

# Pulmonary involvements in systemic juvenile arthritis

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## Research article

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# Abstract

## Background

Systemic juvenile idiopathic arthritis (sJIA) is a chronic inflammatory disease of childhood. Pulmonary involvements in sJIA have been recently described. Herein, we assess unusual clinical and radiological features of patients with sJIA, and possible risk factors for pulmonary involvements in sJIA.

## Methods

A total of thirty-nine patients with sJIA were retrospectively enrolled. Data extracted included demographics, medical history, clinical manifestations, laboratory results, serum cytokine levels, radiological findings, management, and prognosis.

## Results

Macrophage activation syndrome (MAS) had been observed at the initial diagnosis or during disease flares in eleven patients (11/39, 28%). Cerebral venous sinus thrombosis was observed in one patient with paroxysmal headache during the MAS phase. Twenty-three patients demonstrated abnormal radiological features on chest Computed Tomography (CT). Only eleven patients had subtle respiratory symptoms with normal oxygen saturation. Eight patients had lung disease (LD) before biologic exposure. sJIA-LD occurred in another six patients after the introduction of tocilizumab. All these patients continued to receive tocilizumab therapy, and sJIA-LD was improved in twelve patients with complete resolution of pulmonary presentations, and partially relieved in two patients. Only one of the two patients with possible anaphylaxis to tocilizumab presented with LD. Severe sJIA-LD was found in two patients with trisomy 21 and Kabuki syndrome, respectively.

## Conclusions

Pulmonary involvements are increasingly observed in children with sJIA. Possible high risks for sJIA-LD include the occurrence of MAS, some inherited diseases, and evidence of drug hypersensitivity. It is still a question of whether IL-1/IL-6 inhibitor exposure increases the risk of sJIA-LD. Vasculitis and thrombosis should be considered in sJIA during the MAS phase, particularly in patients with pulmonary involvements.

## Trial registration:

Not applicable; this was a retrospective study.

## Background

Systemic juvenile idiopathic arthritis (sJIA) is a chronic inflammatory disease of childhood, characterized by destructive arthritis, daily spiking fevers, an evanescent rash, lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis. Macrophage activation syndrome (MAS), as a life-threatening complication, is observed in approximately 10% of sJIA patients, manifesting as a cytokine storm with cytopenias, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, and hemophagocytosis on biopsy<sup>[1]</sup>.

In recent years, pulmonary involvements of sJIA have been described, including pleuritis, pleural effusion, and the usual chronic parenchymal lung disease (LD)<sup>[2-5]</sup>. Twenty-five sJIA patients were diagnosed with pulmonary arterial hypertension (64%), interstitial LD (28%), pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia (PAP/ELP) (20%)<sup>[2]</sup>. Imaging findings include pleural and septal thickening, “tree-in-bud” and “ground-glass” opacities, and peripheral consolidation<sup>[3]</sup>. Possible risk factors for development of sJIA-LD include younger age at disease onset, trisomy 21, concurrent MAS, evidence of drug hypersensitivity, and prominently elevated serum IL-18 levels<sup>[2-4]</sup>. IL-1/IL-6 inhibitor exposure may promote the development of PAP/ELP-like disease in a subset of patients with sJIA<sup>[4]</sup>. However, sJIA-LD in some patients has been improved following IL-1/IL-6 inhibitor therapy<sup>[3]</sup>. Here, we performed a single, retrospective study of thirty-nine patients with sJIA. Clinical and radiological features were described, and possible risk factors for sJIA-LD were analyzed.

## Methods

### Study population

A total of thirty-nine patients with sJIA were retrospectively enrolled between February 2014 and April 2019. All patients met sJIA classification criteria by the International League of Associations Rheumatology (ILAR). Whole-exome sequencing and sequence data analyses were performed in twenty-six patients, and monogenic auto-inflammatory diseases were excluded. The follow-up time ranged from one to five years.

### Data Collection

Clinical data extracted from inpatient or outpatient medical records included demographics, medical history, clinical manifestations, laboratory results, radiological findings, management, and prognosis.

### Quantification Of Cytokines

Serum samples from healthy controls and patients with sJIA were isolated from peripheral blood collected in vacutainers containing sodium heparin. According to the manufacturer's protocol, serum cytokine analyses were performed on a bead-based immunoassay (Milliplex, HCYTOMAG-60K, Millipore, USA). IL-18 was determined using specific ELISA kits obtained from Raybiotech.

# Statistical analysis

All data for cytokine levels were represented as mean of triplicates  $\pm$  S.E.M. Variance analysis was performed using Student's unpaired t-test or Mann Whitney test. All analyses were performed with GraphPad Prism 8.0 statistical software (GraphPad Software Inc., La Jolla, CA, USA). A value of  $P \leq 0.05$  was considered to be statistically significant.

## Results

### Clinical manifestations and laboratory features

Patients with fifteen females and twenty-four males were included. The median age of disease onset was five years ((interquartile range: IQR 14 months – 13 years). Eleven patients had subtle respiratory symptoms with normal oxygen saturation, such as cough, chest pain on inhalation, and mild resting tachypnea. Two patients presenting with bilateral bulbar conjunctival injection and injected-fissured lips were initially diagnosed with Kawasaki disease (KD). MAS had been observed at the initial diagnosis or during disease flares in eleven patients (11/39, 28%). Two patients had weakly positive anti-SSA and anti-pANCA autoantibodies, respectively. Infectious pneumonia was excluded from extensive microbiological screening negatives and unresponsiveness to antibiotics in most patients with sJIA-LD. However, it was hard to exclude infection in two patients with trisomy 21 and Kabuki syndrome, respectively. Cerebral venous sinus thrombosis occurred in one patient concurrent with MAS and sJIA-LD, presenting with paroxysmal headache (Fig. A Left). This patient received intravenous methylprednisolone pulse (IVMP), tocilizumab, and warfarin therapy, showing a good response with complete resolution of MAS, image abnormalities, and headache (Fig. A Right). Coronary artery dilation was seen in one patient at the initial diagnosis and resolved following glucocorticoid therapy. Hyperinflammation was observed in all patients at the initial diagnosis and during disease flares, including elevation of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IFN- $\lambda$ , and IL-18 levels (Fig. B and Fig. C). In contrast to patients with KD, ferritin (FER) level and FER/ESR ratio were significantly increased in patients with sJIA (Fig. B). Tocilizumab therapy was discontinued in two of twenty-five patients for the occurring of rapid itching rashes, tachypnea, and tachycardia within several minutes of the second and third infusion. Glucocorticoids was discontinued in eight patients after 6 months of tocilizumab therapy and re-added to one of them during disease flares.

### Radiological features on chest CT

Chest high-resolution chest computed tomography (CT) scans were performed at diagnosis in all patients. CT scans were re-examined in some patients with severe pulmonary involvements at diagnosis or during disease flares. Radiological features were comprehensively reviewed. Twenty-three patients demonstrated pulmonary presentations, including eighteen occurring at diagnosis and four during follow up. Radiological findings included localized pleural thickening (n = 14), lobular septal thickening (n = 10), subpleural nodules (n = 6), mild "ground-glass" opacities (n = 9), peripheral consolidation (n = 4), mild

pleural effusion (n = 9), fiber-like shadow (n = 6), cyst-cavity (n = 2), mild bronchiectasis (n = 2), multiple nodules (n = 1), and lymphadenopathy (n = 8) (Fig. D top). Eleven patients exhibited at least three abnormal changes. Signs for pulmonary artery enlargement and honeycombing were not found.

## Possible risk factors for pulmonary involvements

Both patients with inherited diseases were found to have prominent lung diseases. sJIA-LD was initially diagnosed in fifteen patients During the MAS phase. Only one of the two patients with possible anaphylaxis to tocilizumab presented with LD. Eight patients had sJIA-LD prior to biologic exposure. sJIA-LD occurred in another six patients after the introduction of tocilizumab. All these patients continued to receive tocilizumab therapy, and sJIA-LD was improved in twelve patients with complete resolution of pulmonary presentations, and partially relieved in two patients (Fig. D bottom).

## Discussion

In 2013, Kimura and colleagues reported an unusual life-threatening pulmonary complication in some patients with sJIA, manifested by exposure to a wider range of therapies, susceptible to MAS, and extremely high mortality<sup>[2]</sup>. A recent case series identified 61 additional cases with sJIA-LD, showing an association with trisomy 21, an early-onset age at < 5 years, anaphylaxis to tocilizumab, lymphopenia, hyperferritinemia, and evidence of drug hypersensitivity<sup>[4]</sup>. Schulert et al described 18 patients with a much less severe disease course. Similarly, these patients had a younger onset age at < 2 years, higher frequencies of MAS, and possible adverse reactions to biologics<sup>[3]</sup>.

Herein we have described thirty-nine patients with sJIA-LD, presenting with mild clinical symptoms. The prevalence of LD in sJIA in this case series was much higher, possibly related to ethnic differences, geographic location, and the broader application of CT scans. Twenty-one patients with sJIA-LD showed substantially improved disease, and two showed stable disease. In consistent with previous reports, sJIA-LD was prone to patients concurrent with MAS, and severe pulmonary involvements were observed in one patient with trisomy 21. Severe sJIA-LD was found in another patient with Kabuki syndrome related to KMT2D defect. Severe interstitial lung disease was recently reported in two patients with de novo KMT2D missense variants, suggesting the possible role of KMT2D defect in sJIA-LD<sup>[6]</sup>. Based on limited cases in this study, it is hard to conclude the association of sJIA-LD and anaphylaxis to tocilizumab. It is a difficult question of whether biologic exposure contributes to sJIA-LD since sJIA-LD has been improved in most patients continuing to receive tocilizumab therapy. Additional patients of sJIA with or without LD are required to clarify the exact role of IL-1/IL-6 inhibitor exposure in sJIA-LD.

Two patients concurrent with sJIA-LD during the MAS phase have been found to have vascular involvements, including cerebral venous sinus thrombosis or coronary artery lesions. Vascular function is impaired in patients with sJIA at a very young age, showing increased arterial stiffness, especially in those presenting with MAS<sup>[7]</sup>. Vascular endothelial cells are activated by inflammatory cytokines and further contribute to the intravascular coagulation of sJIA. Angiopoietins (Ang)-1 and - 2 are key

regulators of endothelial cell function. The serum Ang-2/1 ratio has been significantly elevated during the MAS phase in sJIA<sup>[8]</sup>. Disruption of vascular endothelial homeostasis by Ang-1 and Ang-2 abnormalities might play a role in the uncommon features of vasculitis and thrombosis in sJIA. The underlying molecular mechanism accounting for vasculitis in sJIA remains to be determined.

## Conclusions

Pulmonary involvements are increasingly observed in children with sJIA, and possible high risks include the occurrence of MAS, some inherited diseases, an early-onset age, and evidence of drug hypersensitivity. The prevalence of sJIA-LD might be distinct in different populations. It is still a question of whether IL-1/IL-6 inhibitor exposure increases the risk of sJIA-LD. Vasculitis and thrombosis should be considered in sJIA during the MAS phase, particularly in patients with pulmonary involvements. Well-designed multicenter clinical studies are required to identify the specific risk factors for sJIA-LD and sJIA-associated vasculitis.

## Abbreviations

sJIA: Systemic juvenile idiopathic arthritis ; MAS: Macrophage activation syndrome; LD: lung disease; CT: Computed Tomography; PAP/ELP: pulmonary alveolar proteinosis and/or endogenous lipid pneumonia; ILAR: International League of Associations Rheumatology; KD: Kawasaki disease; IVMP: intravenous methylprednisolone pulse; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FER: ferritin.

## Declarations

## Availability of data and materials

The datasets were collected from medical records of participated patients in Shenzhen Children's hospital.

### Ethics approval and consent to participate

All participated members were enrolled with the approval of the ethics committee of Shenzhen Children's hospital and provided written consent from their parents.

### Consent for publication

Written consent for publication of this anonymous information was obtained from the patient's parents.

### Competing interests

All authors declare no conflict of interest.

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# Authors' contributions

Tingyan He designed the work, analyzed the data, and drafted the manuscript. Jiayun Ling collected clinical data of all patients and helped to interpret the analyzed data. Jun Yang reviewed the manuscript. All authors reviewed and approved the final manuscript.

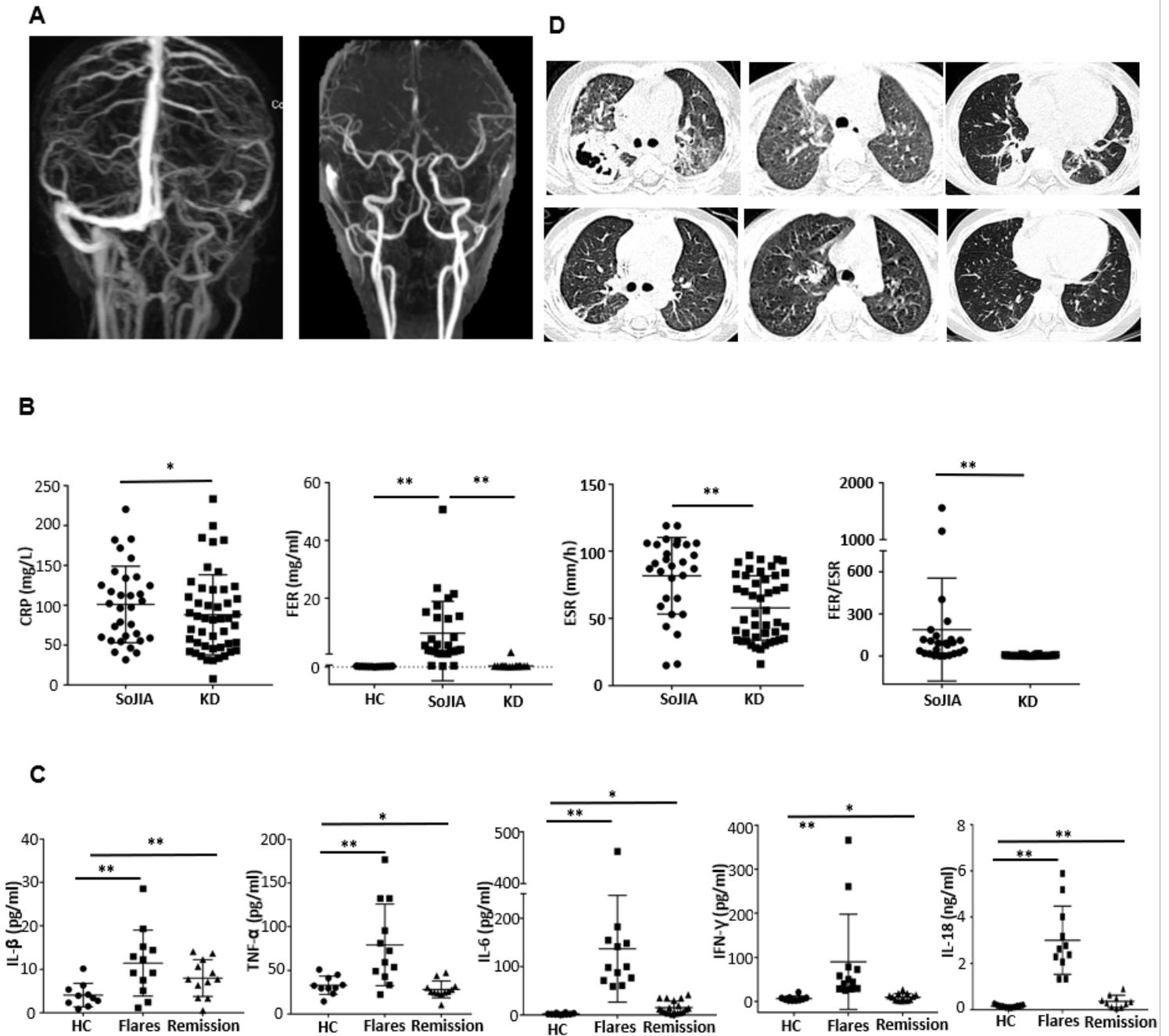
# Acknowledgements

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# Figures



**Figure 1**

Radiological features and hyperinflammation in sJIA A Cerebral venous Magnetic Resonance Imaging (MRI) in one patient concurrent with MAS and sJIA-LD revealed most likely thrombosis in left lateral sinus, sigmoid sinus, and internal jugular vein (Left). Cerebral venous MRI following therapy showed a complete resolution of cerebral venous thrombosis (Right). B Abnormal laboratory tests for hyperinflammation in patients with JIA. Data were pooled from healthy controls (n = 13), patients with sJIA (n = 32), and patients with kawasaki disease (KD, n = 47), respectively (\*\*: P < 0.05; \*: P > 0.05; Student's unpaired t-test). Values were represented as mean ± S.E.M. C Elevated serum cytokine levels in patients with sJIA at flares. Data from healthy controls (n = 10) and patients with sJIA (n = 12) at

remission and flares were pooled, respectively (\*\*:  $P < 0.05$ ; \*:  $P > 0.05$ ; Mann-Whitney test). Values were represented as mean  $\pm$  S.E.M. D Radiological features on chest CT in patients with sJIA-LD included lobular septal thickening, peripheral consolidation, mild pleural effusion, and fiber-like shadow (Top), which were greatly improved following HLH-2004 (Bottom Left) or oral prednisolone combined with tocilizumab therapy (Bottom Middle and Right).