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Clinicopathologic Conference – ELP in autoinflammatory disease

Endogenous lipoid pneumonia in adult autoinflammatory disease

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Abstract

We describe one of the first cases of endogenous lipoid pneumonia (ELP) in an adult patient with the clinical picture of adult-onset Still disease (AOSD) and a low penetrance genetic background of tumour necrosis factor receptor-associated periodic syndrome (TRAPS). This case highlights the complex pathophysiology of lung involvement in autoinflammatory diseases, operating at the interface of the innate and adaptive immune system.

This case presents a 53-year-old immunocompromised woman with treatment refractory autoinflammatory disease and history of macrophage activation syndrome (MAS), presenting to the emergency room with progressive dyspnea and fever. Upon evaluation, chest-CT showed diffuse lung disease. Extensive work-up, including bronchoscopy with bronchoalveolar lavage remained negative. Lung biopsy revealed an ELP with intra-alveolar accumulation of cholesterol crystals and foamy macrophages. In the years preceding the event, her autoinflammatory disease had shown to be refractory to both conventional systemic disease-modifying antirheumatic drugs, as well as biologic treatments including tocilizumab, anakinra and canakinumab. Because of new onset respiratory failure in the context of uncontrolled inflammation, after exclusion of infectious origin, pulse doses of systemic corticosteroids were administered before induction with cyclophosphamide, followed by maintenance therapy with tacrolimus. Upon treatment, our patient recovered, but retained severe interstitial lung disease. Only one case of ELP in adult autoinflammatory disease has been depicted in a patient diagnosed with AOSD, although the entity is more recognized in paediatric literature on systemic onset juvenile idiopathic arthritis (soJIA).

Methods

Literature review on ELP in autoinflammatory diseases was performed in PubMed, without language restrictions, and comprised publications from January 1953 until November 2024. The literature search addressed lung disease in AOSD, TRAPS and soJIA using the following MESH terms: endogenous lipoid pneumonia, pulmonary alveolar proteinosis, parenchymal lung disease, macrophage activation syndrome, adult-onset Still disease, tumour necrosis factor receptor-associated periodic syndrome and systemic onset juvenile idiopathic arthritis.

Data availability: Data can be made available upon reasonable request.

Keywords

Lipoid pneumonia; autoinflammation; tumour necrosis factor receptor-associated periodic syndrome; adult-onset Still disease; systemic onset juvenile idiopathic arthritis; macrophage activation syndrome; biological.

Key messages

- Concerning AOSD-associated interstitial lung disease (AOSD-LD), only one case of ELP and a few cases of pulmonary alveolar proteinosis (PAP) have been reported, while case series of lung disease in soJIA, including ELP, have been documented.
- Although several theories have been proposed, the precise mechanism of lung disease in autoinflammatory conditions remains unclear and poorly characterized.

- Disease severity or the presence of complications, such as MAS, may be precipitating factors for AOSD-LD, including ELP.
- Recognizing AOSD-LD is essential for preventing long-term morbidity and mortality, and screening protocols should be implemented alongside increased awareness.

Case presentation

HISTORY OF PRESENT ILLNESS

A 53-year-old immunocompromised female patient, previously diagnosed with treatment refractory adult-onset Still's disease (AOSD) and recurrent macrophage activation syndrome (MAS) two years earlier, presented to the emergency room with progressive dyspnea and fever.

PAST MEDICAL HISTORY

Two years prior to the present admission, the patient was diagnosed with an autoinflammatory syndrome after being hospitalised for suspected *Chlamydia psittacosis* pneumonia. Her initial presentation consisted of progressive dyspnea, fever, sore throat, myalgia and muscle weakness. The aforementioned diagnosis was considered due to close contact with canaries and a single mildly positive polymerase chain reaction (PCR) swab, after other pathogens had been excluded. After several weeks in the intensive care unit (ICU), the diagnosis of autoinflammation with the clinical picture of AOSD was made by the rheumatologist based on prolonged spiking fever, sore throat, oligoarticular arthritis, mildly itchy maculopapular rash, hepatosplenomegaly and diffuse adenopathy. At the time of diagnosis, the patient exhibited no residual respiratory symptoms nor clubbing. Lab results showed elevated inflammatory parameters, with ferritin up to 134455µg/l and raised liver enzymes, whereas blood eosinophils were normal. A chest-CT performed during the work-up revealed bilateral pleural effusions in the lower lobes and thickened interlobular apical septa, accompanied by minimal ground-glass opacities. There were no definitive signs of pulmonary infection. Later on, genetic testing for periodic fever syndromes revealed a low penetrance variant of unknown significance in the TNFRSF1A gene (c.362G>A(p.Arg121Gln)(R92Q)), a mutation observed in tumour necrosis factor receptor-associated periodic syndrome (TRAPS). Nevertheless, this variant is relatively common in European populations and considered a non-confirmatory genotype for TRAPS.[1] Adult-onset TRAPS accounts for about 22-45% of cases and less commonly presents with abdominal pain or orbital oedema in addition to systemic symptoms.[2, 3]

Apart from endometriosis, the patient's personal medical history up until her current diagnosis was unremarkable. There was no family history of autoimmune disease, nor rheumatic musculoskeletal disorders or pulmonary conditions. She had never smoked, used drugs or medication, nor had she had any occupational exposure to hazardous agents. She denied any recent travel.

Subsequent to her diagnosis, the patient responded well to high-dose systemic corticosteroids. However, tapering proved challenging despite sequential association of non-steroidal anti-inflammatory drugs, methotrexate, colchicine and several biologic treatments including tocilizumab, anakinra and canakinumab. Although there was a therapeutic response to anakinra with resolution of inflammatory symptoms for several months, she displayed secondary inefficacy despite dose escalation up to 200mg per day. During her disease course,

several episodes of suspected MAS with spiking fever, rash, neurological symptoms, diarrhea, hypotension, anemia, elevated inflammatory parameters, hyperferritinemia and high sCD25 developed. Serum cytokine analysis showed strong elevation of IL-1RA, IL-18 (up to 2616,2 pg/ml (normal range < 50pg/ml)), IL-6 and chemokine (C-X-C motif) ligand (CXCL)9 (up to 2908,1 pg/ml (normal range 150-550 pg/ml)). However, bone marrow and lymph node biopsies were negative for hemophagocytosis, whereas the skin biopsy was consistent with neutrophilic urticarial dermatitis showing hemophagocytosis.

MEDICATION

At the time of present admission with fever and dyspnea, the patient was treated with prednisolone 15mg daily and canakinumab 300mg every 4 weeks for refractory autoinflammatory disease.

REVIEW OF SYSTEMS

The patient presented to the emergency room with exhaustion, headache, progressive dyspnea, diarrhea, spiking fever and inflammatory myalgia and arthralgia. Further review of systems revealed no abnormalities, more specifically no skin rash or arthritis.

PHYSICAL EXAMINATION

Upon admission, the patient presented with a temperature of 40°C, a pulse rate of 147 beats per minute, blood pressure of 95/60 mmHg, and oxygen saturation of 96% on 5 liters of oxygen. The patient was tachypneic, with lung auscultation revealing bilateral fine crackles. On cardiac examination, no murmurs were detected. There was no evidence of arthritis, skin rash, or clubbing. Blood gas analysis confirmed hypoxemia with hypocapnia.

LABORATORY AND RADIOGRAPHIC EVALUATION

Laboratory examination included a hemoglobin level of 10,9 g/dL (normal range 11,7-15,1), leukocytes of 15,9x10E3/µL (normal range 4,30-9,64x10E3/µL) with 12.860/µL neutrophils, blood eosinophils within normal range, platelets of 281x10E3/µL (normal range 175-343x10E3/µL). C-reactive protein (CRP) was elevated up to 213,7 mg/L (normal range <5 mg/L), with procalcitonin and ferritin respectively up to 25,2 ng/mL (normal range 0,100 ng/mL) and 14579 µg/L (normal range <250 µg/L). Liver function was normal, as well as the lipid profile including triglycerides. Creatinine was elevated, which was attributed to dehydration due to fever, reduced intake and diarrhea.

Conventional chest-CT indicated bilateral peribronchovascular consolidations and multiple paratracheal, subcarinal and hilar adenopathies, with signs of congestion and limited unilateral pleural fluid. Further, high resolution chest-CT (HRCT) showed diffuse lung disease (LD), predominant in the lower and middle lobes with septal thickening involving the periphery of several lobes, some adjacent ground-glass opacities, bilateral peribronchovascular thickening and some pleural thickening. **(Figure 1)** Upon review of previous imaging obtained at the time of the AOSD diagnosis two years prior, chest-CT already demonstrated limited

septal thickening in the apical lobes and some ground-glass opacities, albeit less pronounced compared to the current imaging. The abdominal CT was unremarkable, and transthoracic ultrasound revealed diffuse hypokinesia in a normal, non-dilated left ventricle, with a mild reduction in global systolic function. A subsequent bronchoscopy with bronchoalveolar lavage (BAL) showed no evidence of opportunistic infection, eosinophilia, alveolar hemorrhage, or proteinaceous material typically seen in pulmonary alveolar proteinosis (PAP).

Figure 1. High resolution computed tomography scan of the chest. A-B.

Case summary

The presented case summarizes the disease course of a 53-year-old female with a refractory autoinflammatory syndrome with the clinical picture of AOSD on high dose immune suppression, presenting with fever, progressive dyspnea and hemodynamic instability. Further diagnostic tests revealed elevated inflammatory laboratory parameters, hyperferritinemia and diffuse progressive interstitial lung disease (ILD) on imaging.

Differential diagnosis

On imaging, the interstitial lung abnormalities were predominantly distributed in the mid and lower lung zones in a peribronchovascular pattern, displaying less involvement of the peripheral regions. The primary finding was peribronchovascular ground-glass attenuation, accompanied by areas of crazy paving, characterized by superimposed smooth interlobular septal thickening.

Noteworthy for their absence were diffuse nodular pleural thickening (as seen in sarcoidosis), signs of fibrosis (e.g., traction bronchiectasis or honeycombing (as in usual interstitial pneumonia)), evident masses or mass-like consolidations (as seen in organising pneumonia and lymphoma), mosaic attenuation (as in hypersensitivity pneumonitis), or thin-walled cysts (as in lymphocytic interstitial pneumonia). The chronic nature of the lesions made acute alveolar conditions, such as pulmonary oedema, acute interstitial pneumonia, or adult respiratory distress syndrome unlikely differential considerations.[4-6]

Given this context, the differential diagnosis for chronic peribronchovascular interstitial lung disease was refined to include infection, drug toxicity including eosinophilic pneumonia and AOSD-associated interstitial lung disease (AOSD-LD)(e.g. nonspecific interstitial pneumonia, diffuse pulmonary hemorrhage, lipoid pneumonia and alveolar proteinosis) among the leading considerations. The following sections provide an in-depth analysis of the remaining differential diagnoses.

Infectious (opportunistic) lung disease

At initial presentation, the suspicion of infection was high, as the patient had been immunocompromised for an extended period of time and presented with fever and respiratory symptoms. Laboratory investigations demonstrated elevated inflammatory markers and significant leucocytosis. In addition, HRCT revealed diffuse interstitial lung

disease of undetermined etiology. The imaging findings were not consistent with a typical bacterial infection; however, viral or opportunistic pathogens such as Cytomegalovirus (CMV) or Pneumocystis jirovecii could not be excluded based on imaging alone. All microbiological studies, including blood cultures, BAL and PCR testing, remained negative. With infection in mind, empirical therapy with amoxicillin/clavulanic acid and azithromycin was initiated and later switched to piperacillin-tazobactam with co-trimoxazole. Additionally, broad-spectrum antifungal and antiviral treatment was added. Despite this treatment the patient deteriorated with progressive hemodynamic instability, increasing inflammatory parameters (CRP > 400 mg/L) and increasing oxygen demand. Hence, she was transferred to the ICU for intubation, ventilation and vasopression. Overall, the clinical picture did not respond to prolonged treatment with broad spectrum antibiotics, nor antiviral/antifungal medication, arguing against an infectious origin of the lung disease.

Drug Induced Interstitial Lung Disease (DIILD) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DIILD can be suspected when findings consistent with ILD occur after temporal exposure to a culprit drug in absence of other more likely causes, with amelioration upon withdrawal of the suspected culprit. Our patient had been exposed to multiple drugs in the months prior to admission. Methotrexate, tocilizumab and anakinra had already been discontinued several months before the event, whereas the ongoing treatment with canakinumab and systemic corticosteroids was considered less notorious in this respect.[7] Clinical status worsened following the withdrawal of canakinumab.

Similarly, the presence of a DRESS syndrome, which is considered a delayed T-cell mediated adverse drug reaction, had been taken into consideration. Symptoms of the latter generally consist of fever, rash, facial edema, eosinophilia and organ involvement, including interstitial pneumonia.[8] Nevertheless, our patient did not display any peripheral eosinophilia, nor skin rash or acute clubbing at the moment of respiratory distress. Moreover, based on the RegiSCAR score—a scoring system developed to classify DRESS as definite, probable, or not a case according to key diagnostic criteria—our patient's presentation was not suggestive of DRESS.

Notably, experts in the field have proposed that DRESS may contribute to the development of LD in systemic onset juvenile idiopathic arthritis (soJIA), considered the pediatric counterpart of AOSD. These conditions are generally regarded as part of the same spectrum of disease at different ages, suggesting a potential overlap in the pathogenesis of lung disease.[9, 10] Compared to the soJIA population without LD, children who developed LD had more frequent adverse reactions to biological therapy, in particular tocilizumab, to which our patient had previously been exposed.[11-13] Half of these reactions fitted the DRESS criteria and were significantly correlated with human leukocyte antigen (HLA)-DRB1*15.[14, 15]

AOSD-associated interstitial lung disease (AOSD-LD)

AOSD is considered part of the autoinflammatory diseases, a heterogeneous group of disorders characterized by dysregulation of the innate immune system, resulting in recurrent or persistent episodes of seemingly spontaneous systemic inflammation.[16] Other examples hereof are soJIA and TRAPS.[9, 13, 17, 18]

While AOSD is characterised by fever, typical rash, arthritis/arthralgia, leucocytosis and sore throat, soJIA is characterised by similar systemic features at earlier onset, alongside with lymphadenopathy, hepatosplenomegaly and/or splenomegaly and serositis.[19, 20] The term AOSD refers to a clinical syndrome, as specific genetic mutations have not been identified, unlike in TRAPS. At diagnosis our patient exhibited clear symptoms of autoinflammation, fulfilling the Yamaguchi classification criteria for AOSD.[3, 20] One might argue whether a diagnosis of TRAPS needed to be considered. Indeed, the patient exhibited myalgia and a migratory rash, fulfilling the Eurofever/PRINTO classification criteria for TRAPS in the absence of a confirmatory TNFRSF1A genotype, with an episode duration exceeding 7 days.[1, 21] Therefore, our patient also met the classification criteria for TRAPS. Nevertheless, classification criteria are not regarded as diagnostic. Hence, given the clinical phenotype of AOSD, and the non-confirmatory genotype of the mutation, we were more inclined to diagnose AOSD. Moreover, in TRAPS, merely anecdotal reports on recurrent pneumonia or persistent cough of unknown origin have been reported.[22]

Lung involvement has been described in 5-12% of AOSD patients, including a range of manifestations such as pleuritis, pulmonary infiltrates, bronchiolitis and interstitial lung disease (including endogenous lipoid pneumonia (ELP), pulmonary alveolar proteinosis (PAP)) and pulmonary arterial hypertension.[13, 23] Although PAP/ELP—rare pulmonary diseases characterized by the accumulation of proteinaceous (surfactant components) and fatty (cholesterol) material in the alveoli—have been infrequently reported in adults with autoinflammatory diseases, larger cohorts examining lung involvement have been described in the pediatric population with soJIA, in which PAP/ELP were identified as the most common pathology among biopsied cases (Supplementary Table S1).[24-26]

Symptoms of AOSD-LD can include cough, shortness of breath and pleuritic pain, whereas clinical examination can reveal cyanosis, bibasal crackles and somewhat more specific digital clubbing.[13, 23] Although our patient presented with shortness of breath and bilateral basal fine crackles on auscultation, she did not exhibit cough, pleuritic pain, nor clubbing. Laboratory findings, including elevated inflammatory markers, ferritin, IL-6, IL-18, and liver enzymes, as seen in our patient, were also observed in ELP.[13] In case of AOSD-LD, HRCT of the chest can be heterogeneous revealing multilobar, predominantly peripheral septal thickening with or without adjacent ground-glass opacities, crazy paving pattern, peripheral consolidations, peribronchovascular consolidation and predominantly ground-glass opacities, most frequently seen in the lower lobes.[13, 23] Indeed, HRCT of our patient showed diffuse lung disease in the lower and middle lobes with septal thickening involving the periphery of several lobes, some adjacent ground-glass opacities, bilateral peribronchovascular thickening and some pleural thickening, fitting with the HRCT patterns described in literature on soJIA/AOSD-

LD. On top of that, lung function testing typically shows a restrictive pattern with impaired DLCO in AOSD-LD, as observed in the follow-up of this case.[27] BAL fluid did not exhibit the milky appearance suggestive for PAP, nor PAS-positive reactions, which would have been indicative of extracellular proteinaceous material. However, the absence of this finding should be interpretated with caution, as in a case series of patients with SoJIA-LD BAL fluid rarely contained proteinaceous material and had less lipid-laden macrophages compared to patients with primary PAP.[12]

Additional evaluation

Given the unclear etiology of the lung disease in our patient and a progressively worsening clinical course, a lung biopsy was performed. Macroscopically, a yellow parenchymal consolidation was noted. Microscopically, organising diffuse alveolar damage with numerous intra-alveolar cholesterol crystals and, focally, foamy macrophages was observed, consistent with ELP. (**Figure 2**) (Immuno)histochemical examination was negative for fungi, yeasts (including Pneumocystis jiroveci) and CMV.

Figure 2. Histopathology of the lung biopsy.

It is worth noting that, although the clinical presentation and radiographic findings in this patient were consistent with soJIA/AOSD-LD, the diagnosis of ELP could only be definitively confirmed through histopathological analysis.[28]

Discussion

We describe one of the first cases of ELP in an adult patient with the clinical picture of AOSD and a low penetrance mutation in the TNFRSF1A gene, as seen in TRAPS. A 53-year-old immunocompromised woman with treatment refractory autoinflammatory disease and history of MAS, presented to the emergency room with progressive dyspnea and fever. Upon evaluation, chest-CT showed diffuse lung disease. An extensive work-up, including bronchoscopy with bronchoalveolar lavage and comprehensive sampling, yielded negative results for an infectious origin. At a later stage, lung biopsy revealed an ELP with intra-alveolar accumulation of cholesterol crystals and foamy macrophages. The patient was then treated with pulse doses of systemic corticosteroids, followed by induction with cyclophosphamide, maintained on tacrolimus. Upon treatment, our patient improved significantly, but retained residual interstitial lung disease. This case highlights the complex pathophysiology of lung involvement in autoinflammatory diseases, operating at the interface of the innate and adaptive immune system.[29]

The aforementioned inflammatory diseases can be complicated by life-threatening MAS, a hyperinflammatory condition orchestrated by macrophages and T-lymphocytes, resulting in a cytokine storm. MAS typically includes extremely high ferritin levels and/or pancytopenia as most prominent laboratory features, and can more specifically show elevation of soluble CD25, whereas natural killer cell activity can be low or absent.[18] MAS has been reported in up to 15% of AOSD patients and is rarely described in pediatric TRAPS cases.[30] Strikingly, in soJIA,

MAS can even occur in up to 40% of cases.[31] Histopathological findings display hemophagocytic macrophages in bone marrow, lymph nodes and spleen, all of which are considered a prelude of multiple organ failure with high mortality in up to of 8-17% in soJIA, increasing up to 10-41% in adults.[32] Our patient exhibited several episodes of MAS with corresponding clinical and laboratory manifestations, as well as a suitable cytokine profile throughout her inflammatory flares.

Although isolated cases of non-specified interstitial lung disease in AOSD have been described before, the term AOSD-LD has only recently been introduced in parallel to the increased awareness of lung involvement in soJIA.[13, 33, 34] Recent reports have gone as far as claiming similar prevalence of parenchymal lung involvement in both AOSD and soJIA.[9, 35] Interestingly, a retrospective case study in soJIA-LD, focusing on parenchymal lung pathology, predominantly identified PAP and/or ELP as the final diagnosis.[11] In literature on AOSD-LD, to our knowledge, only a few biopsied cases have been reported, of which one case of ELP and one case of PAP, while no cases have been described in adult TRAPS.[13, 23-25, 36] Meanwhile, the other AOSD-LD biopsy specimens have shown nonspecific findings of interstitial fibrosis and chronic inflammation.[23, 33, 34, 37-40]

As previously mentioned, ELP is a rare form of interstitial lung disease caused by lipid accumulation within the lung. This can be observed, for example, in airway obstruction or systemic diseases with chronic inflammation amongst other causes. These endogenous lipids consist of the body's own cholesterol, originating from type ll epithelial cells within the alveolar walls. Further, intra-alveolar macrophages engulf the accumulated lipids in the alveolar cavities forming lipid-laden macrophages or so-called foam cells. There is no established standard of care for the treatment of ELP, although the first step is to address the underlying cause. Different strategies have been explored, including corticosteroids, immunoglobulins, whole-lung lavage, lung transplantation and even anti-TNF.[27] Our patient has been successfully treated with high-dose corticosteroids and cyclophosphamide induction followed by tacrolimus maintenance therapy.

As demonstrated in our patient, pulmonary manifestations of AOSD can be severe and even lethal, therefore, in concordance with soJIA-LD, screening should be considered to facilitate early detection and intervention.[13, 41]

Possible mechanisms: what we can learn from literature on soJIA

First, multiple studies have shown a link between soJIA-LD and disease severity. Compared to the soJIA population without LD, children who developed LD were younger at diagnosis, had a more active disease and MAS occurred more frequently.[11-13, 15, 42-44] Concordantly, our patient had a treatment refractory disease with the occurrence of several flares of MAS, an utterance of severe disease. The cytokine storm occurring in MAS may lead to an altered cytokine environment, dominated by IFN-γ and IL-18.[12] In the proximity of specific cytokines, CD4+ T-cells are known to differentiate into certain subtypes. This mechanism may alter the phenotypes of immune cells in the lung, contributing to ELP through an as yet unidentified

pathway.[45] Supportive of this theory, some studies showed that higher serum IL-18, elevated ferritin and lymphopenia preceded the diagnosis of LD. [11, 12] Accordingly, the cytokine analysis in our patient showed strong elevation of IL-1RA, IL-18, IL-6 and chemokine (C-X-C motif) ligand (CXCL) 9, an interferon (IFN)-dependent chemokine, as seen in a cytokine storm such as MAS. Based on these data, IL-18 blocking agents may have a role in patients with concomitant lung disease. Indeed, a recent article reported a case of soJIA-LD that showed a favorable response to combined IL-18 and IL-1β blockade. [46]

Second, it has been suggested in some studies that soJIA-LD might be related to the coincident increased use of biologicals. Saper et al. described that 80% of lung biopsies in soJIA-LD cases with pre-exposure to cytokine blockers showed PAP/ELP-features compared to only 36% in cytokine blocking treatment naive soJIA-LD patients.[11] The DRESS hypothesis, as previously mentioned in the differential diagnosis, was proposed to explain this link. Nevertheless, LD was also seen in patients who had not been exposed to cytokine blocking agents, arguing against their causative role.[42, 44, 47] Certainly, the use of biologics is more likely to reflect the severity of the disease, necessitating more advanced therapeutic interventions.

As presented, our patient had been treated with several biologic treatments including tocilizumab, anakinra and canakinumab before being diagnosed with ELP. Nevertheless, prior to the diagnosis of AOSD and before the initiation of any biologic treatment, chest-CT revealed bilateral septal thickening in the apical lobes, already suggesting the presence of AOSD-LD early in the disease course. In retrospect, the initial presentation with suspected *Chlamydia psittacosis* infection might already have been an underappreciated manifestation of AOSD-LD.

A graphical overview of possible mechanisms is shown in **Figure 3**.

Figure 3. Possible mechanisms of soJIA-LD.

Third, there might be a role for the cholesterol crystals in the alveolar cavities in itself as a self-maintaining trigger for chronic inflammation. It is shown that cholesterol crystals can lead to NLRP3 inflammasome activation with subsequent release of cytokines IL-1β and IL-18 and pyroptosis, an inflammatory form of cell death.[48, 49] A possible mechanism of NLRP3 inflammasome activation is shown in **figure 4**. Our patient's lung biopsy showed marked neutrophilic infiltration, with serum cytokine panels displaying elevated IL-18. Through a similar mechanism the cholesterol crystals might induce Neutrophil extracellular traps-(NET)osis of those neutrophils leading to an exacerbation of pro-inflammatory responses.[50]

Figure 4. Possible mechanisms of NLRP3 inflammasome activation by cholesterol crystals in macrophages and neutrophils in the alveolar space and their crosstalk.

In summary, we describe a patient with refractory autoinflammatory syndrome with the clinical picture of AOSD complicated by several episodes of MAS, presenting with respiratory distress secondary to ELP. This case illustrates the disease continuum of autoinflammation both in adults and children, and highlights the complex and unidentified pathophysiology of

lung disease herein. Importantly, disease severity and/or MAS seem to be a key precipitating factor in predisposed patients. Overall, more research is needed to disentangle the complex interplay between host and environmental factors on the pathophysiology of ELP across the disease spectrum. A role may be assigned to IL-blocking agents, although their role as proxy for severe disease or as a true catalysator needs to be elucidated.

The patient's course

The patient was pulsed with 1000mg methylprednisolon intravenously (IV) for three days, with considerable response. Due to the life-threatening nature of her disease and refractory status despite exhaustive anti-inflammatory treatment against the underlying autoinflammatory syndrome, she underwent induction therapy with cyclophosphamide IV 500 mg/m^2 body surface area every 4 weeks for 4 cycles with subsequent tacrolimus maintenance therapy. This regimen was empirically employed based on experience in other systemic inflammatory diseases. Arguably, this approach was effective, although the EUROLUPUS regimen may have been a suitable alternative. Nevertheless, due to relapse of her inflammatory symptoms a couple of weeks after completion of the cyclophosphamide induction, canakinumab was reintroduced. Since then, the patient has remained out of hospital, with successful tapering of the corticosteroids. During follow-up, lung function examination revealed restrictive impairment with a forced vital capacity of 45%, a total lung capacity of 64% and significant diminished diffusion capacity (DLCO) of 55%. Clinically, radiologically, and functionally significant residual interstitial lung disease persists, although features of fibrosis, such as traction bronchiectasis and honeycombing, remain absent.

Final diagnosis

Endogenous lipoid pneumonia in adult autoinflammatory disease with the clinical picture of AOSD.

Statements

Ethics approval and consent to participate: Not applicable.

Consent for publication: Informed consent for publication of this information was obtained from the patient.

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Legends figures

Figure 1. High resolution computed tomography scan of the chest. A-B. Chest-CT showed diffuse LD, predominant in lower and middle lobes with septal thickening involving the periphery of several lobes, some adjacent ground-glass opacities, bilateral peribronchovascular thickening and some pleural thickening.

Figure 2. Histopathology of the lung biopsy. A. Deposition of needle-shaped cholesterol crystals in the alveolar spaces. The interstitium of the alveoli is inflamed, showing mononuclear inflammatory cells and some neutrophils. **B.** Area in which both organizing diffuse alveolar damage and deposition of cholesterol crystals are seen. The alveolar walls are thickened and there is obvious type II pneumocytes hyperplasia (arrows). Some residual hyaline material is indicated by arrowheads. **C.** At high magnification clusters of foamy macrophages are visualized between the cholesterol crystals (arrowheads).

Figure 3. Possible mechanism of soJIA-LD. Figure by Katrien Slabbynck adapted from Schulert et al.[12] The cytokine storm in MAS attributes an important role to IL-18 and IFN-γ, which activate alveolar macrophages and other immune cells in the lungs. Presence of IL-6 and IL-1 favours differentiation into Th17 cells, whereas absence promotes polarization towards Th1 cells.[45] The latter produce IFN-γ, further enhancing macrophage activation. These activated immune cells release cytokines and chemokines, including CXCL9 and CXCL10. This recruits even more Th1-lymphocytes, leading to a self-sustained inflammatory response in the lung. This pro-inflammatory environment disturbs homeostasis of resident alveolar macrophages, resulting in accumulation of lipids and proteins, leading to PAP-like features.[12] These lipids can induce NLRP3 inflammasome formation in macrophages and neutrophils, respectively leading to pyroptosis and NETosis, further sustaining the inflammation.[48-50] Abbreviations: MAS: Macrophage Activation Syndrome; soJIA: Systemic-onset Juvenile Idiopathic Arthritis; NLRP3: NOD-like receptor family pyrin domain containing 3; IL: interleukin; IFN-γ: Interferon

gamma; TNF: Tumor Necrosis Factor; CXCL: C-X-C Motif Chemokine Ligand; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; Th: T helper cell; NET: Neutrophil Extracellular Traps.

Figure 4. Possible mechanisms of NLRP3 inflammasome activation by cholesterol crystals in macrophages and neutrophils in the alveolar space and their crosstalk. Figure by Katrien Slabbynck with BioRender, adapted from Tall et al.[51] Cholesterol crystals in the alveolar space are engulfed by macrophages and neutrophils. The oxidized lipids lead to inflammasome activation and caspase-dependent cleavage of pro-interleukins into their active form as well as pore formation leading to pyroptosis, NETosis and release of IL-18 en IL-1β. The expulsion of intracellular material again leads to DAMPs and further activation of inflammation.[51] Abbreviations: DAMP: damage-associated molecular pattern; PAMP: pathogen-associated molecular pattern; NET: Neutrophil Extracellular Traps; IL: interleukin.

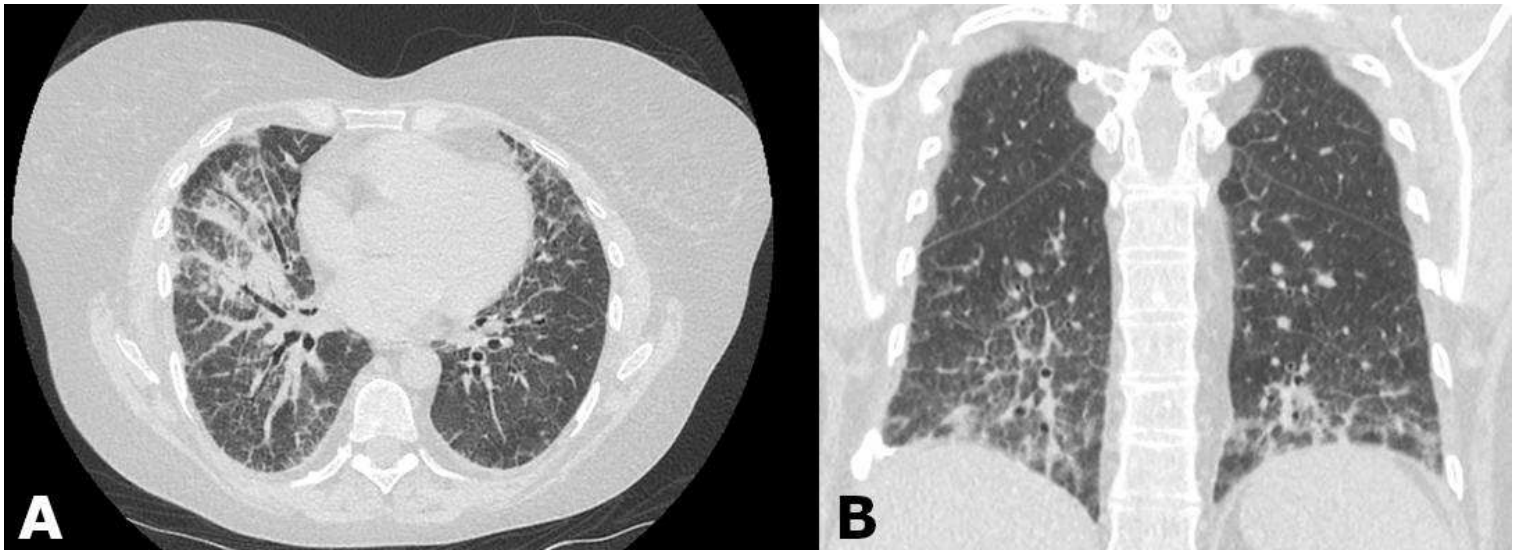

Figure 1. High resolution computed tomography scan of the chest. A-B.

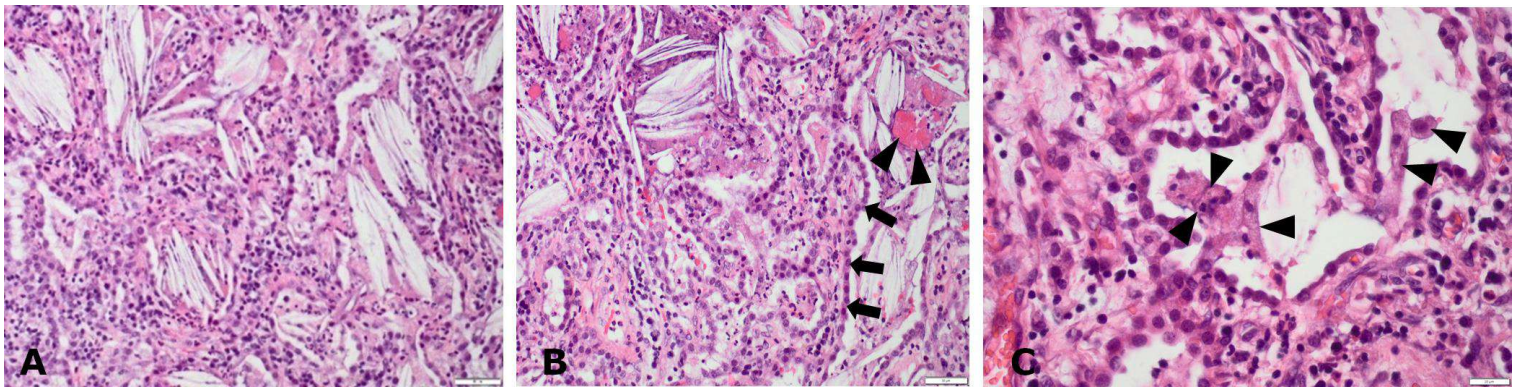

Figure 2. Histopathology of the lung biopsy.

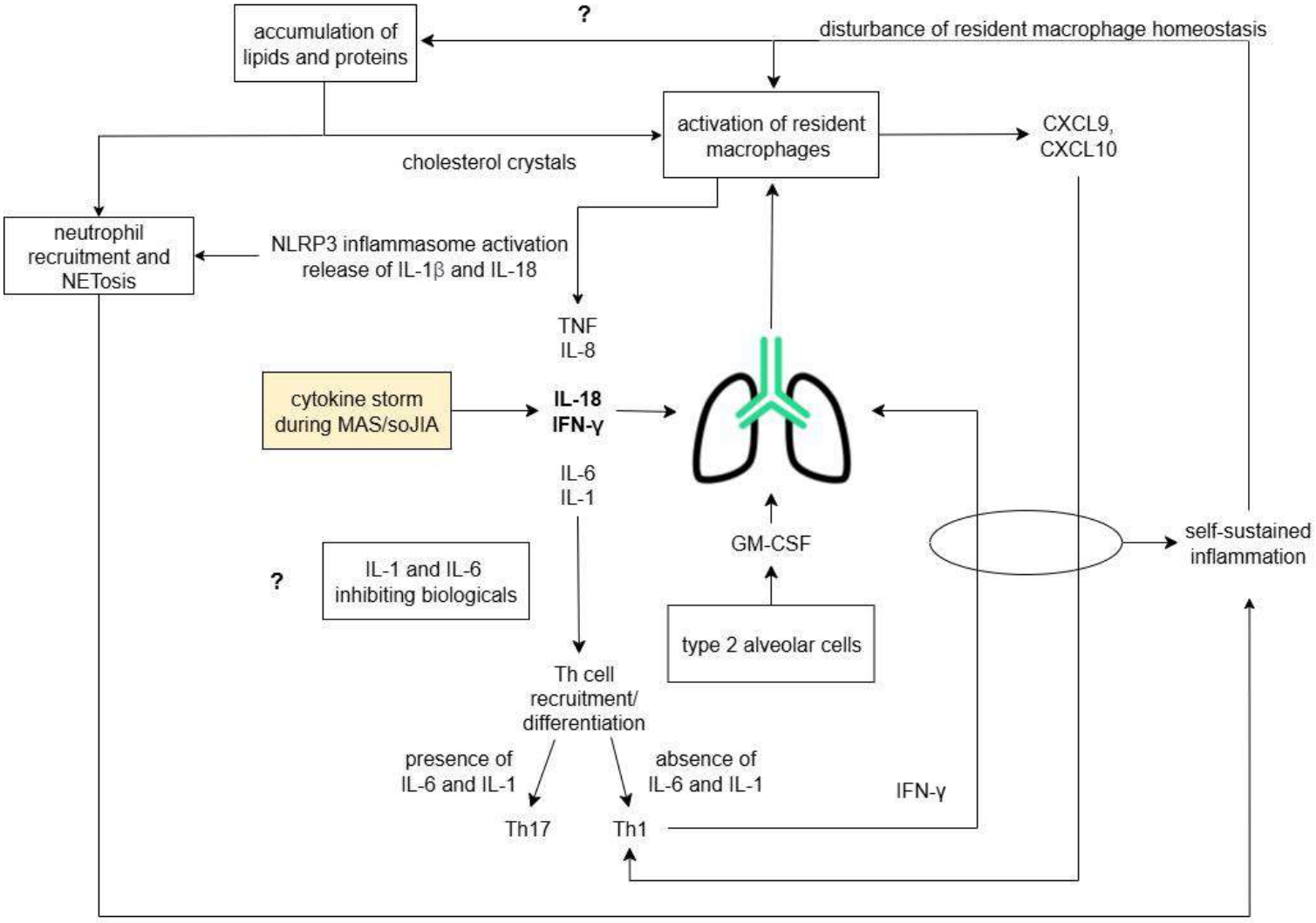

Figure 3. Possible mechanism of soJIA-LD.

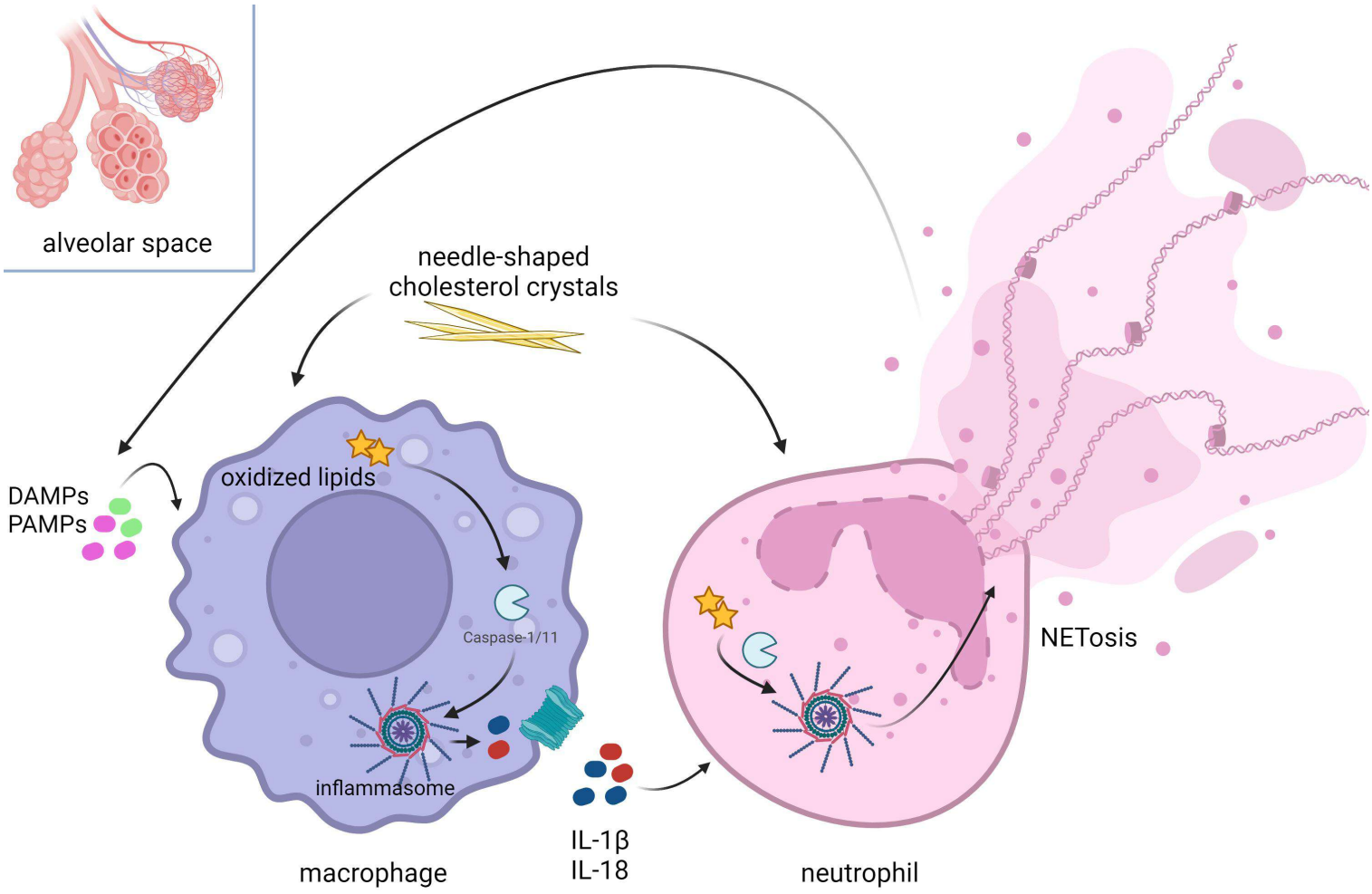

Figure 4. Possible mechanisms of NLRP3 inflammasome activation by cholesterol crystals in macrophages and neutrophils in the alveolar space and their crosstalk.

Supplementary data

Article	Total soJIA-LD cases	LD cases with biopsy specimen n (%)	PAP/ELP spectrum within biopsied cases n (%)
Saper et al.[1]	61	36 (59)	23 (64)
Schulert et al.[2]	18	8 (44)	8 (100)
Schultz et al.[3]	1	1 (100)	1 (100)
Athreya et al.[4]	8	UNK	UNK
Kimura et al. [5]	25	12 (48)	5 (42)
Sato et al. [6]	1	1 (100)	1 (100)
Sato et al. [7]	1	0 (0)	NA
Belozerov et al.[8]	5	0 (0)	NA
Huang et al.[9]	41	13 (32)	UNK
Ruscitti et al.[10]	7	UNK	UNK
Swanson et al.[11]	9	3 (33)	3 (100)
Aires et al.[12]	4	UNK	UNK
Rood et al.[13]	1	1 (100)	1 (100)
Côte et al.[14]	8	1 (13)	1 (100)
Zhan et al.[15]	35	UNK	UNK
Gao et al.[16]	60	UNK	UNK
TOTAL	**285**	**76 (27)**	**43 (57)**

Table 1. Amount of PAP/ELP in biopsied cases in soJIA. soJIA: systemic onset juvenile idiopathic arthritis; LD: lung disease; PAP: pulmonary alveolar proteinosis; ELP: endogenous lipoid pneumonia. NA: not applicable; UNK: unknown.

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