—Case Reports—

Clinical Course and Cytokine Profile of Systemic Juvenile Idiopathic Arthritis in a Patient with Trisomy 21

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Trisomy 21 (Down syndrome) is sometimes complicated by congenital heart disease; however, comorbid type I diabetes mellitus and diseases involving autoantibodies, such as Hashimoto disease and Graves disease, are not uncommon. Autoinflammatory diseases such as Kawasaki disease and systemic juvenile idiopathic arthritis are rare. We report a rare case of trisomy 21 with systemic juvenile idiopathic arthritis that responded well to the initial course of methylprednisolone pulse therapy but flared up and was complicated by macrophage activation syndrome (MAS). Subsequent methylprednisolone pulse therapy and cyclosporine resolved this condition. Cytokines were analyzed at several time points during the clinical course and revealed that interleukin-18, interleukin-6, and chemokine ligand 9 levels were elevated at MAS onset in the present patient, even though clinical symptoms had abated. Thus, early analysis of cytokine profiles should be performed to assess MAS risk and determine treatment intensity, even in T21 patients. (J Nippon Med Sch 2023; 90: 419–424)

Key words: cytokine, interleukin-18, macrophage activation syndrome, systemic juvenile idiopathic arthritis, trisomy 21

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is caused by abnormal activation of T lymphocytes and macrophages and overproduction of inflammatory cytokines such as interleukin (IL)-6, IL-1β, and IL-18[1,2]. Several recent reports have emphasized the importance of cytokine profiling for the diagnosis and follow-up of patients with sJIA, which is difficult to diagnose without arthritis[3-6]. However, to our knowledge, no study has evaluated cytokine profiles of patients with sJIA and trisomy 21 (T21).

Some acquired immune disorders involving autoantibodies, such as type 1 diabetes, Hashimoto disease, and Graves disease, are associated with T21[7,8]. However, autoinflammatory diseases comorbid with T21, such as Kawasaki disease[9], are extremely rare and usually idiopathic.

In most cases, comorbid arthritis in patients with T21 is Down syndrome—associated arthritis (DA)[10,11], which has characteristics similar to polyarticular juvenile idiopathic arthritis (pJIA)—an acquired immune system disorder. In contrast, there are no detailed reports on conditions similar to sJIA. Currently, there is no standard treatment protocol for DA, and patients are managed in accordance with the guidelines for management of pJIA[11]. Methotrexate (MTX) is less tolerable, more toxic, and less effective in T21 patients. The efficacy and incidence of adverse effects of other immunomodulators and biologics are often unknown, and several studies have reported difficulties in using them to manage affected patients[12,13].

Here, we report a case of macrophage activation syndrome (MAS)-complicated sJIA, diagnosed by cytokine profiling, in a T21 patient presenting with fever of un-

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Table 1 Laboratory data on admission

WBC	6.3 10^9/L	T-Cho	140 mg/dL	amiroid A	1,125.1 μg/mL
Neut	5.54 10^9/L	LDL-C	88 mg/dL	ferritin	1,521.9 ng/mL
RBC	3.98 10^{12}/L	TG	90 mg/dL	pβ2-MG	3.2 mg/L
Hb	113 g/L	Na	139 mEq/L	MMP-3	63.7 ng/mL
Hct	33.7 %	K	4.2 mEq/L	KL-6	334.5 U/mL
Plt	262 10^9/L	Cl	100 mEq/L		
AST	33 IU/L	CRP	6.14 mg/dL	PT/INR	1.2
ALT	18 IU/L			APTT	27.5 sec
LDH	461 IU/L	IgG	1,162 mg/dL	Fib	487 mg/dL
CK	22 IU/L	ASO	7 IU/mL	D-dimer	3.4 μg/mL
T-Bil	0.33 mg/dL	RF	<3 IU/mL		
AMY	47 mg/dL	C3	124 mg/dL		
TP	6.4 g/dL	C4	34 mg/dL		
Alb	3 g/dL	CH50	52 U/mL		
UA	3.8 mg/dL				
BUN	9.9 mg/dL	ANA	160 × (SPECKLED)		
Cre	0.31 mg/dL	ACPA	1.1 U/mL		

ANA: antinuclear antibodies; ACPA: anti-citrullinated protein antibody; pβ2-MG: plasma beta2-microglobulin; MMP-3: matrix metalloproteinase-3; KL-6: sialylated carbohydrate antigen KL-6

known origin.

Case Report

A 4-year-old boy with a 3-week history of fever, gait disturbance, and a gradual decrease in activity was admitted to hospital. He had a history of T21 with an endocardial-repaired complete atrioventricular septal defect (4 years previously). On admission, his body temperature was 38.8°C and he had multiple pale, erythematous patches of varying size (1-2 cm) on his right lower leg. Blood tests revealed an elevated erythrocyte sedimentation rate and high levels of serum amyloid A and ferritin, which are indicative of an elevated inflammatory response. Serum levels of antinuclear antibodies were elevated 160-fold (**Table 1**). Intravenous fluids and cefotaxime were administered initially. On the second day of admission, bone marrow aspiration to rule out hematologic disease revealed no monoclonal cell growth or hemophagocytosis. Blood tests performed on the fifth day of admission revealed no improvement in the inflammatory response. Gallium scintigraphy performed on the same day revealed abnormal accumulations in the sacroiliac and knee joints. Methylprednisolone (mPSL) pulse therapy was considered because of the final diagnosis of sJIA and a high ferritin level of 1,521.9 ng/mL. However, mPSL half-dose pulse therapy (15 mg/kg/day) was administered to prevent adverse effects in our patient because of the low severity of clinical symptoms, his history of cardiac surgery, and the fact that T21 patients are at risk for glaucoma and metabolic abnormalities.

After one course of mPSL pulse therapy, he responded extremely well: his laboratory test results and gait disturbance improved. A few days later, we learned that serum IL-18 had been markedly elevated (117,311 pg/mL) on the day of admission. However, mPSL pulse therapy was terminated after one course, as laboratory test results and clinical symptoms had markedly improved. Unfortunately, 2 weeks later, serum levels of C-reactive protein (CRP), ferritin, and hepatic transaminases were again elevated. In addition, fever and gait disturbance returned. Because the patient met the criteria for MAS, mPSL pulse therapy and continuous intravenous cyclosporine (CyA) were initiated. After two courses of mPSL pulse therapy, his condition improved; therefore, the route of CyA administration was changed from intravenous to oral administration and prednisolone was tapered off. He was discharged on day 43 of hospitalization with a negative CRP and normal levels of liver devitalization enzymes and ferritin. After discharge, canakinumab was administered every 4 weeks to avoid prolonged administration of high-dose prednisolone. The dose of oral prednisolone was reduced by 10% every 2 weeks until a dose of 0.5 mg/kg/day was reached and the patient's remission was maintained.

In a previous study, serum IL-18, IL-6, CXC chemokine ligand 9 (CXCL9), and sTNF-RII levels in the present patient; in patients with sJIA with MAS, sJIA without MAS, and KD; and in healthy controls were measured by

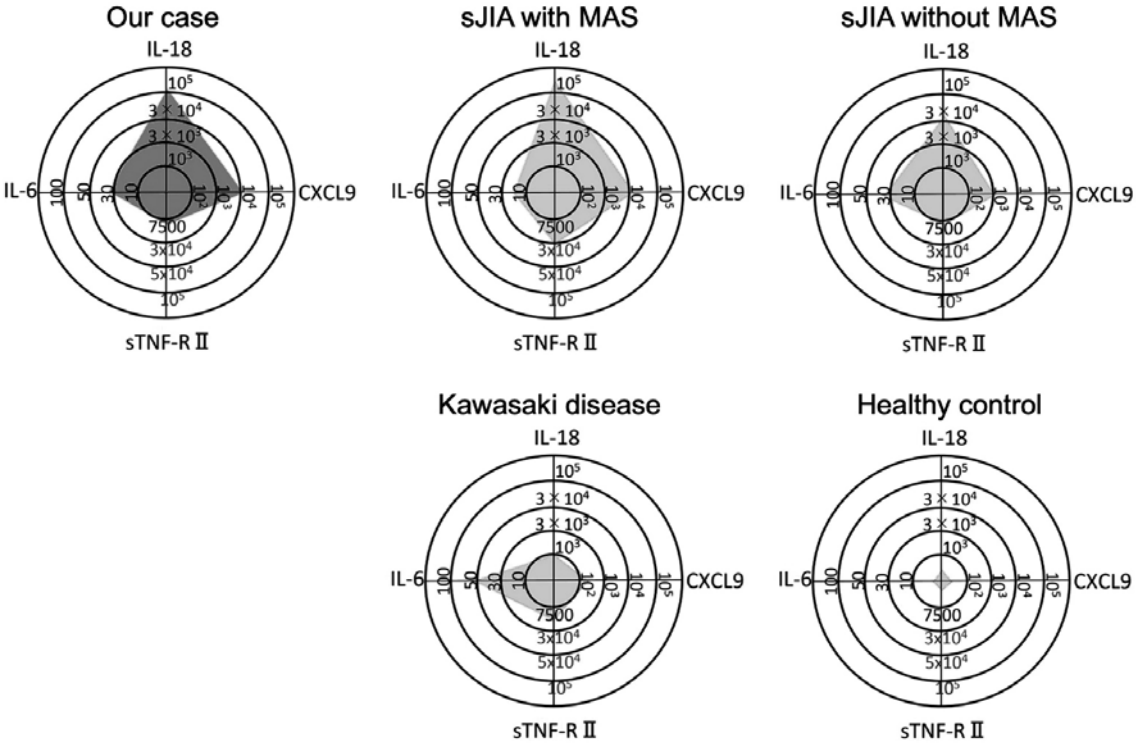


Fig. 1 Radar charts show serum cytokine profiles for IL-6, IL-18, CXCL9, and sTNF-RII in the present patient and other patient groups. Our patient was evaluated at disease onset. Regarding the phase and numbers for each disease group, sJIA with MAS (n=16), sJIA without MAS (n=30, acute phase), Kawasaki disease (n=30, acute phase), healthy control (n=15). The mean age of the healthy control group was 48.1 months (range: 1–480 months).

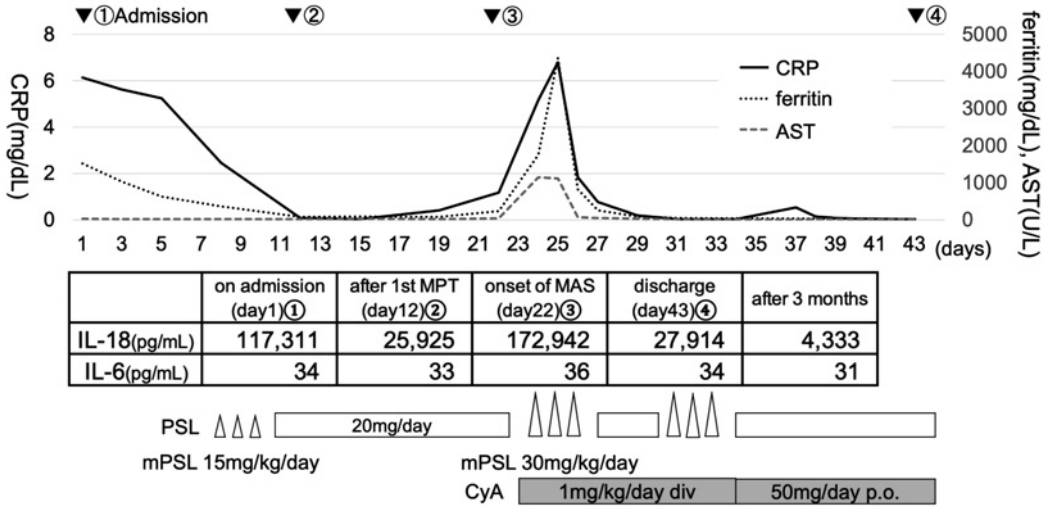
enzyme-linked immunosorbent assay[14,15] (**Fig. 1**). The cytokine profile of the present patient was similar to that of sJIA patients who developed MAS. After initial mPSL pulse therapy, laboratory values such as CRP level improved but inflammatory cytokines such as IL-6 and IL-18 did not. These findings suggest a risk of MAS recurrence or progression[14,16]. The serum IL-18 value was re-elevated at 22 days after admission and was higher than at admission. In T21 patients, cytokine profiles have proven useful in assessing disease activity and risk of sJIA recurrence. Furthermore, at 3 months after discharge, IL-18 remained elevated, at 4,333 pg/mL. This confirms that IL-18 levels persist in T21 patients with inactive sJIA , as well as in sJIA without T21[17] (**Fig. 2**). At this writing, our patient remains in clinical remission, with no need for further treatment, and has remained relapse-free.

This article does not contain any studies with human or animal subjects performed by any of the authors. Because the patient is a child, written informed consent was obtained from the parents of this patient for the publication of this case report.

Discussion

Previous reports suggest that persons with T21 have impaired immunity against infection, including neutrophil chemotaxis and impaired natural killer and dendritic cell functions[18]. Acquired immunity is also affected, as indicated by decreased total lymphocyte counts. However, T-cell function improves with growth, in contrast to B-cell function, which remains low[19]. Decreased thymus size is another common finding. These findings suggest that defects in innate and acquired immunity increase the risk of infection[20]. Moreover, autoimmune diseases that involve autoantibodies, such as type 1 diabetes, Hashimoto disease, and Graves disease, are often seen in T21 patients[7,8], whereas autoinflammatory diseases such as Kawasaki disease[9] and sJIA are extremely rare, and their causes are unknown. Our patient had sJIA complicated with MAS.

T21 patients have immune abnormalities and developmental disabilities of varying severity, which can make it difficult for them to accurately describe their symptoms. In addition, to our knowledge, reports on DA are rare in Japan, probably because JIA is rarely considered a cause of gait disturbance in T21 patients. Therefore, although



	on admission (day1)①	after 1st MPT (day12)②	onset of MAS (day22)③	discharge (day43)④	after 3 months
IL-18(pg/mL)	117,311	25,925	172,942	27,914	4,333
IL-6(pg/mL)	34	33	36	34	31

Fig. 2 Clinical course.
CRP (solid line), ferritin (dashed line), and AST (long dashed line) over time. Levels of IL-18 and IL-6 at the indicated time points.
PSL: prednisolone; mPSL: methylprednisolone; CyA: cyclosporine A; div: drip infusion into vein; p.o.: per os

our patient was hospitalized for gait disturbance, it was difficult to determine whether the condition was due to arthralgia or fatigue. Gallium scintigraphy and a cytokine assay ultimately identified sJIA as the cause of fever and gait disturbance. The patient responded well to mPSL pulse therapy, and the disease was easily controlled after a single course. Glucocorticoids (prednisolone 1 mg/kg/day) were then continued. His vital signs and general blood laboratory data improved; thus, we thought the patient would continue to improve. However, he subsequently relapsed and met the diagnostic criteria for MAS[21]. Two more courses of mPSL pulse therapy and continuous intravenous CyA led to remission. Subsequent cytokine analysis revealed a marked increase in IL-18 levels and elevated levels of IL-6, CXCL9, and sTNF-RII. Elevated levels of these cytokines are associated with a high risk of MAS. Early cytokine profiling will likely predict MAS development, and early intensification of therapy may prevent development of severe MAS. In our patient, IL-18 and sTNF-RII levels improved, but IL-6 and CXCL9 levels remained high, so we introduced biological agents to control the disease while monitoring the patient for possible relapse.

Recent reports suggest that T21 is a risk factor for new lung parenchymal disease during sJIA treatment[22]. Type 1 interferonopathy and high susceptibility to drug side effects and viral pneumonia are thought to be associated with new parenchymal lung disease in T21 patients. Therefore, patients should be evaluated for pulmonary involvement at the onset of respiratory symptoms during follow-up or when a flare-up of the underlying disease is suspected.

As with DA, management of sJIA in patients with underlying T21 should be performed while considering the limited efficacy of biologics and the inability to receive adequate doses of therapy because of drug-related side effects, as these factors make disease control more challenging[11].

Conclusion

We reported the first cytokine profile of a T21 patient with sJIA who developed MAS. Although subjective findings were difficult to assess because of his developmental disability, he responded to mPSL pulse therapy and his clinical symptoms improved. However, he developed MAS before complete remission. We were able to determine MAS risk by retrospective evaluating the cytokine profile of our patient. In the future, cytokine evaluations, including risk assessments for MAS, should be performed as early as possible in the diagnosis of sJIA and other autoinflammatory diseases, especially in T21 patients with fever of unknown origin and symptoms that are difficult to assess.

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