk factors, close attention to subtle pulmonary symptoms is advised, and approaches for early detection of altered pulmonary function, guided by a pulmonary specialist, should be considered. In light of high fatality, efforts to determine LD prevalence, uncover molecular mechanism(s), and devise treatment and prevention approaches are urgently needed.

Supplementary Material

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Acknowledgements

The CARRA registry has been supported by the NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Arthritis Foundation. We thank all participants and hospital sites that recruited patients for the CARRA registry. The authors thank Drs Joseph A Kovacs, Jay K Kolls and Sergio Vargas for their expert input on pneumocystis pneumonia, Dr James Verbsky for contributing unidentified genetic data, and Dr Xuan Qin for PCP staining of a subset of biopsies. The authors also thank Dr Yuki Kimura for critical reading of the manuscript, Dr Claudia Macaubas for statistical assistance and Ms Melinda Hing for assistance with the manuscript.

Funding This work was supported by the sJIA Foundation (EDM), the Lucile Packard Foundation for Children's Health (EDM), CARRA-Arthritis Foundation grant (EDM, VES), Life Sciences Research Foundation (GC), Bio-X Stanford Interdisciplinary Graduate Fellowship (JoB), Stanford Graduate Fellowship and the Computational Evolutionary Human Genetics Fellowship (KJ), Bill & Melinda Gates Foundation (PK), and NIH 1U19AI109662 (PK), U19AI057229 (PK) and RO1 AI125197 (PK).

Competing interests VES reports personal fees from Novartis. GD reports personal fees from Novartis. SC reports personal fees from Novartis and grants from AB2 Bio. GS reports personal fees from Novartis. KB reports personal fees from Novartis. RQC is co-PI of an investigator-initiated clinical trial funded by SOBI. RD reports personal fees from Boehringer Ingelheim, other from NowVitals, personal fees and other from Triple Endoscopy, other from Earables, and NowVitals with patents and lung-related device development. AAG reports grants and personal fees from Novartis and grants from NovImmune. SL reports personal fees from Novartis. RS reports personal fees from Novartis, NovImmune and SOBI. SS reports personal fees from Novartis. MLS reports personal fees from Novartis. LRY reports other from Up-To-Date and other from Boehringer Ingelheim, outside the submitted work. EDM reports grants from Novartis.

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Key messages

What is already known about this subject?

- Pleuritis is common in systemic-onset juvenile idiopathic arthritis (sJIA), but parenchymal lung disease (LD) is very rare, with sporadic reports and one multicentre series of 25 cases (Kimura *et al*, 2013) in the literature.

Key messages

What does this study add?

- In the last decade, increasing numbers of cases of high fatality, parenchymal LD are being detected worldwide, with a majority characterised by unusual clinical and radiological features, in association with a variant of pulmonary alveolar proteinosis/endogenous lipid pneumonia.
- Children with trisomy 21 and sJIA or with sJIA onset at <5 years are at increased risk of LD, and an unexplained association with anaphylaxis to tocilizumab is observed.
- Prodromal features can include lymphopaenia, rising serum ferritin and evidence of drug hypersensitivity (peripheral eosinophilia, extensive atypical rash).

How might this impact on clinical practice or future developments?

- This study highlights risk factors, prodromal features and clinical characteristics that should raise suspicion of LD, which otherwise can remain subclinical until severe and life-threatening.
- Clinician awareness of delayed drug hypersensitivity to interleukin (IL)-1 and IL-6 inhibitors could lead to earlier recognition and management, including cessation of the implicated drug.
- Pneumocystis pneumonia may complicate LD in sJIA; consideration of prophylaxis is warranted.

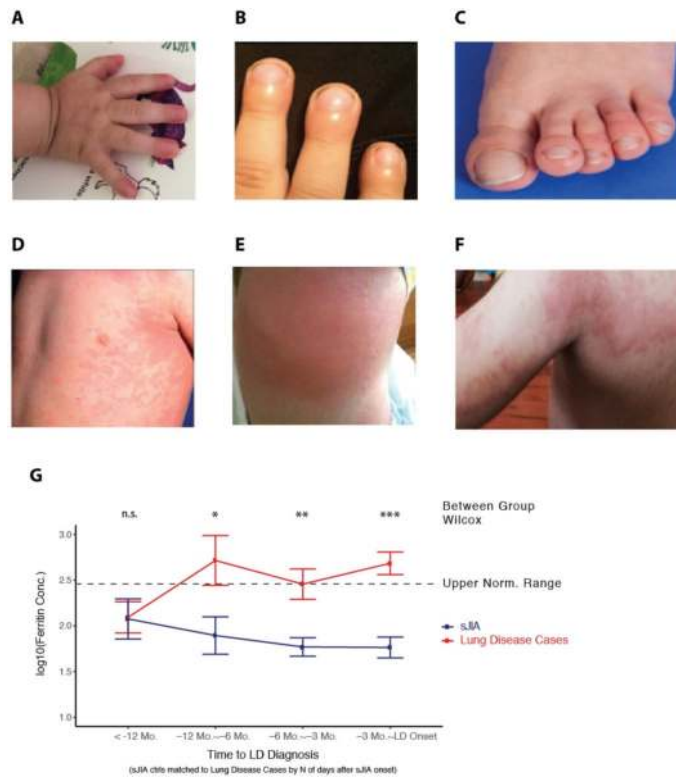


Figure 1. Distinctive clinical features in systemic juvenile idiopathic arthritis (sJIA) with lung disease (LD) and survival outcome. (A) Acute erythematous digital clubbing; (B, C) bulbous deformity with erythematous clubbing of fingers (B) and toes (C); (D) typical salmon-coloured, macular sJIA rash (evanescent); and (E, F) atypical rashes that occur before LD detection: (E) oedematous, urticarial, non-evanescent rash (knee) and (F) serpiginous, eczematous, non-evanescent rash with hyperpigmented borders. (G) Mean \pm SE blood ferritin values of propensity-matched (online supplementary figure S3) sJIA controls (blue) and LD cases (red) across time points relative to LD diagnosis. n.s., $p>0.1$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, by Wilcoxon rank-sum test.

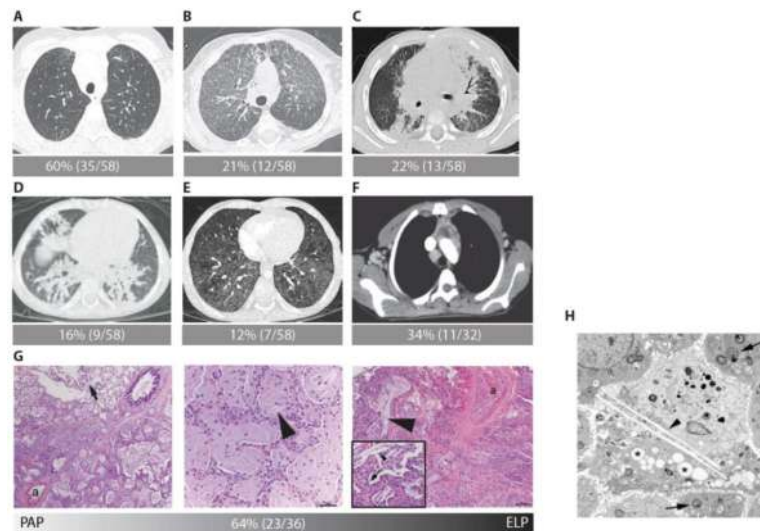


Figure 2.

Distinctive radiological and pathological features. Panels A–E: representative axial chest CT images: (A) multilobar, predominantly peripheral septal thickening, most marked in the lower lung, parahilar and/or anterior upper lobes with or without adjacent ground-glass opacities; (B) crazy-paving; (C) peripheral consolidations; (D) peribronchovascular consolidations; (E) predominantly ground-glass opacities; and (F) hyperenhancing lymph nodes on contrast-enhanced CT. Panels G–H: histopathological findings (H&E staining) along the pulmonary alveolar proteinosis/endogenous lipid pneumonia (PAP/ELP) spectrum. Alveolar filling with eosinophilic proteinaceous material (G, left), admixed with a variable degree of ELP, indicated by cholesterol clefts (arrowheads) and foamy (lipid-containing) macrophages (G, middle and right), as described.⁸²⁸³ Regions of PAP/ELP accompanied by type II alveolar epithelial cell hyperplasia (G, right insert, arrow), mild to moderate interstitial infiltration by inflammatory cells and lobular remodelling (airspace widening with increased interstitial smooth muscle). Typically, PAP/ELP findings were patchy, with involved areas juxtaposed to the normal lung (G, left, arrow). Pulmonary arterial wall thickening; a, artery (G, right). In A–G, the number of cases with pattern/number of assessable cases are indicated. (H) Electron micrograph showing normal lamellar bodies within type II cells (arrows) and macrophage (centre), containing lamellar debris, lipid (*) and cholesterol clefts (arrowhead). Original magnification $\times 7000$. Four PAP/ELP cases (one each: ABCA3 and CSF2RB variants), stained for surfactant proteins (SP-B, proSP-C, SP-D, ABCA3, TTF-1), demonstrated robust immunoreactivity (not shown).

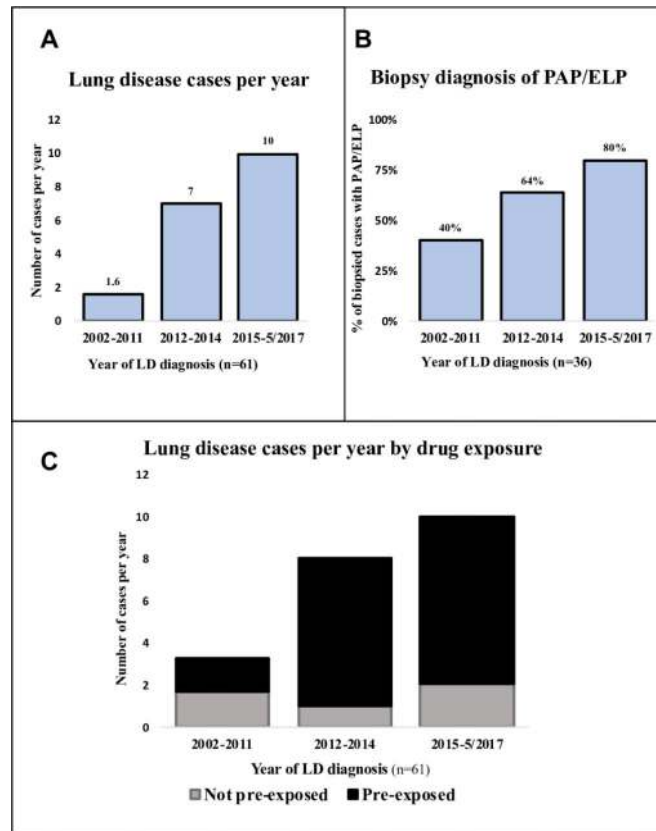


Figure 3.

Annual number of reported cases of LD and PAP/ELP pathology. (A) Annual number of LD cases in this series (total n=61). (B) Percentage of biopsied LD cases (n=36) with PAP/ELP pathology, grouped by year of LD diagnosis. (C) Annual incidence of LD, indicating proportions exposed (black) or not (grey) to anti-IL-1/IL-6 inhibitors. ABCA-3, ATP binding cassette subfamily A member 3; IL, interleukin; LD, lung disease; PAP/ELP, pulmonary alveolar proteinosis/endogenous lipoid pneumonia; proSP-C, prosurfactant D; SP-B, surfactant protein B; SP-D, surfactant protein D; TTF-1, thyroid transcription factor 1.

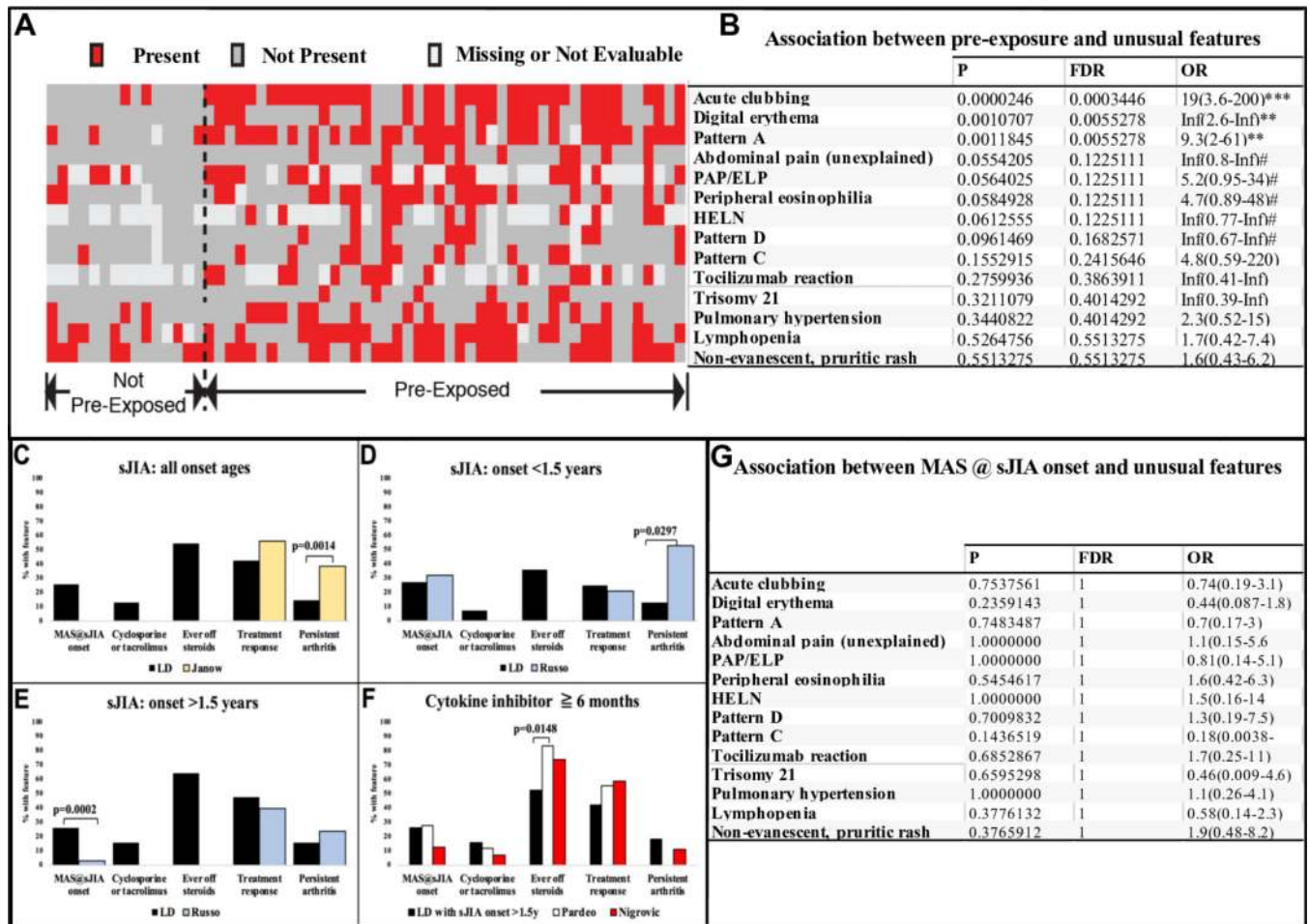


Figure 4.

Association between unusual features and pre-exposure to anti-IL-1/IL-6 or MAS at sJIA onset. (A) Heat map indicating occurrence of unusual clinical and radiological features (rows) by subjects (columns), grouped by pre-exposure status. (B) Statistical analysis for panel A, indicating p values, FDR and OR with 95% CI. Inf, infinite, # $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (C–F) Comparison of severity-related features in pre-exposed LD cases versus published sJIA cohorts. (C) Pre-exposed LD cases compared with Janow *et al*⁴² (D) Pre-exposed LD cases with sJIA onset <1.5 years, compared with comparable age group in Russo and Katsicas⁴³; cut-off at <1.5 years was chosen by Russo and Katsicas, based on developmental difference before versus after 18 months. (E) Pre-exposed LD cases with sJIA onset >1.5 years, compared with comparable age group in Russo and Katsicas.⁴³ (F) Pre-exposed LD cases treated with IL-1/IL-6 inhibitors for ≥ 6 months compared with comparable groups in Pardeo *et al*⁸⁴ and Nigrovic *et al*.⁸⁰ No bar indicates unavailable data. For details on definitions and published cohorts, see online supplementary table S6. (G) Statistical analysis of associations between MAS at sJIA onset and unusual clinical features of LD in sJIA, indicating p values, FDR and OR with 95% CI. FDR, false discovery rate; HELN, hyperenhancing lymph nodes; IL, interleukin; LD, lung disease; MAS, macrophage activation syndrome; PAP/ELP, pulmonary alveolar proteinosis/endogenous lipid pneumonia; sJIA, systemic juvenile idiopathic arthritis.

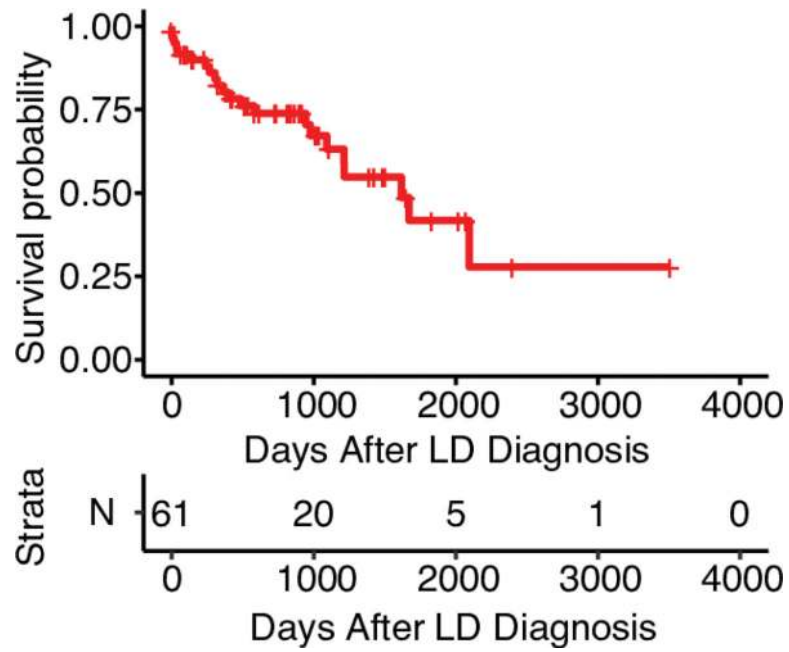


Figure 5. Survival outcome in systemic juvenile idiopathic arthritis cohort with lung disease (LD). The number of survivors at a given time point after LD diagnosis is shown (strata).

Table 1

Demographic characteristics

	sJIA-lung disease cohort vs CR [†] control		sJIA-lung disease cohort by subgroup [‡]			
	sJIA-lung disease	sJIA (CR)	P value [§]	sJIA-like	sJIA-ILAR+	OR (95% CI) [¶]
Sex (female, %)	66% (40/61)	59% (278/471)	0.41	81% (13/16)	60% (27/45)	0.35 (0.056 to 1.5)
Age, median years (IQR)	2.8 (1.2–6.3)	5.2 (2.8–9.8)	1.7×10 ⁻⁵ ***	2.3 (0.9–7.8)	3.1 (1.5–6.2)	0.43 (0.13 to 1.45)
Race			0.53			
White	62% (38/61)	66% (308/466)		50% (8/16)	67% (30/45)	2 (0.53 to 7.4)
Black	8.2% (5/61)	11% (50/466)		6.2% (1/16)	8.9% (4/45)	1.5 (0.13 to 77)
Other ^{††}	30% (18/61)	23% (108/466)		44% (7/16)	24% (11/45)	0.42 (0.11 to 1.7)
Region (only USA) ^{‡‡}			0.02*			
Northeast	19% (10/53)	28% (123/442)		27% (4/15)	16% (6/38)	0.5 (0.12 to 2.17)
Midwest	25% (13/53)	29% (129/442)		20% (3/15)	26% (10/38)	1.43 (0.33 to 6.1)
South	17% (9/53)	23% (101/442)		20% (3/15)	16% (6/38)	1.25 (0.29 to 5.3)
West	40% (21/53)	20% (89/442)		33% (5/15)	42% (16/38)	1.45 (0.42 to 5.1)
Genetics						
Trisomy 21	9.8% (6/61)	0.2% (1/471)	0.04 ^{¶¶}	12% (2/16)	8.9% (4/45)	0.69 (0.087 to 8.4)
Familial HLH	7.1% (2/28) ^{§§}	–	–	22% (2/9)	0% (0/19)	0 (0 to 2.4)

* P<0.05

** p<0.01

*** p<0.001.

For OR, 95% CI is shown.

[†] CR, CARRA registry. Diagnosed as sJIA per physician report without specific verification of ILAR features.

[‡] sJIA-ILAR+ or sJIA-like classification verified (see the Methods section). sJIA-like had no arthritis (13) or failed modified fever criteria (3).

[§] For categorical items, Fisher's exact tests (including the multicategory form) were performed. For age, a Wilcoxon rank-sum test was performed.

[¶] OR showed no significant difference with the exception of trisomy 21 vs CR (OR=50).

^{††} Other: Hispanic (5), Middle Eastern (1), Asian (2), multiethnic (8) and other (2).

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Based on US Census Bureau population-balanced regions: www2.census.gov/geo/pdfs/maps-data/maps/reference/aus_regdiv.pdf.

§§ Diagnosed by clinical testing; one with 2 UNC13D mutations and one with UNC13D/PRF1 mutations; both sJIA-like.

HLH, haemophagocytic lymphohistiocytosis; ILLAR, International League of Associations for Rheumatology; sJIA, systemic juvenile idiopathic arthritis.