Pediatric Systemic Juvenile Idiopathic Arthritis related Lung Disease: Description of clinical cohort and review of management.

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Abstract

Beginning in the early 2010s, an increased incidence of interstitial lung disease in systemic juvenile idiopathic arthritis (sJIA-LD) in pediatric patients has been identified. Despite the increase in prevalence of sJIA-LD, little is known about this disease process and effective therapeutic management. In this single-center, retrospective case series of 9 patients, we analyze demographic, clinical, radiographic, and laboratory data to corroborate common clinical characteristics and describe an approach for diagnosis and monitoring of interstitial lung disease in children with sJIA. Our results were similar to other described cases of sJIA-LD as patients in our cohort were more likely to be younger, have a history of macrophage activation syndrome and prior use of biologic therapies. In contrast to prior studies, they did not present with lymphadenopathy and hepatosplenomegaly. We discuss our management of this rare disease process. More research is necessary to understand the increased incidence and treatment of sJIA-LD in pediatric population.

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA), the least common subtype of juvenile idiopathic arthritis (JIA), is a chronic inflammatory disease characterized by fever, arthritis, and at least one of the following: rash, generalized lymphadenopathy, hepatomegaly/splenomegaly, and/or serositis ¹. Compared to other subtypes of JIA, sJIA can cause more severe systemic complications including pericarditis and pleuritis. Pulmonary complications of sJIA such as pulmonary hypertension, interstitial lung disease, and pulmonary alveolar proteinosis are rare, but can cause significant morbidity and mortality²³. Childhood interstitial lung disease (chILD) in general is a rare and heterogenous group with prevalence ranging from 0.8 - 2.1 per million in Australia and Asia to 3.6 cases per million in the United Kingdom and Ireland ⁴⁵. Since the early 2010s, researchers identified an increased incidence of interstitial lung disease (sJIA-LD) in pediatric patients with sJIA, with a 2020 cohort estimating a new prevalence of almost 7% ⁶. This is a new development in the clinical presentation of sJIA, as prior to 2000, published literature on sJIA-LD were primarily case reports⁷. In 1980, Athreya et al reported a rough estimate of 4% of patients with juvenile rheumatoid arthritis had pleuropulmonary disease, but they did not describe percentage of lung disease in sJIA⁸. Given the high mortality rate of sJIA-LD⁹, researchers have attempted to identify the pathophysiology and underlying risk factors of sJIA-LD. Identified demographic risk factors include disease onset at less than 2 years of age and presence of trisomy 21 ²⁹. Common clinical features were minimal respiratory symptoms, lymphadenopathy, hepatosplenomegaly, and clubbing ⁶¹⁰. Radiographic findings included septal thickening and ground glass opacities⁶⁹.

Therapeutic management plans are complicated in children with sJIA-LD. Some studies have identified a correlation between increased use of anti-cytokine therapy for sJIA in the early 2010s and the increase in sJIA-LD ⁶⁹. However, one confounding factor is that patients with sJIA-LD often have increased severity of systemic symptoms, which could require increased medication exposures. For instance, a history of macrophage activation syndrome (MAS), a life-threatening complication of rheumatic disease, appears to
be a common finding in those with sJIA-LD, highlighting the severity of these patients’ disease. Despite the increase in prevalence of sJIA-LD, little is known about this disease process, and we seek to broaden the field of knowledge on this subject. In this single-center, retrospective case series of 9 patients, we analyzed demographic, clinical, radiographic, and laboratory data to corroborate common clinical characteristics and present our clinical guidelines for diagnosis and monitoring of interstitial lung disease in children with sJIA.

METHODS

A retrospective case review was performed with identification of all patients from a single tertiary care center providing service throughout the Midwest region. Patients were identified from electronic medical records from January 2003 to July 2021 with the diagnostic codes for systemic juvenile idiopathic arthritis and with diagnostic codes for interstitial lung disease, dyspnea, or hypoxemia at any time throughout their lifetime. A total of 134 patients were identified to have both a diagnosis of sJIA and at least one of the above respiratory complaints; 9 were confirmed on manual chart review to have true interstitial lung disease related to sJIA. Of these 9 patients, they had to meet both the International League of Associations for Rheumatology (ILAR) criteria for sJIA from two different pediatric rheumatology reviewers and meet criteria for ChILD from two different pediatric pulmonology reviewers. Race/ethnicity data were obtained via review of medical records and were categorized by self-identified ethnicity as well as self-identification with Hispanic/Latino or Non-Hispanic/Latino origin. The case series was reviewed by the Children’s Mercy Institutional Review Board and an exemption was granted.

RESULTS

Patients in this case series were more likely to be female, white, and non-Hispanic. The average age of presentation for sJIA-LD was 4.6 years, approximately 1.5 years after initial presentation for sJIA. No significant family history was identified (Table 1). Clinical presentation and treatment exposure before and after diagnosis of sJIA-LD are summarized in Table 2. On initial presentation, the majority (n=8, 89%) of patients had active sJIA disease, and almost half (n=4, 44%) had a diagnosis of macrophage activation syndrome (MAS).

Prior to sJIA-LD diagnosis, all patients had received treatment with high-dose steroids, NSAIDs, and anakinra at various times. Cyclosporine and tocilizumab, an IL-6 inhibitor, had been used in 5 patients (56%). Many patients had previously received intravenous immunoglobulin (IVIG) for suspected Kawasaki or incomplete Kawasaki disease prior to diagnosis of SJIA (n=5; 56%). Adverse effects were common and included weight gain and Cushingoid appearance secondary to steroid exposure (n=6), transaminitis secondary to anakinra and methotrexate (n=3), hirsutism secondary to cyclosporine (n=2), and suspected DRESS syndrome secondary to tocilizumab (n=1).

The most common respiratory symptoms around time of sJIA-LD diagnosis were cough (n=6, 67%) and clubbing (n=5, 56%). Due to age and ability, only two patients completed pulmonary function testing; one was found to have decreased FVC and FEV1 consistent with a restrictive pattern, while the second showed only mild decrease in DLCO. Of those unable to complete pulmonary function testing, four patients completed a 6-minute walk test, with results less than expected for age. The remaining participants were unable to complete this evaluation due to physical limitations or developmental ability.

Following sJIA-LD diagnosis, most common rheumatologic treatments included high dose steroids, tofacitinib, and tocilizumab. Iatrogenic adverse reactions were prevalent, with six patients developing exogenous Cushing syndrome, including one progressing to osteoporosis with vertebral compression deformities and cataracts. Additional common pulmonary treatment included inhaled corticosteroids and prophylactic antibiotics for Pneumocystis jiroveci in those with significant immunosuppression.

Laboratory Findings

Most patients had elevated interleukin-18 (IL-18), lactate dehydrogenase, erythrocyte sedimentation rate, c-reactive protein, and ferritin for age at time of sJIA-LD diagnosis (see Supplemental Table 1). Lymphopenia and anemia were the most common hematologic abnormalities identified.
Diagnostic Imaging Studies

Clinical diagnosis of sJIA-LD was supported by chest computed tomography (CT) for all patients. Representative images from the initial diagnostic image are shown in Figure 1 for all nine patients. The most common findings were septal thickening (n=9), ground glass opacities (n=8), and peripheral consolidation (n=5). Other reported findings included adenopathy, interstitial opacities, subsegmental mosaic attenuation, mild bronchiectasis, and findings suggestive of pulmonary fibrosis (Table 3). One patient had findings consistent with larger pulmonary artery concerning for possible pulmonary hypertension. The lower lobes were most frequently affected.

In five patients, serial CT imaging was obtained to guide management (Figure 2). For patient 1, chest imaging showed improvement after intensive treatment with monthly IV methylprednisolone, etoposide, IVIG and tocilizumab; subsequently this patient was able to be weaned to IVIG and tocilizumab alone. For patient 4, chest imaging showed clinical progression of sJIA-LD despite intensive treatment with failure of multiple immunosuppressive medications. This was subsequently stabilized after bone marrow transplantation for refractory sJIA. Despite similar chest imaging before and after bone marrow transplantation, patient 4 did have reversal of spirometry findings. Patient 5 showed improvement in chest imaging after treatment with tocilizumab and tofacitinib. Imaging for patient 6 reflects initial worsening fibrosis, which followed COVID infection, admission for MAS, and prolonged cough. Subsequent imaging showed stable changes following increased rheumatologic and pulmonary treatment, including tocilizumab, methylprednisolone, tofacitinib, fluticasone propionate / salmeterol, azithromycin, and montelukast. For patient 9, the initial presentation was concerning for MAS, and chest CT findings reflect mainly ground glass opacities and pleural effusions. Subsequent images lead to diagnosis of sJIA-LD as they were more consistent with septal thickening, peripheral consolidation, and bronchial thickening. Patient 9’s imaging also stabilized after treatment with methylprednisolone, tocilizumab and tofacitinib.

Eight patients completed at least one echocardiogram, with the most recent results within normal limits for five cases. Significant findings include left ventricular diastolic dysfunction for one case, mild left ventricular dilation for one case, and mild right coronary artery and left anterior descending coronary artery dilation for one case.

Histopathology

Most of our cohort were diagnosed via chest imaging and with a history of known sJIA. Four patients underwent bronchoscopy and three of the four also underwent lung biopsy for further confirmation of suspected diagnosis (Table 4). Pathological findings from bronchoalveolar lavage (BAL) were mixed. Two patients showed neutrophil predominance while the remaining two patients showed macrophage/monocyte predominance. Two patients showed hemosiderin-laden macrophages and two patients showed lipid-laden macrophages on BAL. All patients were negative for bacterial, fungal, and pneumocystis-like organisms on BAL. Regarding lung biopsies, all 3 cases showed findings of mixed neutrophilic, lymphocytic, eosinophilic inflammation with cholesterol clefts or lipid laden macrophages, findings of pulmonary alveolar proteinosis, with no signs of vasculitis or capillaritis. Two cases showed alveolar and interstitial inflammatory changes consistent with chronic inflammation with pulmonary alveolar proteinosis. The third case showed an “acute patchy to diffuse bronchopneumonia,” with concern for possible lipid pneumonia; the interpretation was complicated by an acute inflammatory process overlapping with mild chronic interstitial changes. In this patient’s case, there was a bronchoscopy with BAL after lung biopsy which demonstrated Periodic Acid-Schiff positive staining and an elevated lipid laden macrophage index concerning for pulmonary alveolar proteinosis on BAL sample.

Genetics

Genetic analyses were completed for 7 of 9 cases. One patient was known to have Trisomy 21, and another patient had a known diagnosis of Kabuki syndrome. Analyses for 2 cases revealed variants of uncertain significance (VUS) associated with hemophagocytic lymphohistiocytosis (HLH). One VUS for primary ciliary dyskinesia (PCD) was identified in one patient. For this patient, bronchoscopy and ciliary brushing was
completed with results being inconsistent with PCD. One VUS for PLCG2-associated Antibody Deficiency and Immune Dysregulation syndrome/APLAID/FCA3 immune dysfunction syndrome was also identified.

DISCUSSION

Our patients shared many clinical characteristics with previously described patients. Previously identified demographic risk factors included younger age of disease onset, specifically less than 2 years of age, and presence of trisomy 21 \(^2,9\). Seven of our patients (78\%) were under school age at diagnosis of sJIA-LD, though our average age (4.6 years) was older than previously described. The majority presented within 2 years after initial diagnosis of sJIA. Of note, due to their mild presentation, one patient did present with sJIA-LD in early adolescence, almost 7 years following initial diagnosis of sJIA. One of the nine patients had trisomy 21 (11\% compared to the pediatric prevalence of approximately 1 out of 700 per the CDC). Additionally, in our cohort, patients were more likely to be female and to self-identify as white. One prior study identified a female predominance \(^\text{10}\), but our literature review did not identify other studies that showed race/ethnicity differences in sJIA-LD cohorts. Patients with sJIA-LD have high morbidity and mortality; at the time of this paper, none of our patients have passed from sJIA-LD.

Rheumatology

From a rheumatologic perspective, all patients in our cohort had active sJIA disease; 89\% of participants had a history of macrophage activation syndrome (MAS), with 33\% having MAS recently before their diagnosis of sJIA-LD. History of MAS, particularly recurrent episodes of MAS, is also a common finding in other sJIA-LD cohorts\(^2,6,10\). Our patients showed elevations in inflammatory cytokines, specifically IL-18, which has also been seen in other studies. IL-18 elevation has been implicated as a marker of sJIA disease activity, development of MAS, and in sJIA patients with pulmonary alveolar proteinosis \(12,13\). Other laboratory trends include a prodrome of lymphopenia, ferritin, and peripheral eosinophilia \(9\). These trends hint at sJIA-LD’s underlying pathophysiology, but further investigation is needed. Common clinical features identified in previous cohorts included lymphadenopathy and hepatosplenomegaly \(6,10\). However, these were not identified in our patient population.

Saper, et al. identified several patients with delayed drug hypersensitivity in their case series \(9\). They noted a high frequency of anaphylactic reactions to the interleukin (IL)-6 inhibitor, tocilizumab. In a cohort of 25 cases, 68\% of patients were taking a biologic disease-modifying antirheumatic drugs; two subsequent cohorts likewise observed a higher number of adverse effects related to anti-cytokine drugs \(6,9,10\). As previously mentioned, all patients in our case series were treated with anakinra (an IL-1 inhibitor). Five patients also received IL-6 inhibitor tocilizumab; one patient received IL-1β inhibitor canakinumab. In our case series, one of the four patients treated with tocilizumab developed confirmed DRESS. No other treatment was associated with DRESS. No patients developed anaphylaxis following use of tocilizumab.

Interestingly, five out of nine patients initially presented with symptoms concerning Kawasaki disease. This highlights the importance of keeping sJIA on the initial differential and completing early evaluation if other aspects of the clinical course are not consistent with Kawasaki disease. There is no current evidence that treatment for Kawasaki disease (such as steroids, IVIG, and infliximab) precipitates interstitial lung disease.

Pulmonology

Common reported clinical features were minimal respiratory symptoms and clubbing \(6,10\). Saper et al specifically describe clubbing as acute and erythematous \(9\). In contrast to the minimal respiratory symptoms previously reported, the majority of our patients did have chronic cough. Clubbing was the second most common finding in our patients. Other respiratory symptoms of sJIA-LD reported included tachypnea and decreased exercise tolerance \(14\). Similarly, other respiratory signs within our cohort included tachypnea, crackles, retractions, failure to thrive, and respiratory failure. 6-minute walk tests and spirometry were used to quantify patients’ pulmonary function, but results were limited for several reasons. First, only 2 patients were over 5 years old on age of presentation of sJIA-LD diagnosis and eligible for spirometry. Second, the joint symptoms of sJIA limited patients’ ability to complete the 6-minute walk test, confounding the inter-
pretation of results. Although pulmonary function testing was limited in our patients, abnormal spirometry can be a presenting sign of developing lung pathology in patients with juvenile arthritis. A study completed in India demonstrated that children with juvenile idiopathic arthritis, even without respiratory symptoms, significantly more likely to show a restrictive pattern on spirometry. There is an ongoing need to identify appropriate measures of pulmonary function to evaluate and monitor patients with sJIA-LD as these patients are typically too young to perform spirometry and too large for infant pulmonary testing.

The most common radiographic findings in our cohort are consistent with those previously reported, specifically peripheral opacities, septal thickening, and ground glass opacities. In four patients, subsequent CT imaging was useful in monitoring response to treatment and helped to guide management of disease. While high-resolution computed tomography (HRCT) remains the gold standard imaging method for evaluating sJIA-LD, a recent study found that lung ultrasound findings correlated well with HRCT findings. In the future, lung ultrasound may provide a useful, lower cost, radiation free imaging modality for monitoring sJIA-LD.

Lung biopsy has also been recommended as part of the diagnostic workup of patients with sJIA-LD, as pathological results may inform and guide clinical management. For example, pathologic findings can be helpful in establishing a diagnosis, justifying empiric therapy, and narrowing treatment modality in specific cases. Prior common findings on histopathology included pulmonary alveolar proteinosis, endogenous lipoid pneumonia, and vasculopathy. Two of the three lung biopsies completed for our patients clearly demonstrated proteinaceous material consistent with pulmonary alveolar proteinosis, while the third had findings consistent with pulmonary alveolar proteinosis on BAL. In addition, all 3 had evidence of either lipoid pneumonia, cholesterol clefts, or lipid laden macrophages.

In a few of the cases of sJIA-LD, inhaled therapies such as inhaled corticosteroids and bronchodilators were attempted for symptomatic relief. These were primarily in patients with evidence of bronchodilator responsiveness either by physician assessment or parental report. In one severe case of sJIA-LD in our cohort, anti-inflammatory oral azithromycin was attempted prior to discussion of bone marrow transplantation. Oral azithromycin has been used in treatment for general childhood interstitial lung disease to suppress inflammation; one study hypothesized that the benefits seen in treating lymphocytic airway inflammation in patients following lung transplant could also benefit patients with sJIA-LD, who often have lymphoplasmacytic infiltrates on biopsy. Bone marrow transplant was offered to families of two of our patients with severe refractory sJIA-LD; one successfully completed bone marrow transplant. In that patient, there was improvement of clinical symptoms and reversal of mixed obstructive and restrictive lung disease with normalization of spirometry (FEV1, FVC, FEV1/FVC) and air trapping on plethysmography after bone marrow transplantation.

**Echocardiogram / Cardiac Function**

Of the 8 patients who completed echocardiograms, only 3 showed abnormalities, involving most commonly the left ventricle. This is consistent with a prior study which showed that patients with sJIA in general had larger left ventricle size and volume.

**Genetic Evaluation**

While the expanded availability of genetic testing has improved the general identification of chILD diseases, a specific genetic variation has not been implicated in the development of interstitial lung disease in patients with sJIA. Two patients had known genetic diagnoses – Trisomy 21 and Kabuki syndrome. Beyond this, genetic testing completed on 7 patients in our cohort identified only variants of uncertain significance. No common genetic change was observed.

**Limitations**

There may be several limitations to these findings. Without a comparison group, it is difficult to prove which specific findings may predict development of interstitial lung disease or response to treatment. As a small case series conducted at a single center, the study is prone to bias, which can limit generalizability to
broader populations. The study design did include clear objectives and well-defined inclusion and exclusion criteria for cases, which limited selection bias. We followed all patients to the conclusion of the designated time frame, improving validity.

Medical Management

At our institution, we have found standardization of diagnostic testing and medical management provided more consistent care for patients with SJIA-ILD. These complex patients should be routinely evaluated by a multidisciplinary group including rheumatology, pulmonology, nutrition, social work, respiratory therapy, and physical therapy for diagnosis, surveillance, and management of disease and comorbidities. Our recommended diagnostic testing and medical management are summarized in Table 5.

In conclusion, sJIA-LD is a rare presentation of an uncommon disease process. Our cohort is similar to those previously described. These children have high morbidity from both disease and iatrogenic side-effects requiring multi-disciplinary care. It is important to note though, at the time of this article, in our cohort none are deceased and with aggressive interventions, can have improvement in their clinical symptoms. Further research is necessary to describe the pathophysiology of sJIA-LD, appropriate treatment, and effective management of this complex disease process.

REFERENCES


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