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症　　例

A Japanese Case of Severe Refractory Adult Still's Disease: Serum Interleukin-18 is a Possible Marker of the Response to Low-Dose Cyclosporin A Therapy

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Abstract A 22-year-old man was admitted to our hospital with a high fever, fatigue, mild arthritis, and bilateral pleural effusions. Laboratory tests revealed a high ESR, leukocytosis, high serum C-reactive protein level, and high serum ferritin level. Various antibiotics had been given by a local hospital with no response. He was diagnosed as having severe refractory adult Still's disease and was subsequently treated with high-dose steroid therapy and low-dose cyclosporin A. The serum interleukin-18 level was monitored throughout treatment and was found to be a potentially useful marker of disease activity as well as of the response to cyclosporin A therapy.

Key words: Adult Still's disease, Cyclosporin A, Interleukin-18

Introduction

Adult Still's disease (ASD) is a rare condition of unknown origin, characterized by a high spiking fever, transient maculopapular rash, arthralgia or arthritis, lymphadenopathy, hepatosplenomegaly, sore throat, and serositis. Cyclosporin A (CyA), a well-known immunosuppressive agent, alone or in combination with other medications can induce remission of the arthritis without severe side effects, or can at least decrease the steroid requirement of these patients[9]. ASD may be acute and self-limiting, or may follow a relapsing or chronic course. Interleukin (IL)-18, originally termed IFN-γ-inducing factor, is a newly identified cytokine of 18kDa[6]. Although there is no apparent similarity of the protein sequence according to nucleotide databases, a structural reletionship between IL-18 and the IL-1 family has been described[1]. Recently, systemic overproduction of IL-18 was suggested to be involved in the pathogenesis of ASD[3]. Here we report on the treatment of an adult patient with severe refractory ASD in whom the serum IL-18 level was monitored. The relationship between IL-18 and disease activity is also discussed.

Case report

A 22-year-old man was admitted to a local hospital on July 21, 2000 with a high

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spiking fever over 39°C, a sore throat, and tonsillitis. Laboratory tests revealed slightly elevated serum aminotransferases, a white blood cell (WBC) count of 23,000/mm^3 (83% neutrophils), and an erythrocyte sedimentation rate (ESR) of 35mm/h.

Because there was no response to numerous antibiotics (cefazolin, cefotiam, piperacillin, panipenem/betamipron, isepamicin, imipenem/ cilastatin, clindamycin, and fluconazole), he was referred to our hospital on August 1, 2000. He had a high fever, fatigue, mild arthritis, and bilateral pleural effusions. Laboratory tests revealed an elevated ESR (66/107mm/h), leukocytosis (WBC count 35,590/mm^3; 89% neutrophils), a hemoglobin of 12.7g/dl, a platelet count of 355 x10^3/mm^3, a high serum C-reactive protein (CRP) level (33.0mg/dl), a high serum ferritin level (19,777.00ng/ml; normal limit in males 35-370ng/ml), negative blood cultures, negative serology for human immunodeficiency virus (HIV), and negative Q fever serology. Antinuclear antibody and rheumatoid factor were also negative (Table. 1). The serum levels of soluble interleukin (IL)-2 receptor, IL-6, IL-18, and tumor necrosis factor (TNF)-α were 253 U/ml, 868pg/ml, 74,800pg/ml, and 60.3pg/ml, respectively. He fulfilled the criteria for adult Still's disease proposed by Yamaguchi et al.[10]. On August 7, 2000, he was treated with methylprednisolone pulse therapy (14.3mg/kg/day for 3 days) and he was also given prednisolone (0.86mg/kg/day). Before therapy, the serum levels of CRP, ferritin, soluble IL-2 receptor, IL-6, IL-18, and TNF-α were 12.4mg/dl, 4,488.4ng/ml, 2,450U/ml, 334pg/ml, 106,000pg/ml, and 8.98pg/ml, respectively. He responded modestly to treatment, but his disease flared again with fever and a leukocyte count of 27,810/mm^3. On August 16, 2000, he was again treated with methylprednisolone pulse therapy (11.4mg/kg/day for 3 days), after which the prednisolone dose was increased from 0.86 to 1.00mg/kg/day. This led to resolution of his symptoms. However, the response was incomplete, so he was also treated with cyclophosphamide (14.3mg/kg) for 1 day on August 22, 2000.

On August 28, 2000, in addition to prednisolone, CyA was started at 1.4mg/ kg/day to achieve a better clinical response. The daily dose of CyA was then increased to 3.2mg/kg. Two months after starting CyA therapy, there was dramatic improvement of his fever. He was discharged on October 31,2000 and followed at our outpatient department.

Eight months after starting CyA treatment, prednisolone (0.21mg/kg/day) was given in addition to CyA. The mean serum CyA level was 187.4μg/l (target range: 150-225). The white blood cell count decreased from 27,200 to 10,600 /mm^3 (normal 4,000-10,000/mm^3), the platelet count decreased from 915 to 350 x103 /mm^3 (normal 150-350 x103/mm^3), and the hemoglobin increased from 85 to 112g/l (normal 118-154). Serum levels of CRP, ferritin, soluble IL-2 receptor, IL-6, IL-18 and TNF-α were 3.2mg/dl, 105.3ng/ml, 192U/ml, 1.42pg/ml, 894pg/ml, and 42.4pg/ml, respectively.

On May 23, 2001, he was readmitted with fever, chills, and arthritis of the knees. Laboratory tests revealed a high ESR (62/102mm/h), leukocytosis (WBC count 23,330/mm^3; 93% neutrophils), a CRP of 9.97mg/dl, a ferritin level of 401ng/ml, a soluble IL-2 receptor level of 580U/ml, an IL-6 level of 107pg/ml, an IL-18 level of 5,230pg/ml, and a TNF-α level of 16.8ng/ml. The mean serum CyA level was 106.1μg/l. In June 2001, his symptoms were uncontrolled, with recurrent fever and arthritis of the

Table. 1 Laboratory data on admission

Urine		
Occult blood	(−)	
Protein	(+)	
Feces		
Occult blood	(−)	
ESR		
	66/107	mm/hr
Peripheral blood		
WBC	35590/mm³	
Neu	90.7%	
Lym	3.4%	
Mon	3.0%	
Eos	0%	
Baso	0%	
RBC	458x104	/mm³
Hb	12.7	g/dl
Plt	355x10³	/mm³
Blood chemistry		
TP	6.5	g/dl
	Alb 41.3	%
	α1 7.5	%
	α2 17.6	%
	β 11.2	%
	γ 22.4	%
Alb	3.2	g/dl
BUN	16	mg/dl
Cr	0.6	mg/dl
T-bil	0.4	mg/dl
D-bil	0.1	mg/dl
TTT	2.0	KU
ZTT	4.7	KU
AST	97	U/l
ALT	55	U/l
LDH	1180	U/l
ALP	348	U/l
γGTP	35	U/l
ChE	64	U/l
Na	139	mmol/l
K	4.2	mmol/l
Cl	97	mmol/l
Glu	102	mg/dl
TB	9.8	μmol/l
Ca	9.2	mg/dl
UA	0.8	mg/dl
TC	101	mg/dl
TG	111	mg/dl
Fe	19	μg/l
Ferritin	19777	ng/ml
CRP	28.3	mg/dl

Sero-immunology		
STS	(−)	
TPHA	(−)	
HBsAg	(−)	
anti-HCV	(−)	
ant-HTLV-1	(−)	
anti-HIV	(−)	
anti-Q fever-IgG	(−)	
anti-Q fever-IgM	(−)	
RF	20	
ANA-QL	(−)	
Anti-ds-DNA	(−)	mg/dl
C3	153	mg/dl
C4	27	
P-ANCA	(−)	
C-ANCA	(−)	pg/ml
Endotoxin	5.0	pg/ml
β-D-glucan	3.0	
Viral marker		
EBV-VCA-IgG	40	
EBV-VCA-IgM	10	
EBV-EBNA	10	
CMV-IgG	(−)	
CMV-IgM	(−)	
Tumor marker		
CEA	(−)	
CA19-9	(−)	
AFP	(−)	
PIVKAII	(−)	
Coagulation test		
PT	15.1	sec
APTT	31.8	sec
HPT	51	%
Lupus anticoagulant	(−)	
Culture		
Sputum	(−)	
Blood	(−)	
Urine	(−)	
Stool	(−)	
Bone marrow puncture		
NAP score	99	%
	436	
Bcr/abl	3.3	%
Pleural effusion		
TP	3.7	g/l
Glu	93	mg/dl
LDH	1914	U/l
CEA	0.5	ng/ml
ADA	21.7	IU/l
ABG(room air)		
pH	7.477	
pO_2	47.4	mmHg
pCO_2	37.6	mmHg
HCO_3	27.5	mmol/l
ABE	4.2	mmol/l

knees. The serum levels of CRP, ferritin, soluble IL-2 receptor, IL-6, IL-18, and TNF-α were 17.6 mg/dl, 1,297ng/ml, 725U/ml, 332pg/ml, 13,000pg/ml, and 13.1pg/ml, respectively. The mean CyA level was 71.5μg/l. Eventually, his therapy achieved good disease control, but all attempts to reduce the dose of prednisolone led to relapse. He was again treated with methylprednisone pulse therapy (14.3mg/kg/day for 3 days) and the prednisolone dose was increased from 0.21 to 1.00mg/kg/day, leading to the resolution of his symptoms. CyA was also increased from 3.2mg/kg/day to 3.9mg/kg/day. On July 24, 2001, his discharge medications consisted of CyA at 3.2mg/kg/day and prednisolone at 0.50mg/kg/day. His fever and arthritis had resolved.

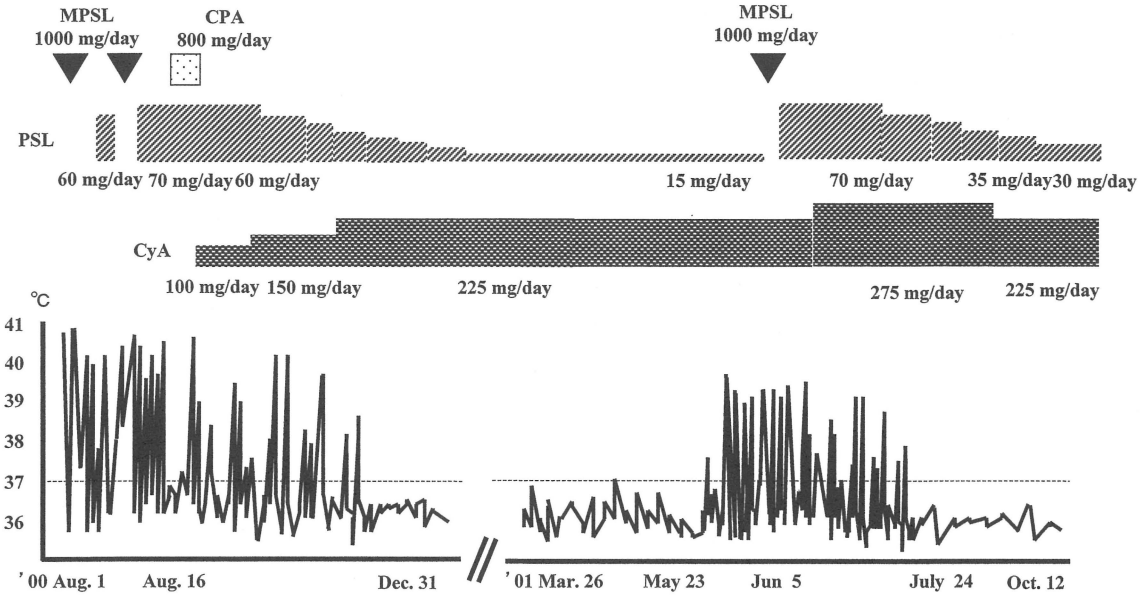
On October 12, 2001, the serum creatinine level before starting CyA was 0.6mg/dl (normal: 0.6-1.1). The serum levels of CRP, ferritin , soluble IL-2 receptor, IL-6, IL-18, and TNF-α were 0.41mg/dl, 69.9ng/ml, 185U/ml, 29.4pg/ml, 1,330pg/ml, and 35.9pg/ml, respectively. Hypertension has not been a problem during CyA therapy since his blood pressure has shown little change (from 120/70 to 120/74 mmHg). Fatigue is no longer a problem, and he has had no further rash or fever (Fig. 1).

Discussion

ASD is an inflammatory disorder characterized by high spiking fever, arthritis, and an evanescent rash. Marked elevation of the serum ferritin concentration is a characteristic feature and is seen in about 70% of ASD patients[7]. Elevation of ferritin is correlated with disease activity, and has been suggested as a marker for monitoring the response to treatment[8]. Serum ferritin concentrations exceeding 3,000ng/mL (normal: 40 to 200ng/mL) have been observed in patients with ASD, and some patients even have values above 10,000ng/mL[2]. Hyperferritinemia was also a characteristic feature in our patients, but the origin of the great increase of serum ferritin still remains unknown. Moreover, the serum ferritin level of our patient was normal when he was readmitted with a similar flare-up of ASD, making it difficult to diagnose recurrence at an early stage. For more accurate assessment of the activity of ASD, we monitored the serum levels of various cytokines (soluble IL-2 R, IL-6, IL-18, and TNF-α).

It has been reported that TNF-a, IL-1, and IL-6 can specifically induce the synthesis of ferritin by fibroblasts and other cells[5]. IL-18 has been reported to have an IL-1 like sequence in its structure[6], with a similarity to the IL-1 family and fibroblast growth factor in terms of their trefoil structure[1]. Recently, Kawashima et al.[3] reported that systemic overproduction of IL-18 may be closely linked to the pathogenesis of ASD. We found that the serum IL-18 level was not only significantly increased at the onset of ASD in our patient, but also at the early stage of its recurrence. The IL-18 level appeared to increase in parallel with the activity of ASD, so IL-18 may play a more important role than other cytokines in the pathogenesis of this disease. To our knowledge, there have been no other reports on daily changes of IL-8 during the treatment of an ASD patient with CyA. Further investigation over a longer observation period will be necessary to determine the precise relationship between IL-18 and the pathogenesis of ASD.

ASD is often acute and self-limiting, and can respond well to nonsteroidal anti-inflammatory drugs (NSAID) and/or steroid therapy, but it can show a chronic or relaps-



	'00 Aug. 1	Aug. 16	Dec. 31	'01 Mar. 26	May 23	Jun 5	July 24	Oct. 12
WBC (/mm3)	35,590	27,810	8,570	9,520	23,330	23,420	8,410	12,460
CRP (mg/dl)	33.0	12.4	0.2	3.2	9.97	17.6	0.14	0.41
Ferrtin (ng/ml)	19,777.0	4,488.6	183.3	105.3	401.1	1297.4	155.1	69.9
sIL-2R (U/ml)	253	2,450		192	580	725	255	185
IL-6 (pg/ml)	868	334		1.42	107	332	10.7	29.4
IL-18 (pg/ml)	74,800	106,000		894	5,130	13,000	1790	1330
TNF-α(pg/ml)	60.3	8.98		42.4	16.8	13.1	328	35.9
Serum CyA(μ g/L)			187.4	81.4	106.1	71.5	149.7	132.2

Fig. 1 Clinical course
PSL ; prednisolone
MPSL ; methylprednisolone
CyA ; cyclosporin A
CpA ; cyclophosphamide
sIL-2R ; soluble interleukin-2 receptor
IL-6 ; interleukin-6
IL-18 ; interleukin-18
TNF-α ; tumor necrosis factor-α

ing course that is not completely controlled by standard therapy. In fact, up to 50% of ASD patients continue to need treatment for several years after diagnosis[4]. CyA is usually given as a second-line agent after treatment with corticosteroids and NSAIDs fails or when the setroid dose is too high[10]. Our patient had severe refractory ASD, and was therefore treated with low-dose CyA (less than 5mg/kg/day), which proved to be very effective in controlling disease activity as well as reducing the dose of steroids. After starting CyA, reduction of the prednisolone dose to 0.21mg/kg/day was possible along with improvement of all his symptoms. When recurrence of ASD occurred with fever and arthritis of the knees, his mean CyA level was very low (71.5μg/l). Although CyA treatment achieved good disease control, any attempt to reduce the dose of prednisolone led to relapse. Our case suggests that prednisolone should be tapered gradually while monitoring the serum CyA concentration (target range: 150-200 ± 25ng/ml). The use of CyA to treat ASD has already been described in 8 patients[4][10]. In these patients, CyA was particularly effective and allowed substan-

tial reduction of the steroid dose. Our case confirmed the effectiveness of CyA for ASD.

In conclusion, the serum IL-18 level may be a useful marker of both disease activity and the response of ASD to CyA therapy. Moreover, use of CyA alone or in combination with other medications may achieve remission of arthritis in ASD without severe side effects, or may at least decrease the steroid requirement. At a low dose, CyA therapy seems to be safe and well-tolerated.

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(和文抄録)

難治性成人型スティル病の一例 血清インターロイキン18は少量cyclosporine A療法の治療効果の判定に有用

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柏木征三郎[2]・林　純[1]

22歳の男性が，当院入院の約1ケ月前より高熱及び咽頭痛を主訴に近医入院し，あらゆる抗菌剤が投与されるも改善傾向なく，高熱，倦怠感，関節痛，両側胸水，血沈亢進，血清CRP高値および血清フェチリン高値を認め，精神加療目的で当院紹介となった，入院後，成人型スティル病と診断された，ステロイド抵抗性で再発を繰り返す難治性成人型スティル病であったので，血清インターロイキン18をモニタリングしながら大量ステロイド療法および少量cyclosporine A療法による治療が施行された，血清インターロイキン18は成人型スティル病の病勢およびcyclosporine Aによる治療効果判定の指標となる可能性が示唆された．