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ABOUT COVER

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Cohort Study

Systemic juvenile idiopathic arthritis–associated lung disease: A retrospective cohort study

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Abstract

BACKGROUND

Lung damage in systemic juvenile arthritis (sJIA) is one of the contemporary topics in pediatric rheumatology. Several previous studies showed the severe course and fatal outcomes in some patients. The information about interstitial lung disease (ILD) in the sJIA is scarce and limited to a total of 100 cases.

AIM

To describe the features of sJIA patients with ILD in detail.

METHODS

In the present retrospective cohort study, information about 5 patients less than 18-years-old with sJIA and ILD were included. The diagnosis of sJIA was made according to the current 2004 and new provisional International League of Associations for Rheumatology criteria 2019. ILD was diagnosed with chest computed tomography with the exclusion of other possible reasons for concurrent lung involvement. Macrophage activation syndrome (MAS) was diagnosed with HLH-2004 and 2016 EULAR/ACR/PRINTO Classification Criteria and hScores were calculated during the lung involvement.

RESULTS

The onset age of sJIA ranged from 1 year to 10 years. The time interval before ILD

ranged from 1 mo to 3 years. The disease course was characterized by the prevalence of the systemic features above articular involvement, intensive rash (100%), persistent and very active MAS (hScore range: 194-220) with transaminitis (100%), and respiratory symptoms (100%). Only 3 patients (60%) developed a clubbing phenomenon. All patients (100%) had pleural effusion and 4 patients (80%) had pericardial effusion at the disease onset. Two patients (40%) developed pulmonary arterial hypertension. Infusion-related reactions to tocilizumab were observed in 3 (60%) of the patients. One patient with trisomy 21 had a fatal disease course. Half of the remaining patients had sJIA remission and 2 patients had improvement. Lung disease improved in 3 patients (75%), but 1 of them had initial deterioration of lung involvement. One patient who has not achieved the sJIA remission had the progressed course of ILD. No cases of hyper-eosinophilia were noted. Four patients (80%) received canakinumab and one (20%) tocilizumab at the last follow-up visit.

CONCLUSION

ILD is a severe life-threatening complication of sJIA that may affect children of different ages with different time intervals since the disease onset. Extensive rash, serositis (especially pleuritis), full-blown MAS with transaminitis, lymphopenia, trisomy 21, eosinophilia, and biologic infusion reaction are the main predictors of ILD. The following studies are needed to find the predictors, pathogenesis, and treatment options, for preventing and treating the ILD in sJIA patients.

Key Words: Systemic juvenile arthritis; Interstitial lung disease; Canakinumab; Tocilizumab; Interleukin-6; Interleukin-1

Core Tip: We evaluated 5 patients with systemic juvenile arthritis and interstitial lung disease. This is an ultra-rare, unrecognized, life-threatening and potentially fatal complication of systemic juvenile arthritis. This complication is usually associated with early onset age, systemic features of the disease, especially with pleuritis, severe and long-term macrophage activation syndrome, lymphopenia, trisomy 21 syndrome, and biologic anaphylaxis. The recognition of these symptoms can help in early suspicion of this severe complication.

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INTRODUCTION

Juvenile idiopathic arthritis with systemic onset (sJIA) is the most life-threatening form of JIA due to macrophage activation syndrome (MAS) and internal organ involvement[1,2]. The lung disease is a rare, severe, potentially fatal manifestation of sJIA. Its prevalence has grown in the last 20 years from single cases at the beginning of 2000 to 5% nowadays[1]. Lung involvement in sJIA includes pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), presenting with pulmonary alveolar proteinosis, and lipoid pneumonia[1,2]. Patients may have a combination of ILD and PAH. The mechanisms of lung involvement in sJIA are still unclear. It is known that hyperproduction of interleukin (IL) 1, IL-18, and interferon (IFN) γ pathway signaling are the main key points of the pathogenesis of lung involvement in sJIA. Several risk factors, associated with lung involvement in sJIA were proposed: onset age < 2 years, prevalence of systemic features, chronic or recurrent or poor controlled MAS, persistent and progressed lymphopenia, anaphylaxis to IL-6 and IL blockers, trisomy on 21 chromosomes[3]. The outcomes of the patients with sJIA with lung diseases (sJIA-LDs) are extremely serious. In the first case series of 25 patients published by Kimura *et al*[4], 68% died in 8.8±11.4 mo after the lung involvement appeared. Several recent studies showed better outcomes with a mortality rate near 4.6% which is 7.5 times more than in sJIA patients without lung involvement[5]. There are no approved pathogenic medications for the treatment of lung involvement in sJIA patients. Treatment with IFN-γ direct blocker (emapalumab), indirect blockers (JAK-inhibitors), and anti-IL-18 blockers (IL-18 binding protein) seems to be promising but requires approval[6-8]. Additional treatment options might include corticosteroids (glucocorticosteroids), anti-IL-1 and anti-IL-6 biologics, cyclosporine A and tacrolimus, mofetil mycophenolate, intravenous immunoglobulin, and PAH for specific treatment to control the pulmonary blood pressure and oxygen supplementation[1,2,9]. Children with sJIA and chronic lung involvement are more susceptible to lung infections and require specific prophylaxis[4].

The Information about patients with lung involvement is scarce and related to patients whose chronic lung disease has already been diagnosed.

Our study aimed to describe the patients with sJIA-LD with a focus on the initial clinical and laboratory features.

MATERIALS AND METHODS

Population

In the present retrospective cohort study, we included available information about 5 pediatric patients (onset age < 18 years) with sJIA-LD. The diagnosis of sJIA was made according to the current 2004[10] and new provisional International League of Associations for Rheumatology (ILAR) criteria 2019[11]. If the patient did not fit one of the major criteria he/she was diagnosed with sJIA-like disease (probable"/"possible" sJIA).

ILD was diagnosed with chest computed tomography and the exclusion of other possible reasons for concurrent lung involvement.

MAS was diagnosed with HLH-2004[12] and 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis[13] and hScore was calculated during the lung involvement[14].

Statistics

The sample size was not calculated initially. We included all available cases in our center. We used only descriptive statistics (quantitative and categorical data).

RESULTS

Common symptoms at onset of sJIA

Diagnosis of sJIA was established in all patients. Two patients did not meet the current ILAR criteria in 2004, because patients 1 and 2 did not have arthritis at the onset. All patients corresponded to new provisional criteria for sJIA 2019. Patient 2 developed severe polyarthritis 2 years after the disease onset. The correspondence of the patients to current (2004) and new provisional (2019) ILAR criteria is shown in Table 1. Serositis was presented by pericarditis in 3 cases (patients 1, 2, and 4), pleurisy in 4 cases (patients 1,2,3 and 4), and peritonitis in patient 2. One patient (patient 5) developed leucopenia at onset due to MAS. The demographic characteristics of patients are in Table 2.

Lung involvement

All patients had dyspnea, but only 1 patient had a cough (patient 2). Clubbing (Figure 1) of the fingers was in 3 (60%) patients. Respiratory failure was diagnosed in 4 (80%) patients. They were admitted to the Intensive Care Unit for respiratory support.

In 2 cases, lung disease was diagnosed at the sJIA onset (patients 3 and 4) and in 3 cases, lung disease developed later in patients 1, 2, and 5 (Figure 2).

Two patients developed PAH, patient 1 had persistent PAH and required PAH-specific treatment, and patient 2 had temporary PAH at the lung disease onset and this was successfully resolved in 1 mo after high-dose systemic glucocorticosteroid treatment.

MAS and ILD development

All patients have met the above mentioned MAS criteria. Severe full-blown MAS had all 5 (100%) patients at the onset with a score range of 194-220 points. All patients had persistent/relapsed courses of MAS. In all cases, ILD was detected in patients with features of MAS. Interestingly, MAS was more aggressive and hardly controlled in patients with early onset (patients 1 and 2) and patients with trisomy 21 syndrome (patient 5).

Assessment of the known risk factors of LD-sJIA

We observed the risk factors which were previously described[1,3]. Infusion reaction on tocilizumab had 3 (60%) patients. Trisomy 21 syndrome had 1 patient (Patient 5). Four patients developed sJIA at the age of 2 years or younger, and patient 3 developed sJIA at the age of 10 years. All patients had severe MAS.

Treatment

All patients received corticosteroids. High doses of intravenous corticosteroids were received at the onset and with a major flare, including MAS. Inhalational corticosteroids (budesonide and fluticasone) were used in 1 case with lipoid pneumonia. All 5 patients have experienced tocilizumab treatment, and as we have already pointed out, infusion reaction was diagnosed in 3 cases (patients 1, 2, and 4). In 4 of 5 (80%) cases, tocilizumab was changed to canakinumab; abatacept was added to canakinumab therapy in patient 1. Patient 1 with PAH has received sildenafil with positive dynamic and stabilization in PAH.

Outcomes

The outcomes of our cases were different. Patient 5 with trisomy 21 (Down Syndrome) had a fatal outcome. The female developed a flare of sJIA with respiratory and heart failure. Two patients (patients 2 and 3) achieved sJIA remission with the improvement of ILD, but patient 2 initially had deterioration followed by improvement. Two patients had incomplete sJIA remission (patients 1 and 4) with ILD improvement in patient 4, but patient 1, despite the combination treatment of canakinumab and abatacept has not achieved ILD improvement. His PAH is under the control of sildenafil. Patients with early onset had more severe ILD. Demographic characteristics, clinical with ILAR criteria, radiological features, and

Table 1 Correspondence of our patients to current[10] and provisional International League of Associations for Rheumatology criteria for systemic juvenile arthritis[11]

No. ID	Major criteria			Minor criteria				Overall correspondence ILAR2004 criteria	Overall correspondence ILAR2019 criteria
	Fever	Erythematous rash	Arthritis	Lymphadenopathy/hepatomegaly/splenomegaly	Serositis	Arthralgia	Leukocytosis as/mm^3		
1	Yes	Yes	No	Yes	Yes	No	53.300	No	Yes
2	Yes	Yes	No	Yes	Yes	Yes	15.100	No	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	47.200	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	30,820	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	No	2.300	Yes	Yes

ILAR: International League of Associations for Rheumatology.

Table 2 Demographic characteristics of the patients

No.	Sex	Age of onset in yr	Age of last follow-up visit in yr	Time to sJIA-LD	Concomitant disease
1	Male	1	10	3 yr	--
2	Female	2	11	3 yr	--
3	Female	10	17	1 month	--
4	Male	2	11	4 months	Atopic dermatitis
5	Female	2	7	4 yr	Trisomy 21 syndrome

sJIA-LD: Systemic juvenile arthritis with lung diseases.

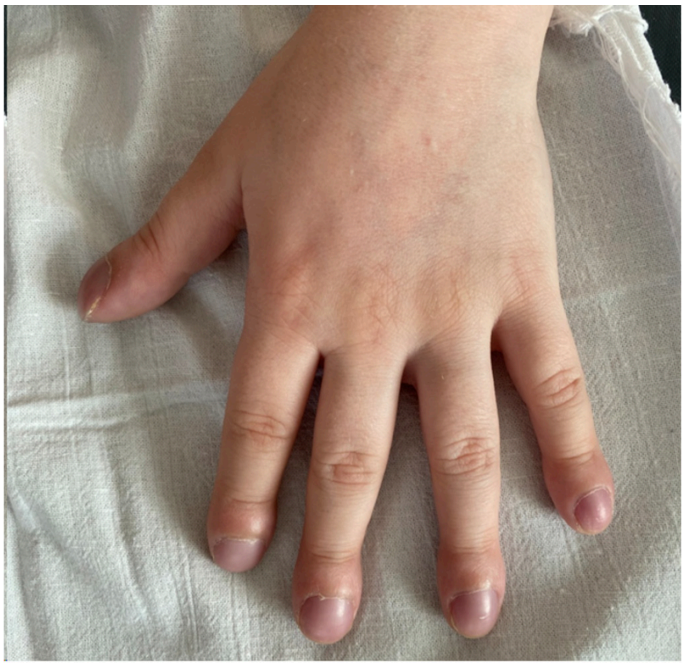

Figure 1 Clubbing of the fingers in patient 2. The changes of the distal phalanges and the nails are apparent.

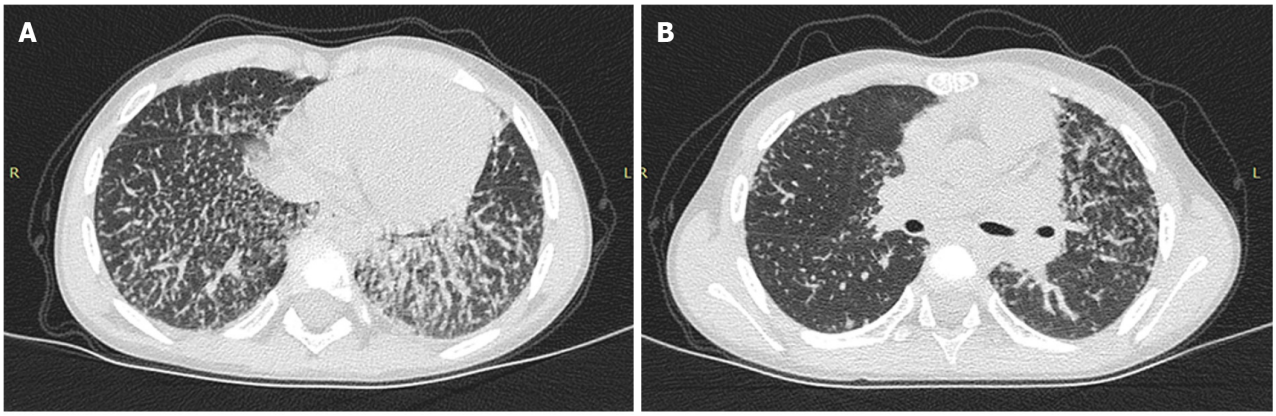

Figure 2 Chest computed tomography in patient 2 with lipoid pneumonia. A and B: Representative signs of interstitial changes in all lobes of the lungs with damage to the distal parts of the tracheobronchial tree. There are diffuse changes with the presence of multiple intralobular foci, with thickening of the peribronchovascular interstitium.

treatment outcomes are in Tables 1-4.

DISCUSSION

sJIA is an autoinflammatory disease that is characterized by fever, rash, arthritis, and damage to other organs[1].

MAS is a life-threatening complication in children with sJIA, related to the hyperproduction of proinflammatory cytokines, especially: IL-1, IL-6, IL-18, IFN-γ[2,9,15,16]. sJIA-LD is a troupe of nosology that is characterized by chronic lung disease in patients with sJIA[1] Now, it is clear, that lung involvement in sJIA patients is associated with persistent systemic inflammation, especially with MAS[1-3].

Clinical symptoms, associated with ILD

Unfortunately, typical respiratory symptoms at the beginning of the disease are usually absent or poorly expressed, and because of this, sJIA-LD occurs unexpectedly in many patients. For example, the cough was present in 33%-43%, tachypnea in 33%-38%, auscultative changes in the lungs in 30%, while hypoxemia was already registered in 43% of patients, and symptomatic PAH in 30%[1,3].

Sometimes, the main clinical symptoms indicating lung lesions are distal phalangeal dilation or the so-called clubbing symptom (61%) and erythema of the distal phalanges (34%).

Despite the diagnosis of sJIA, patients with lung involvement had unusual clinical presentations such as an itchy rash (56%), eosinophilia (37%), and unexplained intense abdominal pain (16%)[3].

In our group, patient 2 had a severe sJIA flare with aseptic peritonitis that required diagnostic surgery 1 year before the lung involvement.

Another important feature is the development of a hypersensitivity reaction (anaphylaxis) to 2-3 injections of tocilizumab in many children with JIA and lung damage[1,3,9]. The estimated probability of a hypersensitivity reaction during treatment with tocilizumab is up to 9.1%[17-19]. Three (60%) of our patients had a tocilizumab anaphylaxis. Hypersensitivity to biological agents was found to be a risk factor for ILD[1,3].

Laboratory symptoms associated with ILD

Lymphopenia (< 60% of the lower normal limit for age) was detected in sJIA patients with lung involvement. This could not be explained by the current MAS and was found in 42%. The combination of hyperferritinemia and severe lymphopenia serves as a marker of the risk of lung involvement in patients with sJIA[3]. Another important laboratory symptom is eosinophilia, associated with ILD in sJIA patients[3].

Interstitial lung involvement

Pulmonary alveolar proteinosis is a poorly studied disease manifested by the accumulation of lipid substances in the alveoli due to ineffective excretion of lipid substances by macrophages[20]. Macrophage dysfunction in sJIA-LD is not associated with congenital defects of macrophages, as in primary lung disease[1,20-22]. Patients with MAS have a highly active systemic inflammation that contributes to macrophage differentiation disturbances[1]. Similar cytokine transmission pathways in MAS and sJIA-LD explain the close similarity between both conditions. Several cytokines, such as IFN-γ and IL-18 are now the focus of MAS pathogenesis[6,23].

The persistence of high levels of IL-18 in patients with sJIA receiving canakinumab may explain the development of lung damage in children being in remission under the biological treatment[24].

In IL-18-dependent diseases, specific therapy with IL-18-binding protein is required, since other treatments may be ineffective[7].

Table 3 Clinical and radiological characteristics of the patients with systemic juvenile arthritis at the moment of diagnostics of lung involvement

No.	Rash	Hepatitis	Lymphadenopathy	Cough	Dyspnea	Clubbing	Respiratory failure	Infusion reaction on TCZ	PAH	MAS	hScorein points	Heart involvement	X-ray, CT, or MRI or US findings	Eosinophils as × 10^9/L
1	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	220	Pericarditis	ILD, pleurisy	0.63
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	209	Myocarditis, Pericarditis	Interstitial lung disease with intralobular foci, pleurisy	0.19
3	Yes	Yes	No	No	Yes	No	No	No	No	Yes	224	N	Alveolitis, diffuse focal lesions, pleurisy	0.29
4	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	194	Pericarditis	ILD, atelectasis, pleurisy	0.4
5	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	220	Heart Failure	ILD, pleurisy	0.12

CT: Computed tomography; ILD: Interstitial lung disease, MAS: Macrophage activation syndrome; MRI: Magnetic resonance imaging; PAH: Pulmonary arterial hypertension; TCZ: Tocilizumab; US: Ultrasound.

It is known that the lungs are the main source of physiological production of IL-1β and IL-6. These proinflammatory cytokines, as well as the levels of the endogenous antagonist of IL-1 receptors, are higher in children under the age of 4 years, which may explain the higher frequency of ILD in younger children[25-28].

IL-1β, IL-6, and IFN-γ are the main cytokines involved in the pathogenesis of sJIA and MAS[1]. The same cytokines play a key role in lung tissue damage, in particular, due to activation and/or dysfunction of macrophages in the pulmonary interstitium[20-22]. Hyperinfection and increased regulation of innate immunity lead to an increase in the production of IL-1β, which stimulates the levels of granulocyte-macrophage colony-stimulating factor, as well as hyperproduction of surfactant and its accumulation in tissues and impaired clearance. Elevated levels of IL-6 inhibit the production of type II bone morphogenetic protein receptors, which control cell growth and differentiation. IL-18, associated with the IFN-γ signaling pathway, is also associated with severe forms of MAS and ILD in patients with sJIA. The level of this cytokine remains elevated, despite the control of systemic inflammation by IL-1 or IL-6 blockade. This may explain lung damage in patients with sJIA who are in remission with IL-1 and IL-6 blockade[6,23,24]. Chronic lung inflammation with accumulation of surfactant and lipoproteins in the alveoli leads to interstitial pulmonary fibrosis, decreased elasticity of the pulmonary artery with the formation of pulmonary hypertension[1]. A brief pathogenesis of lung damage in sJIA is shown in Figure 3.

PAH

The pathogenesis of PAH is a result of systemic inflammation with proinflammatory cytokine disbalance. It's known, that the low expression of *BMPR2* (bone morphogenic protein receptor type II) associated with potential endothelial dysfunction and PAH, in turn, one of the central cytokines in the pathogenesis of systemic arthritis (IL-6) *in vitro* BMPR reduced its activity[29-31].

Radiological findings of the interstitial lung involvement

In clinical practice, radiological methods are often used to diagnose lung lesions. sJIA-LD is characterized by compaction/infiltration of lung tissue, thickening of the interlobular septa, and damage to the peripheral parts of several

Table 4 Main treatment outcomes of the patients with systemic juvenile arthritis and interstitial lung disease

No.	First biologic	Biologic at the ILD onset	Final therapy	Respiratory symptoms at the last follow-up visit	Dose reduction of non-biologic DMARDs	Dose reduction of BA	Discontinuation of GCS therapy	The outcome of sJIA-LD	The outcome of sJIA
1	TCZ	TCZ	CAN + ABT + CsA + GCS + SDF	No	No	No	No	Progression	Improvement
2	TCM	CAN	CAN + MMF + inhGS	No	Yes	No	Yes	Progression with the following improvement	Remission
3	CAN	CAN	TCZ + CsA	No	No	No	Yes	Improvement	Remission
4	TCZ	TCZ	CAN + MMF	No	No	No	Yes	Improvement	Improvement
5	TCZ	TCZ	CAN + GCS + IVIG	-	-	-	No	Death	Death

ABT: Abatacept; CAN: Canakinumab; CsA: Cyclosporine A; DMARD: Disease-modifying anti-rheumatic drug; GCS: Glucocorticosteroids; inhGCS: Inhaled glucocorticosteroids; IVIG: Intravenous immunoglobulin; ILD: Interstitial lung disease; SDF: Sildenafil; sJIA: Systemic juvenile idiopathic arthritis; TCZ: Tocilizumab.

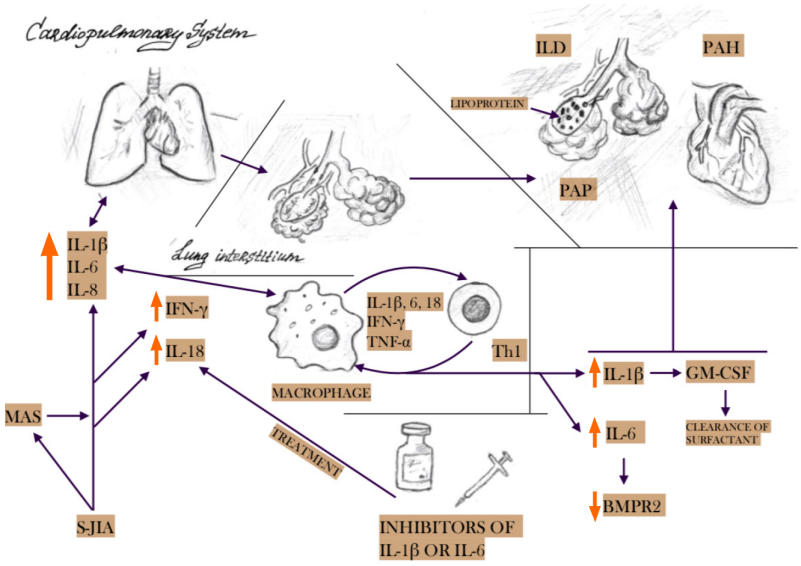

Figure 3 Brief summary of the pathogenesis of lung involvement in systemic juvenile arthritis. BMPR2: Bone morphogenetic protein receptor type II; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN: Interferon; IL: Interleukin; ILD: Interstitial lung disease; MAS: Macrophage activation syndrome; PAH: Pulmonary arterial hypertension; PAP: Pulmonary alveolar proteinosis; sJIA: Systemic juvenile idiopathic arthritis; TNF: Tumor necrosis factor.

lobes, mainly basal, para mediastinal, or anterior parts of the upper lobes in combination with the symptom of frosted glass, as well as the detection of enlarged lymph nodes with an increased density in CT of the chest with contrast[1,3].

Outcomes of the patients with sJIA-LD

The most alarming problem of sJIA-LD is the high mortality and a short life expectancy because of the development of lung damage. According to available data, 68% (n = 17) of patients died after 8.8 ± 11.4 mo from the onset of lung damage [4]. Unfortunately, mortality was about 40 times higher in the group of people with sJIA-LD[3]. In males, hypoxia at the beginning of lung damage, and neutrophilia in bronchial lavage (> 10 times higher) were considered the main predictors of death[3,31].

Management of the patients with LD-sJIA

In managing children with ILD, a multidisciplinary approach is required with the participation of specialists in various fields, including a rheumatologist, pulmonologist, infectious disease specialist, rehabilitation specialist, psychologist, transplant surgery, as well as comprehensive laboratory and instrumental support, including, in particular, spirometry,

pulse-oximetry, assessment of diffusion ability lung, computed tomography of the chest, echocardiography with assessment of pressure in the pulmonary artery, electrocardiography, assessment of sJIA and MAS laboratory activity. Sometimes, with chronic progressive hypoxemia, lung transplantation is the only method that can prolong the patient's life. Knowledge of the pathogenesis of this condition is important for the formation of potential prediction markers, targeted therapy, and prognosis. The following studies are needed to find the predictors, pathogenesis, and treatment options, for preventing and treating the ILD in sJIA patients.

Limits of the study

The main limitations of this study are related to the retrospective analysis and the very small sample size. The authors could not influence the treatment and could not if the treatment chosen in the past could influence the development of the complication and its severity or not. The absence of molecular studies decreased the value of this study.

CONCLUSION

ILD is a severe life-threatening complication of sJIA that may affect children of different ages with different time intervals since the disease onset. Extensive rash, serositis (especially pleuritis), full-blown MAS with transaminitis, lymphopenia, trisomy 21, eosinophilia, and biologic infusion reaction are the main predictors of ILD.

ARTICLE HIGHLIGHTS

Research background

Chronic lung involvement is an ultra-rare, unrecognized, poorly understood condition in children with systemic juvenile idiopathic arthritis.

Research motivation

To describe this ultra-rare complication and disease course in children with systemic juvenile idiopathic arthritis with interstitial lung involvement.

Research objectives

The clinical and laboratory data of these patients are not well-diagnosed. The number of patients is nearly a hundred.

Research methods

The clinical, radiological, and laboratory features were described in detail. The H score was applied to these patients for the first time.

Research results

The main clinical features of the disease are associated with early onset, chronic course of macrophage activation syndrome, pleuritis at onset, protracted lymphopenia, eosinophilia, and anaphylaxis drug-reaction on biologics.

Research conclusions

This life-threatening complication is associated with chronic, persistent macrophage activation syndrome, drug-associated anaphylaxis similar to DRESS syndrome.

Research perspectives

The future collection of information on these patients requires the following study of the features of the macrophage activation syndrome (cytokine profile, interferon signatures), and new target drugs are needed.

FOOTNOTES

Author contributions: Kostik MM and Belozerov KE contributed to the conceptualization, writing, review, editing and original draft preparation; Kostik MM and Kuznetsova AA contributed to the methodology; Belozerov KE contributed to the software and formal analysis; Solomatina NM and Isupova EA contributed to the validation and resources; Belozerov KE, Solomatina NM, and Isupova EA contributed to the investigation; Kuznetsova AA contributed to data curation; Kostik MM contributed to funding, supervision and project administration; All authors read and approve the final manuscript, were involved in drafting the article or revising it critically for important intellectual content.

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Informed consent statement: Written consent was obtained according to the Declaration of Helsinki. All patients or patient representatives (for patients under the age of 15 years) gave their consent in their case report forms authorizing the anonymous use of their medical information. All patients were appropriately anonymized.

Conflict-of-interest statement: All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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