

Hemophagocytic Syndrome and Inflammatory Myopathy with Abundant Macrophages in a Patient with Adult-onset Still's Disease

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Abstract

We herein describe a 71-year-old woman with adult-onset Still's disease (AOSD) who developed fever, myalgia, and pancytopenia. The bone marrow aspiration and muscle biopsy revealed hemophagocytic syndrome (HPS) and inflammatory myopathy with abundant macrophages (IMAM). Immunostained specimens were positive for expression of retinoic acid-inducible gene-I (RIG-I), which recognizes viral RNA in infiltrated mononuclear cells as well as muscle tissues. These findings suggest that RIG-I may be involved in induction of HPS and IMAM in AOSD.

Key words: inflammatory myopathy with abundant macrophages, hemophagocytic syndrome, adult-onset Still's disease

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Introduction

Hemophagocytic syndrome (HPS), also known as macrophage activation syndrome (MAS), sometimes develops in patients with adult-onset Still's disease (AOSD) (1, 2). MAS is thought to be caused by the uncontrolled activation and proliferation of T lymphocytes and macrophages that can develop as a primary condition or secondary to malignancy, infections, autoimmune diseases and pharmacotherapy resulting in fever, splenomegaly, pancytopenia, and disseminated intravascular coagulation (DIC).

Inflammatory myopathy with abundant macrophages (IMAM) has been proposed as one spectrum of inflammatory myopathy (3-6). IMAM is mainly detected among pa-

tients with a dermatomyositis (DM)-like disease; infiltration of macrophages is diffuse and positively correlates with both T cell infiltrates and acute muscle fiber damage.

The complication of HPS and IMAM in patients with AOSD is rare. We herein describe a patient with AOSD who presented with HPS and IMAM and suggest the existence of a relationship between these serious complications.

Case Report

A 71-year-old woman was admitted to our hospital complaining of throat pain, arthralgia of wrist joints, myalgia of left upper extremity and a fever up to 38°C that had persisted for one month. On admission, her body temperature was 37.5°C. Her blood pressure, pulse rate, and respiratory

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Table. Laboratory Data on Admission

【Blood count】		【Biochemistry】		【Serology】			
WBC	5400/ μ L	Na	138 mEq/L	Ferritin	2634 ng/mL	ANA	<20 index
Neut.	73 %	K	3.8 mEq/L	sIL-2R	1781 U/mL	RF	60.9 IU/mL
Lym.	18 %	Cl	103 mEq/L	IgA	306 mg/dL	a-RNP Ab	(-)
Mon.	0 %	Ca	8.8 mg/dL	IgG	2287 mg/dL	a-Sm Ab	(-)
Eo.	0 %	TP	7.8 g/dL	IgM	111 mg/dL	a-SS-A Ab	(-)
RBC	3.34×10^6 / μ L	Alb	3.1 g/dL	CH50	45.3 U/mL	a-dsDNA Ab	(-)
Hgb	9.4g/dL	BUN	9.0 mg/dL	C3	133.9 mg/dL	ACPA	(-)
Plt	18.8×10^4 / μ L	Cr	0.54 mg/dL	APR test	(-)	【Urinalysis】	
ESR	71 mm/hr	T. Bil	0.5 mg/dL	TPHA	(-)	Protein	(-)
		AST	50 IU/L	HBs Ag	1434.6 IU/mL	Occult Blood	(-)
		ALT	31 IU/L	HBc Ab	>100.0 IU/mL	Glucose	(-)
		LDH	529 IU/L	HBV DNA PCR	(-)	Ketone	(-)
		ALP	282 IU/L	HCV Ab	(-)	Bilirubin	(-)
		γ GTP	40 IU/L	HTLV-1 Ab	(-)		
		AMY	51 IU/L	PCT	0.696 ng/mL		
		CK	32 IU/L	CMV IgM	(-)		
		CRP	2.38 mg/dL	Mumps IgM	(-)		
		Glu	101 mg/dL	Parvo B19 IgM	(-)		
				EBV VCA-IgM	(-)		

PCT :Procalcitonin, ACPA :Anti-CCP antibody

rate were normal. Physical examination revealed skin eruptions of anterior chest wall, left axillar lymph node swelling and hepatosplenomegaly. The initial laboratory studies (Table) revealed: white blood cell count 5,400/ μ L (73.0% neutrophils, 18.0% lymphocytes), hemoglobin 9.4 g/dL, platelet count 114,000/ μ L, erythrocyte sedimentation rate (ESR) of 71 mm/hr, and C-reactive protein (CRP) 2.38 mg/dL. The aspartate aminotransferase (AST) was 50 IU/L, alanine aminotransferase (ALT) was 31 IU/L, and lactate dehydrogenase was 529 IU/L. The ferritin and soluble IL-2 receptor levels were elevated to 2,634 ng/mL and 1,781 U/mL, respectively. Although the rheumatoid factor was positive, the antinuclear antibodies (ANA) level was negative. The hepatitis B virus (HBV)-DNA polymerase chain reaction (PCR) also came back negative, although the hepatitis B antigen and hepatitis B core antibody were positive. Other viral markers of primary infection for hepatitis C, human T lymphocyte virus-1, Epstein-Barr virus, cytomegalovirus, parvovirus, and mumps virus were negative.

The patient was diagnosed as having AOSD based on 3 out of 4 major items on Yamaguchi's diagnostic criteria (7) including fever, arthralgia, and typical skin eruption and 3 of 4 minor items including throat pain, lymph node swelling/splenomegaly, and abnormal liver function tests (Fig. 1). She received only non-steroidal anti-inflammatory drugs (NSAIDs). Her symptoms improved with a decline of CRP and ferritin levels two weeks following treatment, and she was thereafter successfully discharged.

One week later, the patient was readmitted to our hospital with the chief complaints of common cold-like symptoms such as throat pain, myalgia of bilateral lower extremities, general malaise, and a fever up to 38°C. Thereafter, she also recognized skin eruption in her left ear just after taking NSAIDs. During the second admission, the laboratory findings demonstrated severe pancytopenia (leukocyte count

2,100/ μ L, hemoglobin 9.3 g/dL, platelet count 67,000/ μ L) with an elevated concentration of ferritin (24,337 ng/mL) and aldolase (31.2 IU/L). The serum concentrations of interleukin-18 (IL-18) and interferon- γ (IFN- γ) were extremely elevated to 229,126 pg/mL and 238.4 pg/mL, respectively. The DIC score was seven points (D dimer 88.8 μ g/mL, prothrombin time (PT) international normalized ratio (INR) 1.25, fibrin/fibrinogen degradation products (FDP) 85 μ g/mL, and fibrinogen 33.2 mg/dL). The aspiration biopsy of the bone marrow revealed hemophagocytosis by macrophages (Fig. 2). Magnetic resonance imaging (MRI) of the lower extremities detected massive inflammatory changes in her thigh muscle and fascia (Fig. 3). The muscle biopsy showed CD68-positive cell infiltration predominantly in the fascia, which suggested IMAM (Fig. 4). Positive expression of interferon-alpha (IFN- α) and retinoic acid-inducible gene-1 (RIG-I) in the cytoplasm of mononuclear cells, as well as muscle tissues, was also seen. The patient was diagnosed with HPS and IMAM complicated with AOSD and successfully treated with methylprednisolone pulse therapy (500 mg/day, 3 days) twice followed by oral prednisolone (30 mg/day). Her clinical symptoms and laboratory data following treatment were stable. No recurrence of HPS, IMAM, or AOSD was seen, even though the prednisolone was tapered to 10 mg/day.

Discussion

HPS is associated with infections, malignant lymphomas, autoimmune diseases, and various drugs (6, 8). Systemic lupus erythematosus (SLE) and AOSD are known underlying autoimmune diseases of HPS (2). Although it has been reported that 12% of AOSD patients are complicated with HPS, it is difficult to distinguish an occurrence of HPS from the flare of AOSD (9). Leukocytosis is seen in flare-up

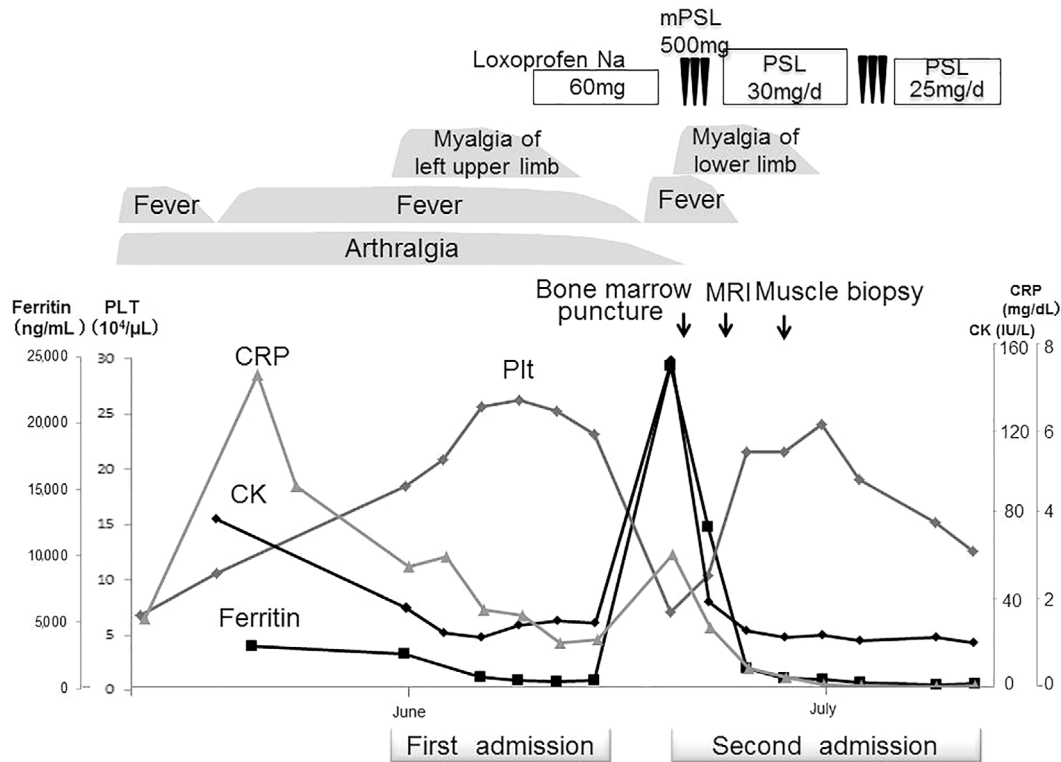


Figure 1. Clinical course.

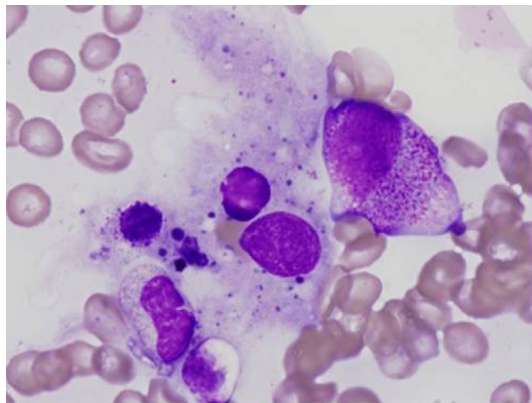


Figure 2. Bone marrow aspiration. May-Giemsa staining showed hemophagocytosis by macrophages (1,000 \times).

cases of AOSD, whereas pancytopenia progresses in cases with complication of HPS. In addition, it is important to detect phagocytosis by activated macrophages in bone marrow aspirations. As AOSD patients with HPS have higher disease severity and are complicated with severe conditions, such as acute respiratory distress syndrome (ARDS), DIC, and multiple organ damage, it is important that patients be treated immediately with appropriate immunosuppressive therapy.

IMAM has been proposed as an independent disease characterized by a massive infiltration of CD68-positive macrophages in the fascia of dermatomyositis or SLE (4). Proximal muscle weakness develops with elevation of serum creatine kinase (CK) (3). The characteristic features of the MRI were hypertrophy and high intensity of the fascia, as well as

muscle, on the short T1 inversion recovery (STIR) (3). IMAM often coexists with a fatal condition, such as ARDS or HPS. Although it was previously reported that infiltrated macrophages showed hemophagocytosis in 21 of 27 IMAM patients (4), we detected hemophagocytosis in the bone marrow aspiration not in the specimens of the muscle and the fascia. Therefore, it is important to carefully monitor the occurrence of these diseases.

In our patient, HPS and IMAM, which are also referred to as MAS, developed during the follow-up course of AOSD. It is known that serum concentration of IL-18 can be elevated in AOSD patients complicated with MAS (10). In our patient, the serum concentration of IL-18 was also extremely high. Although MAS may develop in AOSD patients spontaneously, various bacterial or viral infections and drugs have been reported to be the cause of this syndrome (9). NSAIDs are known to be capable of triggering MAS in systemic juvenile rheumatoid arthritis (11). As NSAIDs-related MAS could not be distinguished from viral-induced MAS symptomatically, NSAIDs could therefore not be completely ruled out as the possible trigger of MAS in this patient. Among the infections, virus infections such as influenza virus, Epstein-Barr virus, and cytomegalovirus may be associated with the occurrence of MAS (2). Although we did not detect these viral markers, immunohistological staining demonstrated positive expression of IFN- α and RIG-I in the infiltrated mononuclear cells and the muscle tissues. The positive expression of IFN- α and RIG-I was also seen in the mononuclear cells that infiltrated the fascia.

RIG-I is one of the RNA helicases that exist in the cyto-

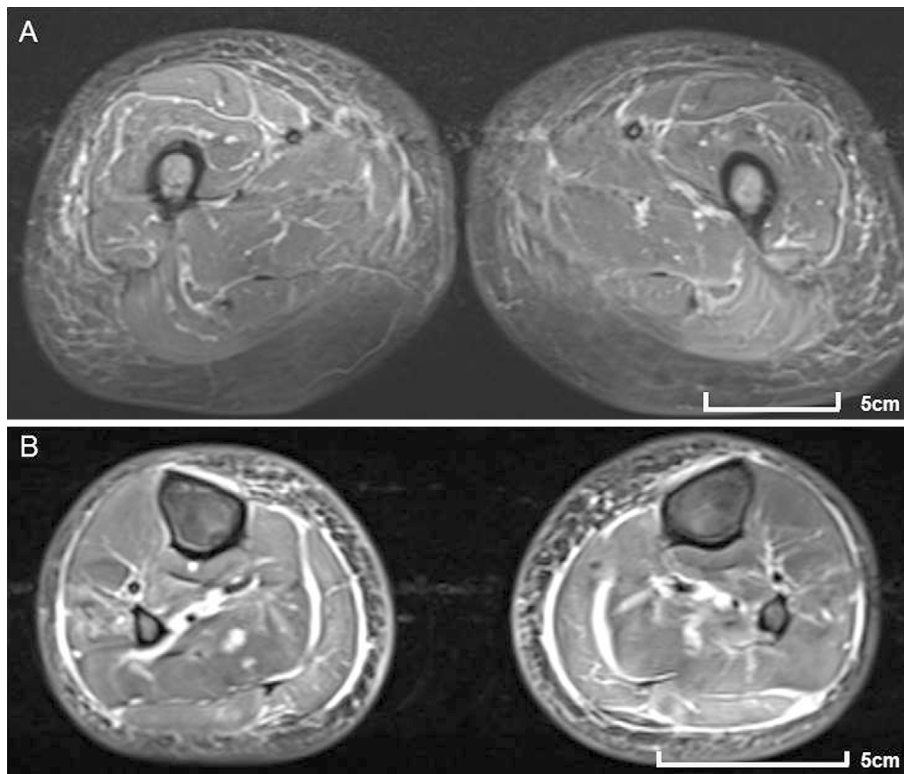


Figure 3. MRI (STIR) of both thighs (A) and lower legs (B). High intensity of STIR was seen overall in the lower extremities. Hypertrophy and high intensity were also seen in the fascia.

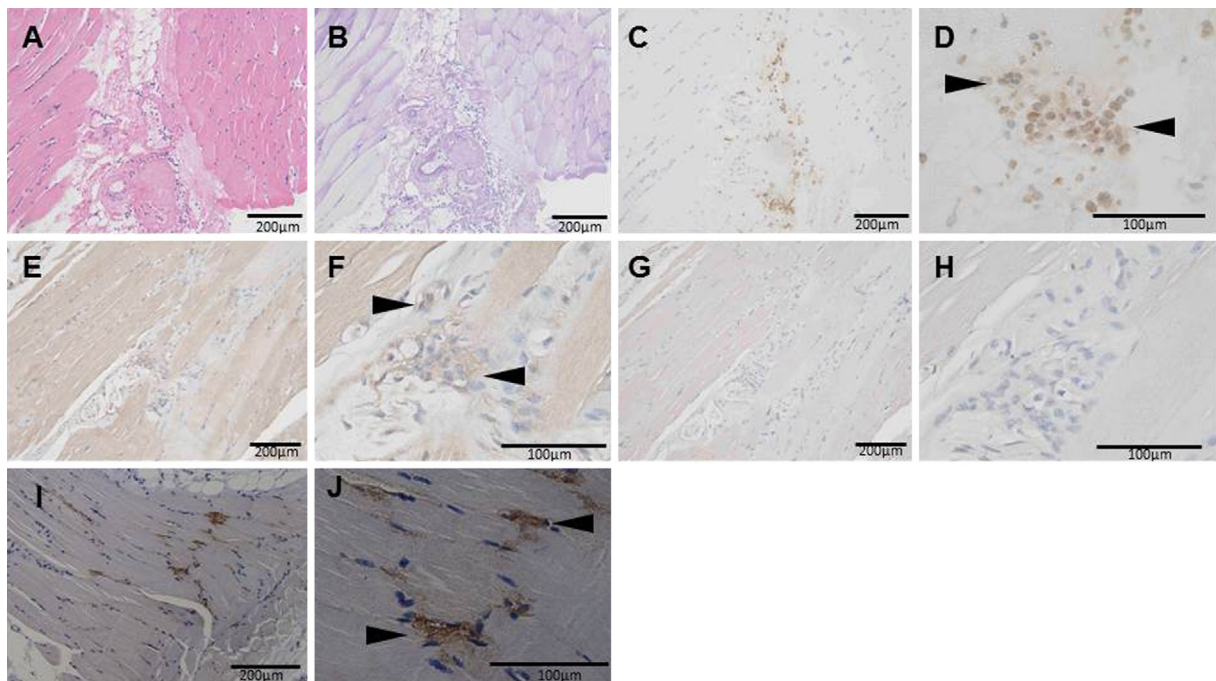


Figure 4. Immunohistochemical staining of muscle and fascia tissues in the thigh, which showed high intensity on the MRI (STIR). (A) Hematoxylin and Eosin staining (objective lens $\times 10$), (B) PAS staining (objective lens $\times 10$), (C) immunostaining for CD68 (objective lens $\times 10$), and (D) immunostaining for CD68 (objective lens $\times 40$) revealed massive infiltration of CD68-positive macrophages predominantly in the fascia. Immunostaining for anti-RIG-I antibody [at objective lens $\times 10$ (E) and $\times 40$ (F) magnification] revealed expression of RIG-I in mononuclear cells as well as muscle tissues [negative control of RIG-I, objective lens $\times 10$ (G) and $\times 40$ (H) magnification]. Immunostaining for IFN- α antibody [at objective lens $\times 10$ (I) and $\times 40$ (J) magnification] revealed expression of IFN- α in mononuclear cells as well as muscle tissues.

plasm (12). This molecule detects diverse viral RNAs in host cells, triggers immune responses, produces antiviral cytokines, namely type I interferon (IFN), and plays a crucial role in the initial response to viral infection. In this case, IFN- α was expressed in the infiltrated mononuclear cells and muscle tissues. It is well known in innate immunity that many cytokines, including IFN, activate macrophages which induce the production of various cytokines. The expression of RIG-I was also detected in autoimmune diseases. Imaizumi et al. found high levels of RIG-I expression in synovial tissues of rheumatoid arthritis (RA) (13) and reported that RIG-I expression in human mesangial cells was involved in the inflammation in lupus nephritis (14). In our case, the common cold-like symptoms suggesting a viral infection preceded the onset of both HPS and IMAM, and RIG-I was expressed in the cytoplasm of mononuclear cells infiltrated in the muscle tissues and the fascia. These findings suggest that excessive innate immunity responses to viral infection through IFN- α expression may therefore be induced in patients with AOSD.

In conclusion, we experienced a rare case of HPS and IMAM in a patient with AOSD who was successfully treated with methylprednisolone pulse therapy. From our findings, antiviral RIG-I signaling may therefore be involved in the initiation of HPS and IMAM.

The authors state that they have no Conflict of Interest (COI).

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