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CASE REPORT

Successful treatment with plasma exchange in adult-onset Still's disease with hyper-IL-18-naemia and hyperallergic state

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Abstract Adult-onset Still's disease (AOSD) is a rheumatoid disorder characterized by high fever, polyarthritis, leukocytosis, hyperferritinaemia, and mild liver involvement. We describe the case of a patient with AOSD with severe liver dysfunction. His serum levels of interleukin-10 and 18 showed a similar trend to his disease activity. Drug lymphocyte stimulation tests were positive for three drugs in the patient. Hypercytokinaemia was controlled by plasma exchange therapy.

Keywords Adult-onset Still's disease · Drug lymphocyte stimulation test · Hepatitis · Interleukin-10

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease characterized by spiking fever, a typical rush, lymphadenopathy, polyarthralgia, leucocytosis and hyperferritinaemia. Liver involvement is found in most patients. However, severe hepatitis with the threat of liver failure is rare [1, 2]. We describe a patient with AOSD associated with severe hepatitis, markedly elevated serum ferritin levels, hypercytokinaemia, and for whom drug lymphocyte stimulation tests for many drugs were positive. Some of these abnormalities improved dramatically after plasma exchange therapy.

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Case report

A 33-year-old man was referred to our hospital in November 2006 to investigate a five-week history of intermittent fever (>39.0 °C), cervical lymphadenopathy, sore throat and polymyalgia. His blood, urine and sputum were examined in duplicate. However, there was no evidence of infection, including from a variety of common viruses and intracellular bacteria. He had been treated on an empirical basis with several antibiotics at a nearby hospital. Even these treatments had failed to reduce his body temperature.

On admission to our hospital, his height was 168 cm, weight 86.0 kg, temperature 40.0 °C. Salmon-pink eruptions that disappeared when his temperature was normalized were present on his anterior chest and extremities. The liver edge was palpable for 3 cm at the midclavicular line. The spleen was not palpable.

White blood cell count was 13,240/mm^3, with 86.5% neutrophils, hemoglobin (Hb) 14.4 g/dl, platelet count (Plt) 114 × 10^9/L. His serum aspartate aminotransferase (AST) level was 91 IU/L, his alanine aminotransferase (ALT) level was 107 IU/L, his γ-glutamyl transpeptidase level was 240 IU/L, his lactate dehydrogenase (LDH) level was 817 IU/L (reference value <230 IU/L), his serum ferritin level was 32,246 ng/mL (reference value < 321 ng/mL), and his C-reactive protein (CRP) level was 13.74 mg/dL (see Table 1). Rheumatoid factor and antinuclear antibody were negative. Initial chest radiograph and cardiac ultrasonography were normal. Abdominal CT showed moderate hepatosplenomegaly.

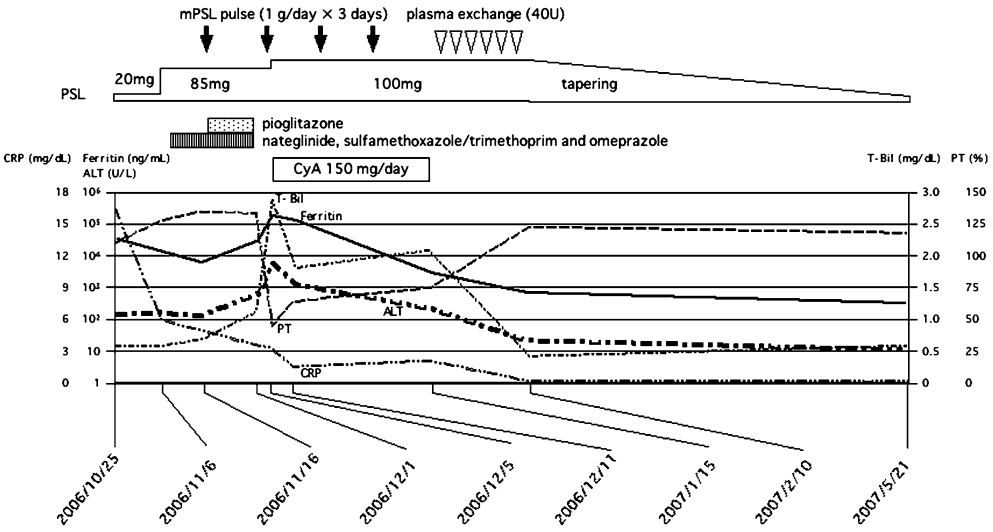
He was diagnosed with AOSD based on spiking fever, typical cutaneous rash, leucocytosis, sore throat, splenomegaly, liver involvement and hyperferritinaemia in the absence of antinuclear antibody and rheumatoid factor [3].

Table 1 Laboratory data

Parameter	Level
Complete blood cell count	
RBC	470 × 10^4/μl
Hb	14.4 g/dl
Ht	42.2%
WBC	13,240/μl
Neu	86.5%
Lymph	7.0%
Mono	4.5%
Eos	1.0%
Baso	0.5%
Plts	11.4 × 10^4/μl
Serology	
IgG	1,294 mg/dl
IgA	404 mg/dl
IgM	149 mg/dl
IgE	142 IU/ml
C3	98 mg/dl
C4	36 mg/dl
CH50	48 U/ml
Ferritin	32,246 ng/dl
sIL-2R	980 U/ml
APTT	26.8 s
PT	106%
PT-INR	0.99
Fbg	378 mg/dl
AT III	112%
Blood chemistry	
Na	143 mEq/l
K	3.6 mEq/l
Cl	101 mEq/l
Ca	9.6 mg/dl
BUN	12.4 mg/dl
Cr	0.70 mg/dl
TP	6.1 g/dl
Alb	2.9 g/dl
T-bil	0.6 mg/dl
LDH	817 U/l
AST	91 U/l
ALT	107 U/l
γ-GTP	240 U/l
ALP	348 U/l
Amy	40 U/l
CK	39 U/l
T-cho	158 mg/dl
TG	162 mg/dl
Glu	143 mg/dl
CRP	13.74 mg/dl
ESR	49 mm/h

Although initially treated with prednisolone (PSL) at a dose of 85 mg (1 mg/kg per day), his CRP level and fever did not improve. Methylprednisolone pulse therapy (1,000 mg × 3 days) was added, which improved the fever and serum CRP level, Fig. 1.

However, on the 26th day of hospitalization, he showed progressive liver dysfunction (AST 291 U/L and ALT 550 U/L) and thrombocytopenia (Plt 58 × 10^9/L, Hb 13.4 g/dl). Antimitochondrial antibody and antinuclear antibody were negative. Abdominal MRI showed moderate hepatosplenomegaly (Fig. 2). Hemophagocytic syndrome was distinguished as a cause of his condition, aggravated by hyperferritinaemia and thrombopenia. However, there was no finding of phagocytosis by bone marrow aspiration. Because steroid diabetes had manifested itself, he was given pioglitazone hydrochloride and nateglinide. He was also given sulfamethoxazole/trimethoprim and omeprazole via prophylactic administration for the bacterial infection and gastric ulcer, respectively. Due to suspicions that these drugs caused his liver dysfunction as an adverse effect, they were stopped and he was examined by drug lymphocyte stimulation test (DLST). Among four drugs tested for, three DLST was positive for three: pioglitazone hydrochloride 436 cpm (control 155 cpm; 281%), nateglinide 362 cpm (233%), sulfamethoxazole/trimethoprim 336 cpm (216%). Despite stopping these drugs, hepatitis developed, with jaundice becoming evident. Routine chemistry showed severe hepatitis (AST 2,869 U/L, ALT 4,910 U/L); total bilirubin was 2.8 mg/dL; LDH was 7,616 U/L; PT was 48.0%. The serum ferritin level was extremely high (160,000 ng/mL). Recent publications emphasize the role of hyperferritinaemia as a marker of AOSD activity [4]. In addition, the serum ferritin levels in AOSD patients are generally higher than those observed during liver cytolysis [5]. We consider that the severe hepatitis with the threat of liver failure in this patient may have been an exacerbation of AOSD. He was treated with methylprednisolone pulse therapy for three more courses following an increase in the dosage of PSL to 100 mg/day. Immunosuppressive therapy was intensified by the addition of cyclosporine (150 mg/day). Over the next six weeks AST returned to its normal range (32 U/L), but total bilirubin, CRP and ferritin were still unstable (2.0 mg/dL, 1.822 mg/dL and 2,889 ng/mL, respectively). We also investigated serum cytokine levels. Interleukin (IL)-6, IL-18 and interferon (IFN) -γ were increased (12.99 pg/mL, 11,514.4 pg/mL, 226.77 pg/mL, respectively). Plasma exchange therapy, which was expected to cause a rapid reduction in the elevated cytokine levels in the peripheral blood, was performed using 40 units of fresh frozen plasma six times (twice a week × 3 weeks). His laboratory data subsequently improved dramatically (AST 14 U/L, total bilirubin 0.5 mg/dL, CRP 0.162 mg/dL, Plt 189 × 10^9/L,



AST	(IU/mL)	91	67	29	291	2869	43	32	14	11
ALT	(IU/mL)	107	126	102	550	4910	845	157	18	9
T-Bil	(mg/dL)	0.6	0.6	0.7	1.1	2.8	1.8	2.0	0.5	0.6
PT	(%)	110.3	125.0	130.8	130.8	48.0	60.4	75.3	118.2	115.9
CRP	(mg/dL)	13.74	5.09	4.26	3.10	2.72	1.23	1.82	0.16	0.21
Ferritin	(ng/mL)	32,246	12,629	5,554	26,200	>160,000	11,484	2,889	622	310
TNF-α	(pg/ml) (< 5.0)					2.39	1.70	2.59		
IL-4	(pg/ml) (< 4.0)					5.97		7.90		3.98
IL-6	(pg/ml) (< 4.0)					12.99	4.22	3.73		1.18
IL-10	(pg/ml) (< 5.0)					110.56	28.74	1.70		2.59
IL-12p70	(pg/ml) (< 5.0)					3.80	2.22	3.40		
IFN-γ	(pg/ml) (< 2.0)					226.77	8.48	10.87		2.29
IL-18	(pg/ml) (< 71.5)					11,514.4	13,034.6	13,007.8		183.8

Fig. 1 Clinical course of the patient (A.N. 33 year-old man). Time courses of liver enzymes, CRP, ferritin and cytokines (October 2006–May 2007). Ferritin increased simultaneously with liver dysfunction. IFN-γ, IL-6, IL-10 and IL-18 were also correlated with liver dysfunction. Prednisolone (PSL), methyl-PSL (mPSL), cyclosporine and plasma exchange therapy were given. *Arrows* show mPSL pulse therapy (1,000 mg/day × 3 days). Plasma exchange therapy was started on January 16. *mPSL pulse* methylprednisolone pulse therapy, *PSL* prednisolone, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T-Bil* total bilirubin, *PT* prothrombin time, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-α, *IL-4* interleukin-4, *IFN-γ* interferon-γ

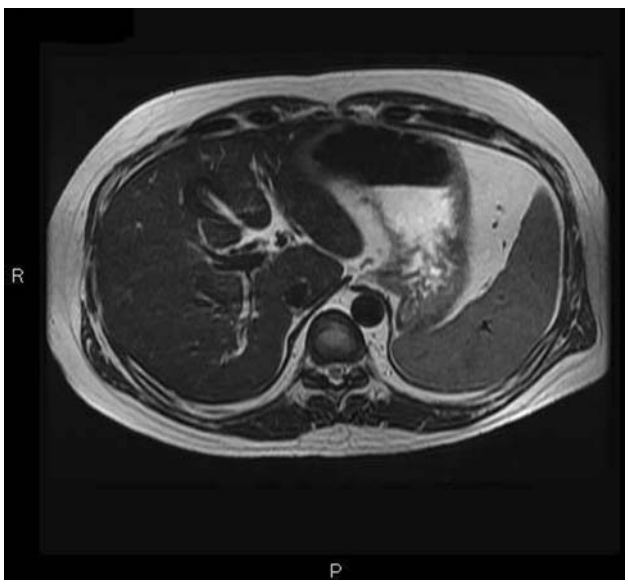


Fig. 2 Abdominal MRI (28th day of hospitalization). Abdominal MRI showed moderate hepatosplenomegaly

Hb 11.9 g/dl and IL-18 183.8 pg/ml), and he was discharged.

Three months after discharge the patient was well with normal acute phase reaction, ferritin and liver enzymes. Interestingly, by this time, the three drugs that had previously been positive on DLST gave negative DLST results instead.

Discussion

Liver dysfunction is frequently seen in AOSD patients, but the elevation of liver enzyme is usually mild [1, 2]. This patient with AOSD presented with an extremely high serum ferritin level and severe liver dysfunction. Hyperferritinaemia (>1,000 ng/mL), which is also seen in variety of inflammatory conditions, is not specific; however, extremely high concentrations (>10,000 ng/mL) are rare [6] and are specific for AOSD [7, 8]. A long period was required for the patient to recover after the three drugs

found to be positive on DLST had been stopped. Therefore, we thought that a drug allergy might be a potential cause of the exacerbation of his liver damage, and that AOSD might amplify it.

As shown in Fig. 1, we also investigated the serial changes in the serum levels of IL-4, IL-6, IL-10, IL-12, IL-18, IFN -γ and TNF-α. The serum concentrations of IL-6, IL-18 and IFN-γ were increased in line with the activity of AOSD, as has previously been reported for AOSD [9–11]. On the other hand, the serum levels of IL-4, IL-12 and TNF-α did not change. Interestingly, the serum IL-10 level showed a similar trend to the patient's disease activity. To our knowledge, there is currently no report on the serum IL-10 level in AOSD patients. Yumoto et al. [12] reported that serum IL-10 levels prior to treatment in patients with fulminant hepatic failure who survived were markedly elevated. The evidence from many reports on human studies suggests that a Th1-mediated process may provide the main contribution to the local immune responses in AOSD [13]. Recent reports indicate that IL-18 is markedly increased in sera from AOSD patients [9, 10]. In collaboration with IL-12, IL-18 stimulates Th1-mediated immune responses, but it can also stimulate Th2 immune responses in the absence of IL-12 [14]. The cytokine pattern of the present patient showed a Th1 pattern similar to that described in recent reports, and thus it seems that his liver dysfunction had been an exacerbation of AOSD. The IL-6, IFN-γ, IL-10, and IL-18 levels correlated with the condition of the patient. In particular, the levels of IL-18 were remarkably high. The high titer of IFN-γ may have been due to the patient being in a state of Th1-mediated inflammation. However, it is unknown whether IL-18 contributed directly to this abnormality because of the normal level of IL-12. In this patient, a high IL-10 titer was also observed. IL-18 might cause abnormal feedback in AOSD. At first, we administered cyclosporine for his liver damage, but his condition did not improve. The immunosuppressive effect of cyclosporine is recognized as being due primarily to its ability to directly suppress T cells. It may be that the plasma exchange resulted in the resetting of the hypercytokinaemia that caused the aggravation of his condition.

It is worth noting that DLST was positive for three drugs in the present patient, which, to the best of our knowledge, is very rare. It was reported that 54% of patients with AOSD have adverse drug reactions [15]. Positive reactions for DLST in this patient appeared in the active phase of AOSD, and changed into negative reactions concurrent with the remission of his disease. The laboratory examination showed that he was in inflammatory and hyperallergic states at the same time, which may correlate with his serological cytokine pattern.

It is very difficult to dispense to a patient with severe liver dysfunction and in a hyperallergic state such as the present patient. Plasma exchange therapy might be a valuable option in the treatment of AOSD with very high serum cytokine levels.

Conflict of interest The authors have no conflicting financial interests.

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