Innovations in the Care of chILD Associated with Connective Tissue Disease and Immune Mediated Disorders

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Abstract

Childhood interstitial lung disease associated with connective tissue disease and immune mediated is the second most common chILD diagnostic category. As knowledge of the molecular and genetic underpinnings of these rare disorders advances, the recognized clinical spectrum of pulmonary manifestations that can be associated with them continues to broaden. This review will focus on chILD and other pulmonary complications associated with primary immune disorders, namely monogenic inborn errors of immunity as well as acquired systemic autoimmune and autoinflammatory diseases. Pulmonary complications, including ILD in these diseases can confer increased risk for morbidity and mortality and can be complex to manage due to the multiple organ systems that can be impacted in these systemic disorders. Thankfully, pulmonologists do not have to work alone. These diseases often have stereotypical patterns of extra-pulmonary features which aid in their recognition. In collaboration with a multidisciplinary team of subspecialists, the pulmonary and other systemic manifestations can be managed effectively together. The goal of this review is to familiarize the reader with the distinct patterns of ILD and associated systemic/immunologic features that are characteristic of monogenic inborn errors of immunity and systemic autoimmune and autoinflammatory diseases. In addition, this review will highlight current, emergent and innovative therapeutic strategies and will underscore the important role of multidisciplinary management to improving outcomes for these patients.

Introduction

Childhood onset interstitial lung disease (chILD) due to connective tissue or immune-mediated disorders comprises 16.5% of patients in the U.S. Children's Interstitial Lung Disease Research Network Registry Cohort [1]—the second largest diagnostic category. This is likely an underestimate, as some patients may have secondary immune-mediated ILD in the "alveolar hemorrhage", "other specific multisystemic disorders", and "environmental/toxic/drug related" categories (9.2%, 7%, and 2.2% of the registry cohort, respectively).

The goal of this review is to familiarize the reader with the distinct patterns of ILD associated with monogenic inborn errors of immunity and systemic autoimmune and autoinflammatory diseases, and to highlight current and emerging therapies. Through advances in our understanding of cellular and genetic pathophysiology and improvements in multidisciplinary management, the care of children with immune mediated chILD is rapidly advancing.

General Approach to Evaluation of the Patient Suspected to have Immune Mediated ChILD—The Importance of a Multidisciplinary Approach

Evaluation of ILD in patients with immunologic diseases ideally involves a multi-Candisciplinary team given the complexity of these patients, many of whom have multiple organ systems involved. Multi-disciplinary discussions (MDDs) are the current gold standard in diagnosis of ILD in adults. Prior studies show that clinicians working together have greater diagnostic accuracy [2-6] and that MDDs often result in a change

in the diagnosis of ILD (over 50% of cases discussed in one case series [7]) with a significant reduction in disease categorized as "unclassifiable" [7, 8].

Given that pulmonary involvement can sometimes be the first, most prominent, most acutely life-threatening and/or most chronically life-limiting manifestations of these diseases, the pediatric pulmonologist is an essential member of the multi-disciplinary care team [9]. Because respiratory complaints can be the first presenting symptom, making a diagnosis of immune-mediated ILD requires a high index of suspicion, as initial clinical presenting signs of ILD may be subtle and frequently mistaken for more common respiratory conditions such as asthma or recurrent pneumonia. A generalized approach to diagnosis of suspected immune-mediated chILD [10] is outlined in Figure 1.

ChILD Associated with Inborn Errors of Immunity

Historically, single-gene or "monogenic" immune system disorders were referred to as primary immune deficiencies, implying susceptibility to infection as a main clinical feature. However, such genetic defects can also drive autoimmunity, lymphoproliferation, and autoinflammation. To capture the broader immune dysregulation associated with these disorders, the currently used term is "inborn errors of immunity" (IEI) [11-15]. There are ten groups of IEIs based on the International Union of Immunological Societies Expert Report, including "diseases of immune dysregulation" and "autoinflammatory disorders [11]. The immune dysregulation (often marked by polyautoimmunity) and autoinflammatory IEIs can predispose to pulmonary complications such as ILD [13-15].

[13]. With greater implementation of clinical genetic testing and confirmatory functional testing of new variants, variants in nearly 500 genes have been identified as causing IEIs [11].Due to strong genetic drivers, ILD secondary to IEIs may present earlier than ILD secondary to acquired systemic autoimmune and autoinflammatory diseases. In fact, pulmonary features may present as the earliest manifestation of an IEI. Thus, pulmonologists may be the first clinician to meet a patient with a yet undiagnosed IEI. Patients with known IEIs are also often referred to pulmonologists for screening or treatment of pulmonary complications. However, it is important to recognize that even monogenic disorders can have incomplete penetrance and variable expressivity based on environmental factors (toxins/infections), resulting in a spectrum of disease severity.

IEIs can present with infectious and non-infectious pulmonary complications. IEIs with predominant features of immune deficiency present most commonly with upper and lower infections, including bronchitis, pneumonia, and complicated pneumonia or with bronchiectasis secondary to recurrent infection [16]. Specific non-infectious pulmonary complications include structural changes (bronchiectasis, small airway disease, pneumatoceles and other parenchymal changes), inflammatory lung disease (interstitial lung disease and granulomatous lung disease), and tumors (lymphoreticular and solid lung tumors) [16]. The pathology of pulmonary complications of IEIs is characterized by patchy or diffuse inflammation, which can occur in multiple compartments of the lung, including the alveolar, interstitial, vascular, pleural or airway compartments [17], with most common patterns summarized in Table 1.

For non-infectious pulmonary complications, understanding the immune and genetic mechanisms underpinning these disorders can assist with diagnosis of ILD [17]. For example, some antibody and combined immunodeficiencies lead to immune dysregulation and ILD when there is some preserved T cell function but loss of T cell immune tolerance. Additionally, lack of B-cell regulation can lead to neutrophil accumulation and activation of lung myofibroblasts causing fibrosis [18]. Patients with congenital defects of phagocytosis, such as in chronic granulomatous disease (CGD) can develop non-infectious pulmonary granulomatous disease [19]. If alveolar macrophages are affected secondary to immune mediated macrophage dysfunction this can lead to pulmonary alveolar proteinosis [20]. In any of these disorders, the lung inflammation can eventually lead to fibrosis if left untreated.

Insight to pathophysiology can also assist with treatment. In patients with common variable immune deficiency (CVID), ILD can be the first sign of the presence of IEI. The ILD in CVID tends to have a pathologic pattern in the spectrum of GL-ILD, which includes granulomatous lymphocytic interstitial lung disease (GL-

ILD), lymphocytic interstitial pneumonitis (LIP) and follicular bronchiolitis (FB) – or an overlap. ILD can be the first manifestation of CVID. CVID and GL-ILD may suggest more specific treatment approaches such as replacing immune globulin and treating with azathioprine and rituximab [21] unless a more specific IEI is identified.

For IEIs with broader immune dysregulation associated with ILD, we have found it helpful to group them into the following categories: STAT gain-of-function disorders (e.g., STAT1, STAT2, and STAT3 gain-of-function (GOF)), IPEX and IPEX-like syndromes (CTLA-4 Haploinsufficiency, LRBA deficiency), and those associated with autoinflammation driven vasculitis (COPA Syndrome, Sting-Associated Vasculopathy of Infancy (SAVI) [22-24], and Aicardi-Goutières Syndrome (AGS)). While this is not a comprehensive list, due to the mostly autosomal dominant or X-linked inheritance patterns, and wide recognition of these IEI in the literature, they may be relatively more commonly encountered/recognized. Importantly, these diseases often have systemic involvement – e.g. in LRBA deficiency, autoimmunity in any tissue is possible due to a defect in the CTLA-4 coinhibitory pathway. Abatacept can thus be used as a targeted therapy for both pulmonary and extra-pulmonary manifestations.

The above examples highlight a complementary approach to thinking about pulmonary disease associated with IEIs, which is to focus on the underlying mechanism of immune dysregulation driving lung disease, taking into consideration systemic involvement so that therapies chosen benefit more than one organ system.

ChILD Associated with Autoimmune and Autoinflammatory Disorders

As with IEIs, pulmonary complications including ILD are among the most severe and life-threatening complications of acquired autoimmune and autoinflammatory disorders. This review will focus on disorders with the most significant pulmonary involvement, including systemic sclerosis (SSc), juvenile dermatomyositis (JDM), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, sarcoidosis, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), and systemic juvenile idiopathic arthritis (sJIA). Pulmonary manifestations of these disorders and representative CT images are summarized in figures 2 and 3 respectively. Through a collaborative approach, rheumatologists and pulmonologists can work together to make earlier diagnosis and improve clinical outcomes for patients with these disorders.

Systemic Sclerosis

In SSc, autoimmune inflammation drives fibrosis of body tissues. Juvenile onset SSc (jSSc) is rare, comprising <10% of SSc cases (incidence 0.27-1 per million children per year). Diagnosis of SSc requires skin thickening [25], with other organ involvement including ILD, pulmonary arterial hypertension (PAH), Raynaud's phenomenon, digital ulceration, myositis, arthritis, esophageal dysmotility, and gastrointestinal reflux. All manifestations are not typically present and needed to make the diagnosis. The average age of onset is 8-11 years, with female predominance (4:1 ratio) [26].

Pulmonary disease, are major causes of morbidity and mortality in SSc, with ILD present in 1/3 of jSSc patients and PAH present in ˜2-5% [26]. There are three main subtypes of SSc: limited cutaneous, diffuse cutaneous, and overlap. ILD can be a feature in diffuse and overlap subtypes. In limited cutaneous SSc, vasculopathy, including pulmonary hypertension, is more common [27-29].

With the development of ILD in SSc, imaging abnormalities may precede clinical symptoms. Thus, baseline studies at diagnosis include high-resolution chest CT, PFTs, echocardiogram (to assess for PAH), and esophageal dysmotility studies (to assess for aspiration) [30, 31]. Children with esophageal involvement have been shown to have significantly decreased forced expiratory volume in the first second (FEV1), forced viral capacity (FVC), and vital capacity (VC) [32]. PFTs can also demonstrate restriction and low DLCO [33, 34], but tight facial skin and reduced oral aperture may lead to technically limited PFTs. PFTs have limited sensitivity and specificity in diagnosis ILD in childhood SSc [35]. CT is more sensitive for diagnosis, with findings including parenchymal/subpleural micronodules, ground glass, linear and diffuse centrilobular opacities, honeycombing, and traction bronchiectasis [36]. Lung biopsy is rarely indicated; however, pathologic

patterns described include bland interstitial fibrosis, usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD), honeycomb remodeling, pulmonary hypertensive changes, findings compatible with aspiration and rarely, alveolar hemorrhage with capillaritis [37].

There have been several randomized controlled trials for ILD-related outcomes in adults with SSc, with multiple sets of consensus guidelines outlining organ-specific therapeutic approaches. Based on adult trials [38-40] first line therapies to treat alveolar inflammation include cyclophosphamide, mycophenolate mofetil, and tocilizumab. Rituximab has some prospective cohort data to suggest its use as a second line therapy. For patients with fibrosis, nintenadib, an oral tyrosine kinase inhibitor, has shown benefit [41] in adults. As a $3^{rd}/4^{th}$ line option, autologous hematopoietic stem cell transplantation (HSCT) has been shown to improve cutaneous and pulmonary features based on RCT in Europe [42] and the United States [43] comparing HSCT to cyclophosphamide. Depending on the extent of lung fibrosis, some patients may require lung transplantation. For PAH, endothelin receptor antagonists, PDE5 inhibitors, and intravenous prostacyclins may be used and have additional benefit for severe Raynaud's [29, 44]. In the pediatric population there is one expert guideline for management [45]. In this guideline for management of heart and lung involvement it is recommended to first treat with mycophenolate mofetil and cyclophosphamide and then if refractory move to biologic treatments. In our practice given fertility considerations and the success of biologic treatments we often add biologics before treating with cyclophosphamide.

Juvenile Dermatomyositis

JDM is a rare inflammatory myopathy and vasculopathy, with an incidence of 0.2-0.4 per 100,000 children [46-48]. Peak incidence occurs from 5-10 years of age, with a female predominance [46, 48, 49]. Clinical manifestations include inflammation of the muscle (proximal weakness) and skin (ulcerations, calcifications, Gottron's rash, heliotrope rash, nailfold capillary changes), with possible involvement of the lung, gastrointestinal tract, and joints [50]. The incidence of pulmonary involvement in JDM is unknown. Pulmonary manifestations in JDM include respiratory muscle weakness, hypoventilation, impaired swallowing leading to aspiration, impaired airway clearance with respiratory tract infections, spontaneous pneumothorax/pneumomediastinum, pulmonary vasculitis, and interstitial lung disease [51, 52].

While the incidence of ILD in JDM is not clear, it represents a significant source of morbidity and mortality [53, 54]. ILD can present with cough and shortness of breath but can also be seen in asymptomatic patients when identified early. ILD in JDM can be rapidly progressive (progression within 3 months of symptom onset) and can occur before or after myositis symptoms. Serum tests elevated in JDM-related ILD include Krebs von den Lungen 6 (KL-6), molecule that is predominantly expressed by damaged alveolar type II cells, and IL-18. In addition, anti-melanoma differentiation-associated gene 5 (anti -MDA-5) and anti-Ro52 antibodies may appear before signs of interstitial lung disease [53, 55-60]. ILD in adult dermatomyositis has been associated with anti-Jo-1 and anti-synthetase antibodies [61, 62], but these antibodies are rarer in children. If any of these antibodies are present, the patient needs to be followed closely by a pulmonologist for the development of ILD.

PFTs and cross-sectional chest imaging are essential for evaluating for pulmonary involvement in JDM. Patients with JDM can have a range of PFT patterns, which may be due to the presence of ILD or other pulmonary complications. Prior reports show abnormal lung function in a high percentage of patients, including asymptomatic patients [63]. From case series the following PFT abnormalities were reported in JDM: obstructive lung disease,15%, abnormal DLCO, 10 – 49%, reduced TLC, 24 – 29%, decreased maximal respiratory pressures, 30% [51, 63-66].

CT findings in ILD associated with JDM cannot distinguish between rapidly progressive and chronic disease, but this is often apparent based on rate of progressive symptoms. [67] Findings previously reported include atelectasis, nodules/micronodules, ground glass opacities, air trapping, bronchial wall thickening, traction bronchiectasis, reticulation, consolidation, and fibrosis [51, 53, 54]. Biopsies are not necessary for diagnosis of ILD in JDM, but reported pathology includes nonspecific interstitial pneumonia (NSIP), cellular

interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), usual interstitial pneumonia (UIP), acute interstitial pneumonitis, diffuse alveolar damage (DAD) and fibrosis [68-76]. Pneumothorax or pneumomediastinum may have a poorer prognosis and complicate ILD in JDM [77].

Early initiation or escalation of immune suppression is critical for ILD given the possibility of severe deterioration. There are no randomized controlled trials for treatment of ILD in JDM. Glucocorticoids and methotrexate with or without immunomodulatory IVIG (1-2g/kg) are the mainstay of treatment for JDM in general [78]. Patients with anti-MDA5 antibody rapidly progressive ILD require rapid escalation of therapy. Case reports/series of ILD associated with JDM have reported efficacy in using calcineurin inhibitors (cyclosporine, tacrolimus) [53, 54, 79], cyclophosphamide, plasmapheresis [67, 80, 81], rituximab [60], and tofacitinib [82-84]. In the most severe cases, some patients have been put on extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplant; however, the mortality rate is still very high [67, 80, 81].

Systemic Lupus Erythematosus

SLE is a multi-system autoimmune disorder characterized by generation of autoantibodies against cellular components and tissue damage from immune complex deposition. While SLE is more common in adults, approximately 20% of individuals present prior to the age of 18 [85], with female predominance in both age groups. The incidence and prevalence of childhood onset SLE (cSLE) varies between populations, with an incidence range of 0.28-0.48/100,000 and a prevalence rate of 6.3-24.0/100,000 [86]. Fever, fatigue, lymphadenopathy, nephritis, neuropsychiatric disease, cytopenia and mucocutaneous involvement (Malar, photosensitive, purpuric vasculitic rashes and oral/nasal mucosal ulcers) are more common in children at presentation than adults [85, 87]. Overall, cSLE is reported to have a more severe course [85].

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Pulmonary involvement in SLE can occur at onset of symptoms or any time during disease course, ranging from asymptomatic to severe and acutely life-threatening. Pulmonary complications in cSLE includes involvement of the upper airway, lung parenchyma, pulmonary vasculature, pleura and respiratory muscles, with prior reports of pneumonia (up to 90%), pleuritis (50-80%), acute pneumonitis (<10%), chronic ILD (3%), pulmonary hypertension (5-14%), diffuse alveolar hemorrhage (DAH) (<2%), shrinking lung syndrome (<1%) and thrombotic disease [52, 88, 89].

Pleuritis can be unilateral or bilateral and may be associated with a pleural effusion. Patients can present asymptomatically or with debilitating dyspnea, pain, and fever. Pleuritis can be treated with NSAIDs, although may require escalation of immune suppression.

Diffuse alveolar hemorrhage (DAH) in SLE is associated with significant morbidity and mortality. Patients may present with dyspnea, hemoptysis, fatigue, anemia, and respiratory failure. It can be difficult to distinguish DAH from infection as both can present with diffuse alveolar opacities. Flexible bronchoscopy, and in some cases lung biopsy, may aid in diagnosis. Infections have been identified at the onset of DAH, so simultaneous treatment of both may be required. Two studies have systematically examined DAH in pediatric SLE cohorts with an incidence of 1.7-2.2% of cSLE patients [90, 91]. Mortality varied widely in these cohorts, close to 50% in one cohort, whereas the second was 14%. In both cohorts, patients often required transfusions and mechanical ventilation [90, 91]. While there are no controlled trials, for critically ill patients, prompt initiation of high dose steroid with an additional agent like cyclophosphamide is often pursued. Rituximab may also be helpful but has a slower time to effect [92-94]. Immunomodulatory dosing of intravenous immunoglobulin (IVIG) and plasmapheresis can be considered in refractory cases.

ILD is a rare pulmonary manifestation in adult SLE, is rarer still in cSLE, and can present as acute pneumonitis or chronic ILD. In a twenty-year retrospective cohort of 157 cSLE patients, lupus pneumonitis/ILD was diagnosed in 3.8% at diagnosis and in 12.1% during disease course. Acute lupus pneumonitis is associated with significant morbidity and mortality [95] and is characterized pathologically by alveolitis, interstitial inflammation and edema. Findings associated with capillaritis and pleuritis can also be seen concurrently

[96, 97]. Chronic ILD in cSLE can occur following acute lupus pneumonitis or develop in isolation, with pathologic findings including cellular interstitial pneumonia, interstitial fibrosis, lymphocytic interstitial pneumonitis, fibrinous pleuritis, organizing pneumonia, desquamative interstitial pneumonitis, nonspecific interstitial pneumonitis, bronchiolitis and peribronchiolitis [98, 99]. ILD with pathologic findings consistent with organizing pneumonia has been described in patients meeting criteria for SLE including a pediatric patient [96]. ILD in SLE has been associated with >10 years duration of disease, Raynaud phenomenon, anti-(U1) RNP anti-bodies, sclerodactyly, and abnormal nailfold capillary loops [97, 100]. Given the rarity of ILD in SLE, drug reaction and other rheumatologic diagnoses such as mixed connective tissue disease should be considered.

Acute lupus pneumonitis warrants aggressive treatment given poor prognosis. The ideal treatment of chronic ILD in pediatric patients with SLE is unknown due to lack of controlled trials in children or adults. As it can be very difficult to determine if it is lupus pneumonitis vs. infection vs. DAH or co-existence of multiple complications, empiric treatment with broad spectrum antimicrobials and extensive infectious disease and DAH evaluation is warranted. Systemic steroids are often employed, given the significance of steroid toxicity, steroid sparing agents such as azathioprine, mycophenolate, cyclophosphamide, and rituximab should be considered [94, 101-103]. Antifibrotic treatment should be considered if there is evidence of fibrosis or progression.

Pulmonary hypertension in pediatric SLE can occur secondary to ILD or without associated ILD, with other potential causes including pulmonary vasculitis, pulmonary thromboembolism (especially with coexisting antiphospholipid antibodies), and cardiac dysfunction [104]. Pulmonary hypertension in SLE can occur at any point during disease course and may be present in asymptomatic patients or patients with fatigue, weakness, shortness of breath, exercise intolerance, presyncope, syncope, hemoptysis, or respiratory failure. Early identification is important [105, 106] as the presence of pulmonary hypertension in SLE negatively affects survival overall [107].

Shrinking lung syndrome (SLS) is a rare complication of pediatric SLE where patients experience dyspnea and pleuritic chest pain, with PFT evidence of restrictive lung disease and reduced maximal respiratory pressures and sometimes radiographic signs of reduced lung volumes and atelectasis. These patients generally do not have evidence of ILD [108, 109]. The pathophysiology of SLS is unclear, but may be related to myositis, myopathy, phrenic nerve dysfunction, and/or parenchymal reorganization impairing lung compliance [109]. Treatment includes immunosuppressive medications and, in our experience, exercise/pulmonary rehabilitation may be beneficial due to improvements in diaphragmatic mobility and lung compliance.

Pediatric SLE patients may be asymptomatic from a respiratory standpoint but have PFT and chest CT abnormalities predating pulmonary symptoms. Abnormalities in spirometry, plethysmography and diffusion have been described, with restrictive defect potentially secondary to parenchymal involvement or respiratory muscle dysfunction and DLCO reduction secondary to parenchymal disease or pulmonary hypertension. Disease duration is a risk factor for development of PFT abnormalities and DLCO may improve with treatment [110, 111].

Mixed Connective Tissue Disease

MCTD is characterized by having features of multiple connective tissue disorders, but primarily SLE, polymyositis/dermatomyositis, and scleroderma. Symptoms can evolve over time and do not present in a specific order [112]. Criteria for diagnosis include 1) Raynaud's phenomenon 2) detectable anti-RNP antibodies 3) one additional sign or symptom of SLE, polymyositis/dermatomyositis or SSc [113, 114].

MCTD can be accompanied by any of the pulmonary manifestations of SLE, JDM, or SSc, most often, pleural effusions, pulmonary hypertension, and ILD. The prevalence of overall pulmonary involvement in children is unknown, but most adults with MCTD have pulmonary involvement [115-119], which increases the risk for mortality.

The disease course of ILD in pediatric MCTD is not well defined. In a prior cross-sectional study of 52

pediatric MCTD patients followed for a mean of 16 years, ILD was diagnosed in 27%. On PFTs, patients with ILD had lower FVC and TLC than controls. Notably, in this study, while FVC declined overtime, CT findings of ILD did not worsen [33]. A second long-term follow up study of pediatric MCTD (n = 34) hints at a potentially progressive nature of ILD in MCTD — at initial presentation, 22% of patients had restrictive lung disease, 21% had reduced DLCO and 14% had pulmonary fibrosis on chest CT, increased to 64% with restrictive lung disease, 58% with reductions in DLCO and 100% with fibrosis at long term follow up. 6% of patients in this series had pulmonary hypertension [120]. In addition to fibrosis, chest CT findings previously reported in MCTD include reticulations, ground glass opacities, interlobular septal thickening, airspace consolidations, and/or traction bronchiectasis [32].

Treatment pediatric MCTD patients is directed at specific complications that emerge and overlap with treatment paradigms used in SLE, polymyositis/dermatomyositis and SSc.

Sjögren's Syndrome

Sjögren's syndrome is an autoimmune disorder involving destruction of exocrine glands which is characterized by sicca (dryness) syndrome, recurrent parotitis, and other extra-glandular symptoms. Sjögren's is poorly defined in children with unknown incidence and variable presentation, with no established diagnostic criteria [121]. Pulmonary manifestations in children and adults include restrictive lung disease from myositis, ILD, airway disease. ILD in children appears to be exceedingly rare, limited to four case reports in female children [122-125] and one case report of a male child [121]. Given the limited data on ILD in childhood onset Sjögren's Syndrome, we urge careful screening for pulmonary involvement through close review of respiratory symptoms and monitoring of PFTs.

Sarcoidosis

Sarcoidosis is a multi-systemic non-necrotizing granulomatous disease which can present with hilar lymphadenopathy, pulmonary infiltration and ocular and cutaneous lesions [126]. Patients can present with involvement of one system or multi-systemic disease. The diagnosis is made when there is pathologic evidence of noncaseating granulomas in affected tissue and other causes of granulomatous disease have been excluded. CVID and IEIs should be evaluated for in a pediatric patient presenting with sarcoidosis. Elevated ACE levels may support the diagnosis, but this is not necessary for diagnosis. While the incidence of sarcoidosis is unknown in the pediatric population, it is considered to be rare – a Danish case series of children > 15 years reported an incidence of 0.22 to 0.27 per 100,000 children per year [127]. Radiographic findings described in pediatric sarcoidosis include bilateral hilar lymphadenopathy with and without pulmonary infiltrates, and nodules with ground glass opacities, and pleural and interlobular septal thickening [128-130]. Reported PFT alterations include hypoxemia, reduced vital capacity, decreased DLCO, and decreased dynamic lung compliance [128, 129].

Decisions around treatment of pulmonary sarcoidosis in adults are challenging, with no consensus around who should receive treatment, given that disease can stabilize or resolve without therapy. These decisions are more complicated still in the pediatric population, with no studies around which patients to treat and optimal length of treatment [129]. Corticosteroids, either daily oral steroids (0.5 to 2 mg/kg/day) or monthly IV pulse steroids are reported as the most-used treatment [128, 129]. We recommend treatment of sarcoidosis in pediatric patients with moderate to severe reduction in pulmonary function, progressive decline in lung function, significant or worsening radiographic disease, persistent or worsening symptoms, exercise desaturation, and/or multisystemic involvement.

ANCA Associated Vasculitis

AAV are small- to medium- vessel vasculitis syndromes primarily affecting the blood vessels of the airways and the kidneys. They are generally divided into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [131]. The incidence of pediatric AAV is not well established, with reported incidence ranging from 0.5 to 2 per million. The most common age of onset is in early teenage years, although some children present in infancy. Lung involvement, considered to

be a hallmark of MPA and GPA, is associated with increased morbidity and mortality — in one cohort of 28 patients, half of children required ICU admission and one third of these admissions were for respiratory failure, with five patient requiring mechanical ventilation [131-133].

Of the AAVs, GPA is most common in children and classification criteria can include some of the following features: granulomatous inflammation on histopathology, renal disease, ANCA positivity and, from a pulmonary perspective any of the , upper airway involvement (chronic purulent or bloody nasal discharge, recurrent epistaxis/crusts/granulomata, nasal septum perforation or saddle nose deformity), laryngo-tracheo-bronchial involvement (subglottic, tracheal, or bronchial stenosis) and/or pulmonary involvement (chest x-ray or CT with nodules, cavities or fixed infiltrates) [134].

In pediatric GPA, pulmonary involvement can range from asymptomatic with radiographic abnormalities (a prior report noted 41% of radiographic abnormalities found in patients with pediatric GPA were observed in asymptomatic patients [135]) to presentation with fulminant DAH [133]. In the ARChiVe cohort, including 183 patients with pediatric GPA, 74% had pulmonary involvement, with 54% reporting chronic cough and 42% with massive hemoptysis or alveolar hemorrhage [136, 137]. PFTs may show abnormal DLCO (related to parenchymal disease or hemorrhage), restrictive lung disease, and/or obstructive disease (related to airway stenosis). CT findings may include nodular lung lesions (secondary to necrotizing, granulomatous inflammation, which may demonstrate cavitation and/or a "halo sign" related to adjacent hemorrhage), fixed pulmonary infiltrates, and more rarely ($< 10\%$ of cases), fibrosis, septal thickening and pneumothorax [133, 136]. Bronchoalveolar lavage (BAL) with serial aliquots can be useful in evaluation for pulmonary hemorrhage.

Data on pulmonary manifestations in pediatric MPA is more limited, with conflicting data. In a case series of 38 patients with AAV (in which MPA was the predominant AAV), MPA patients had higher prevalence of more severe pulmonary manifestations than GPA patients, with a subgroup of five patients experiencing recurrent pulmonary hemorrhage. MPA patients with early onset disease had worse pulmonary outcomes [138]. By contrast, in a retrospective review of 12 children with MPA, the majority of children (66%) had no respiratory symptoms at diagnosis with normal chest radiographs. Pulmonary manifestations at diagnosis were observed in four children, all with DAH. Among children without respiratory involvement at diagnosis, only one child developed DAH after 12 months [139].

Consensus guidelines and consensus treatment plans for treatment of pediatric AAV have been established by the SHARE initiative and Childhood Arthritis and Rheumatology Research Alliance (CARRA) ANCA vasculitis workgroup [140, 141]. For severe disease with multi-organ involvement, induction consists of cyclophosphamide and steroids (pulse or high dose oral) for 3 - 6 months. Other therapeutic options for treatment of pediatric AAVs can potentially be extrapolated from adult RCTs. The RAVE [142]and RITUXVAS [142] trials demonstrated non-inferiority of rituximab for induction therapy, which could be attractive for pediatric patients due the undesirable side effect profile (include effects on fertility) of cyclophosphamide. Without extensive pediatric data however, cyclophosphamide is generally considered first line therapy. In adults, a trial comparing mycophenolate mofetil to cyclophosphamide for induction, while non-inferior to inducing remission, had high rates of relapse [143]. Other therapeutics evaluated in the adult population, but with limited to no data in the pediatric population, include plasmapheresis for patients with severe disease and avacopan [144], an oral C5a receptor inhibitor thought to slow neutrophil trafficking. For patients with less severe or localized disease, oral steroids plus methotrexate or mycophenolate mofetil can be considered for induction. Trimethoprim-sulfamethoxazole has also been used for GPA limited to the upper airways [145]. For maintenance therapy, the three most used agents are methotrexate [146], azathioprine [147], and rituximab [148].

Systemic Juvenile Idiopathic Arthritis

Systemic juvenile idiopathic arthritis (sJIA) is an International League of Associations for Rheumatology (ILAR) subclass of JIA, characterized by disease driven more by autoinflammation than by autoimmunity. Diagnostic features include several weeks of fever, classically in a quotidian or double quotidian pattern,

evanescent rash, and arthritis, which is not always present at disease onset. Males and females are affected equally with a peak onset between ages 1 to 5 years of age [149]. One of the most life-threatening complications unique to sJIA (vs. other classes of JIA) is macrophage activation syndrome (MAS), which is driven by IFN-γ and can be seen in 10% of patients fulminantly and 30- 40% of patients subclincially [150-152].

In recent years, significant attention has also been directed to the pulmonary complications of sJIA, which include pleuritis, pleural effusions, ILD and pulmonary arterial hypertension [153]. ILD in sJIA is referred to as sJIA-LD. Risk factors for sJIA-LD include younger age of onset (<2 years old), trisomy 21, history of MAS, and prior adverse reaction to biologic drugs (including injection site reactions and delayed type hypersensitivity-like reactions to anti-IL-1 and IL-6 biologics) [154-156]. In a multi-center cohort, median time to LD diagnosis after sJIA onset was 1.6 years. Respiratory symptoms were often absent or subtle. Symptoms in sJIA-LD patients included: hypoxemia (43%), pulmonary hypertension (30%), clubbing (61%), digital erythema (50%), pruritic non-evanescent rashes (56%) and eosinophilia (37%). Mortality was increased in sJIA-LD with a 5-year survival of 42%, significantly lower than patients without sJIA-LD [156]. This mortality rate has likely improved since these 2019 studies, as patients are being diagnosed earlier with less severe LD and opportunity for earlier treatment [157, 158].

Curiously, most cases of sJIA-LD have been reported after biologics became first line therapy for sJIA. It is unclear if this is secondary to increased incidence of sJIA-LD or increased awareness. More recently, it has been shown that sJIA patients treated with IL-1 or IL-6 inhibitors may develop eosinophilia with an atypical rash, in association with HLA-DRB1*15 leading to the hypothesis that a drug reaction was driving the development of MAS and sJIA-LD [154]. This hypothesis potentially affects management, as it raises concern about continued use of biologic agents in treatment of sJIA. However, our group and others have noted that eosinophilia in sJIA can occur prior to any treatment with anti-IL-1 and IL-6 therapy [159, 160], rendering it possible that eosinophilia is a reflection of the type of inflammation characteristic of sJIA, which may be further skewed towards a Th2 phenotype in the setting of IL-1 and IL-6 blockade [161].

Diagnosing sJIA-LD can be challenging – imaging changes may precede development of clinical symptoms, and patients at highest risk are often too young to perform PFTs. There are no consensus guidelines for screening for sJIA-LD. Our center developed a screening algorithm recommending patients with sJIA be referred for pulmonary screening if they have 'red flag' features including: diagnosis at age <2 years, presence of the HLA DRB1*15 risk allele, high disease activity (history of MAS, sJIA-related ICU admission, persistently elevated IL-18), anaphylaxis, eosinophilia or atypical rash, respiratory symptoms or an abnormal pulmonary exam [162]. Initial evaluation should include chest x-ray and PFTs, including a 6-minute walk test or exercise saturation testing in ambulatory children. If a patient's pulmonary screening is abnormal, or if patients have uncontrolled disease, we recommended high-resolution chest CT for more sensitive screening of ILD. Overnight oximetry or polysomnography can be considered to evaluate for low pulmonary reserve or nocturnal hypoxemia, which may also suggest the presence of sJIA-LD. Bronchoalveolar lavage to evaluate for infection is frequently employed when there is concern for sJIA-LD. BAL fluid from patients with sJIA-LD have been found to have high levels IL-18 and CXCL9 compared to patients with congenital alveolar proteinosis [155].

CT scan abnormalities in sJIA-LD can include pleural, interlobular-septal, and bronchial wall/perivascular thickening, peripheral and periobronchovascular consolidations, ground glass and tree-in-bud opacities, crazy paving, and lymph node changes (adenopathy, hyper-enhancing). Fibrosis is uncommon and pleural effusions are rare [155, 156]. Pathologic findings include pulmonary alveolar proteinosis, type II pneumocyte hyperplasia, macrophage accumulation, endogenous lipoid pneumonia, lymphoplasmocytic inflammation, pulmonary vascular abnormalities, and rarely, fibrosis [155, 156].

In a single center study of 18 patients with sJIA-LD, all continued biologic treatment after detection of lung disease with a median of 1 year of follow up and range of 0.5 to 13 years. In that cohort, 50% of patients had stable LD, 22.2% worsened, and 27.8% improved. There was no differentiating characteristics of those who improved and those who did not. Importantly, all patients with improved sJIA-LD had control of their underlying sJIA [155].

There are no management guidelines or randomized controlled trials of therapies in sJIA-LD. As poor sJIA disease control is a risk factor for the development of sJIA-LD, achieving overall disease control is a priority. sJIA is thought to be driven by elevated IL-1, IL-6 and IL-18, and thus first line treatment of sJIA is based on IL-1 and IL-6 blockade with biologics. Regarding additional therapies, there are case reports of successful treatment of sJIA-LD with JAK inhibition [163-165], and in our experience, adding mycophenolate mofetil, calcineurin inhibitors or JAK inhibitors to obtain control of sJIA if this is refractory to or develops while on biologic monotherapy [166]. Case reports exist for successful treatment of sJIA-LD with emapalumab [167], an anti-IFNγ monoclonal antibody used to tackle the related inflammation in MAS, etoposide (also used for MAS) [168], bispecific IL-1/IL-18 blockade [169] and allogeneic hematopoietic stem cell transplant (HSCT) [170].

Supportive Care of the Patient Suspected to have Immune Mediated chILD

While disease-specific therapeutic regimens have been discussed throughout, the importance of generalized supportive care measures for all diagnoses, cannot be overstated. With underlying inflammation and increased metabolic demands, patients can experience faltering growth requiring consultation with nutrition and dietary support. Exercise, physical therapy, and pulmonary rehabilitation can improve functional capacity in these patients. Social work and nursing support is critical to assist with care coordination —navigating transportation, education, insurance, durable medical equipment, and the psychosocial and financial implications of these conditions, which can present a significant burden to families [171].

Counseling patients on avoidance of infectious exposures, smoking, vaping, and environmental pollutants is essential. Having a low threshold for evaluating for and treating infections is recommended. Patients should be encouraged to receive all appropriate vaccinations, keeping in mind that for patients with IEI or on immunosuppressive medications, live vaccines are often contraindicated. Depending on the underlying disorder or immunosuppressive treatment, prophylactic antimicrobials and intravenous or subcutaneous immunoglobulin treatment may be considered. In the setting of significant ILD and increased susceptibility, we recommend a goal IgG trough target of 800-1000 mg/dL. Higher dose (1-2g/kg) immunoglobulin can also serve an immune-modulatory purpose in patients with immune dysregulation and autoimmune disease.

In patients with advanced lung disease including ILD, consideration of lung transplantation may be necessary, particularly if the patient is at risk of death from pulmonary complications in the next 1-2 years, has poor quality of life despite optimal medical therapy, and has a reasonable chance of surviving transplantation. With ILD associated with connective tissue and immune mediated disorders, the risk for immune mediated lung disease recurrence in the transplanted lung is an important consideration, with a paucity of data to guide these decisions for most of these disorders. In some IEIs, allogeneic SCT may be curative, but this is more successful if the genetic defect is limited to the hematopoietic compartment and carries the risk for transplant related morbidity and mortality [22]. In advanced ILD cases, consultation with pediatric palliative and advanced care and ethics teams may be helpful for the medical team and families.

Conclusions

Recognition, diagnosis, and treatment of chILD associated with connective tissue disease and immune-mediated disorders requires thoughtful care from a multi-disciplinary team of providers, with the pulmonologist playing a key role. These patients have highly complex systemic disorders, and ILD can have many faces – sometimes presenting subtly and progressing insidiously, while other times presenting with rapid and life-threatening consequences. The diagnostic odyssey and management challenges associated with immune associated chILD can be a significant medical, psychologic, and socio-economic burden to patients and their families. Important next steps in the care of these patients include improving therapy adherence, conducting randomized trials and developing pediatric consensus guidelines to generate more evidence-based and standardized treatment protocols, and developing novel therapeutics with reduced risk for toxicity and infectious risks. Despite significant challenges in the care of these complex patients, advances in molecular and genetic testing have aided in achieving earlier and less invasive diagnoses, and emerging therapies represent promising future innovations.

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