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Adult-Onset Still's Disease Complicated by Immunoglobulin A Vasculitis and anti-CCP Antibody-Positive Arthritis

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A 38-year-old male was admitted to our hospital for arthralgia, fever, skin rash, and purpura. He was diagnosed as having adult-onset Still's disease (AOSD) based on Yamaguchi's criteria. Skin biopsy revealed immunoglobulin A (IgA) vasculitis. He was also found to have anti-cyclic citrullinated peptide (CCP) antibody-positive inflammatory arthritis on a shoulder joint, however he did not fulfill classification criteria for rheumatoid arthritis. Elevated serum cytokine such as serum IL-18 supported the diagnosis of AOSD. His symptoms improved with 40 mg of prednisolone plus cyclosporin A (200 mg/day). Two years after hospitalization, AOSD was relapsed with pleurisy and hyperferritinemia. Finally, he was diagnosed with multicyclic systemic type of AOSD complicated by IgA vasculitis and seropositivity of anti-CCP antibody. Clinicians need to consider the complication of multiple rheumatic diseases, even if the disease-specific autoantibody is positive.

Keywords: adult-onset Still's disease; anti-CCP antibody; IgA vasculitis; interleukin-18
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Introduction

Adult-onset Still's disease (AOSD) is a systemic auto-inflammatory disease characterized by spiking fever, arthritis/arthralgia, evanescent salmon-pink maculopapular rash and multiorgan involvement (Bagnari et al. 2010). Diagnosis of AOSD is based on Yamaguchi's criteria, including negative serological markers for other rheumatic or autoimmune diseases (Yamaguchi et al. 1992). Therefore, serological investigation and clinical evaluation of other diseases are essential for a definitive diagnosis of AOSD. Seronegativity for autoantibodies, such as anti-cyclic citrullinated peptide (CCP), is necessary to diagnose AOSD. However, there are several reports describing the presence of autoantibodies in AOSD (Riera et al. 2011; Reddy Munagala et al. 2012; Saghafi and Sahebari 2013; Ichida et al. 2014). Furthermore, various atypical skin rushes other than salmon-pink maculopapular rash can occur with AOSD (Yamamoto 2012). Here, we present a case of AOSD patient associated with immunoglobulin A (IgA) vasculitis and anti-CCP antibody-positive arthritis.

Case Presentation

A 38-year-old man was transferred to our hospital with remittent fever, arthralgia, myalgia, arthritis, and hyperferritinemia from another hospital. Three weeks prior to referral, he was admitted to a different hospital for evaluation of his fever and arthritis. Infection was suspected as his blood test showed leukocytosis and elevated C-reactive protein (CRP). He was treated with antibiotics for two weeks, but his symptoms continued. He was transferred to our hospital for further investigation. His past medical history included rheumatic fever, and he had a family history of rheumatoid arthritis in his sister. On admission, a physical examination revealed that his body temperature was 39.8°C and blood pressure was 137/78 mm Hg. His heart rate was 94 beats/minute. Auscultation of the chest showed neither heart murmur nor crackles. He had tenderness in both shoulder joints and scattered palpable purpura on his bilateral lower legs (Fig. 1). The laboratory data were as follows (Table 1): white blood cells (WBC), 19,100/μL (neutrophils 87%, lymphocytes 7.0%, monocytes 1.0%, eosinophils 1.0%, and

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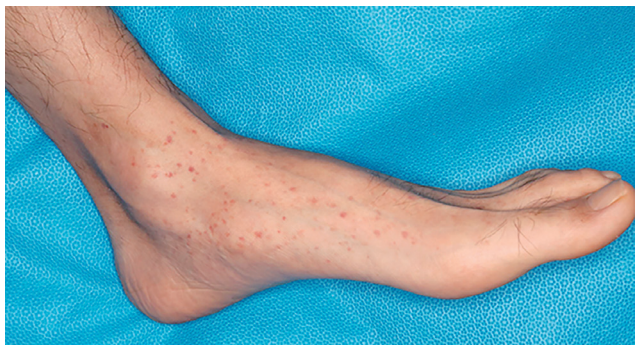

Fig. 1. Cutaneous involvement in this case.
Palpable purpura on both the lower legs was observed.

basophils 1.0%); red blood cells (RBC), 401 × $10^4/\mu$L; hemoglobin, 11.5 g/dL; platelets, 35.6 × $10^4/\mu$L; CRP, 17.27 mg/dL; erythrocyte sedimentation rate, 63 mm per hour; lactate dehydrogenase, 388 IU/L (normal range 124-222 IU/L); aspartate aminotransferase, 98 IU/L (normal range 13-30 IU/L); alanine aminotransferase, 172 IU/L (normal range 10-42 IU/L); creatinine, 0.53 mg/dL (normal range 0.65-1.07 mg/dL); serum ferritin, 6,818.1 ng/mL (normal range 21-282 ng/dL); matrix metalloproteinase-3, 378 ng/mL (normal range 36.9-121 ng/mL); IgG, 1,822 mg/dL (870-1,700 mg/dL); IgA, 523 mg/dL (110-410 mg/dL); and IgM 67 mg/dL (33-190 mg/dL). Autoantibodies were almost negative but only anti-CCP antibody was positive (29.6 U/mL). The serum interleukin-18 (IL-18) level was markedly elevated to 15,024.2 pg/mL. His HLA typing was HLA-A 2, 11, HLA-B 7, 44 and HLA-DR 4, 13. The results of interferon-gamma release assays (IGRA), β-D glucan, hepatitis B surface (HBs) antigen and hepatitis C virus (HCV) antibody testing were all negative. Echocardiography revealed normal left ventricular wall contraction. There were no valvular diseases. Contrast-enhanced computed tomography showed splenomegaly.

Table 1. Laboratory findings and cytokine/chemokine profile on admission.

Peripheral blood		Serological tests	
Red blood cells	401×$10^4/\mu$L	C-reactive protein	17.27 mg/dL (< 0.30)
Hemoglobin	11.5 g/dL	Erythrocyte sedimentation rate	63 mm/hr (< 10)
Hematocrit	35.3%	sIL-2R	1340 U/ml (121-613)
Platelets	35.6×$10^4/\mu$L	IgG	1,822 mg/dL (861-1,747)
White blood cells	19,100/μL	IgA	523 mg/dL (93-393)
Neutriphil	87.0%	IgM	67 mg/dL (33-183)
Eosinophil	1.0%	Complement 3	224 mg/dL (73-138)
Monocyte	1.0%	Complement 4	26 mg/dL (11-31)
Lymphocyte	7.0%	ANA	× 80 (< × 80)
Basophil	1.0%	Anti-ds-DNA antibody	(−) (< 9.9)
Blood chemistry		Anti-Sm antibody	(−) (< 6.9)
Total protein	7.3 g/dL (6.6-8.1)	Anti-U1RNP antibody	(−) (< 4.9)
Total bilirubin	0.7 mg/dL (0.4-1.5)	Anti-SSA antibody	(−) (< 6.9)
Albumin	2.5 g/dL (4.1-5.1)	Anti-SSB antibody	(−) (< 6.9)
Glutamic-oxaloacetic transaminase	98 IU/L (13-30)	Anti-CCP antibody	29.6 U/mL (0-4.4)
Glutamic-pyruvic transaminase	172 IU/L (10-42)	RF	15 U/mL (0-15)
Lactate dehydrogenase	388 U/L (124-222)	ASO	671 IU/mL (0-240)
Alkaline phosphatase	856 U/L (106-322)	ASK	× 5,120 (0-1,280)
Creatine Kinase	88 IU/L (62-287)	PR3-ANCA	(−) (< 2.0 U/mL)
Blood urea nitrogen	12 mg/dL (8-20)	MPO-ANCA	(−) (< 3.5 U/mL)
Creatinine	0.53 mg/dL (0.65-1.07)	HBs Ag	(−)
Ferritin	5,723 ng/mL	HCV antibody	(−)
Sodium	139 mEq/L	CMV antigenemia C10C11	(−)
Potassium	5.1 mEq/L	HLA-typing	
Chloride	100 mEq/L	HLA-A	2, 11
		HLA-B	7, 44
		HLA-DR	4, 13
		Urinalysis	normal

sIL-2R; soluble interleukin-2 receptor, ANA; anti-nuclear antibody, MPO-ANCA; myeloperoxidase-antineutrophil cytoplasmic antibody, Anti-ds-DNA antibody, anti-double stranded DNA antibody; Anti-CCP antibody; anti-cyclic citrullinated peptide antibody; RF, rheumatoid factor; ASO, anti-streptolysin O antibody; ASK, anti-streptokinase antibody; anti PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; HBsAg; hepatitis B virus surface antigen, HCV; hepatitis C virus; CMV antigenemia, cytomegalovirus antigenemia; HLA, human leukocyte antigen. Reference ranges are shown in parentheses.

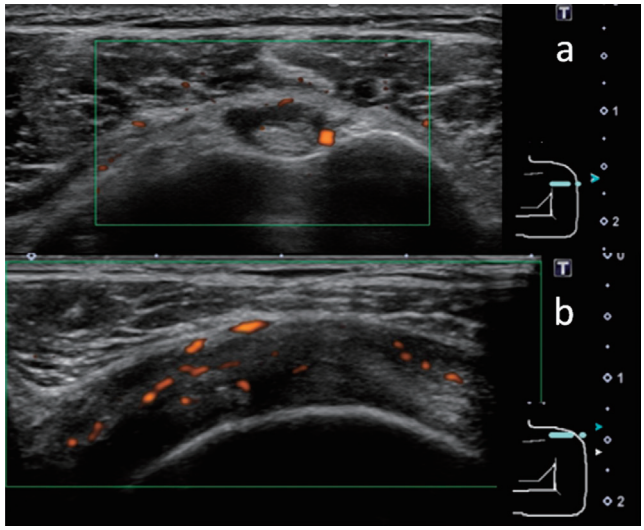

Fig. 2. Joint ultrasonographic findings for the left shoulder. (a) Hypoechoic fluid surrounding the left biceps tendon is consistent with tenosynovitis. (b) Tendonitis in the left supraspinatus. Hypoechoic extension in the supraspinatus tendon is consistent with power Doppler signal-positive tendinosis.

His joint ultrasonography revealed long head of biceps tenosynovitis in the left shoulder and tendonitis in the left supraspinatus (Fig. 2). Small, slightly elevated purplish macules with induration were scattered on both lower legs. A biopsy from an eruption showed perivascular infiltration of lymphocytes and neutrophils in the upper dermis. Nuclear dust and extravasated erythrocytes were also observed. Direct immunofluorescence study revealed deposition of IgA along the capillary walls in the upper dermis (Fig. 3).

The patient was diagnosed as having AOSD based on the Yamaguchi criteria (Yamaguchi et al. 1992). In addition, he was also diagnosed with IgA vasculitis based on the skin eruption and histological findings. We considered that his general symptoms such as fever, splenomegaly, and liver dysfunction mainly derive from the AOSD, not IgA vasculitis; there was no typical symptoms suggesting IgA vasculitis other than purpura in the legs and the cytokine profile such as elevated IL-18 levels was characteristic to AOSD. Although there was anti-CCP antibody positive arthritis in his shoulders, he did not fulfil the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (Aletaha et al. 2010).

The patient received 40 mg/day of oral prednisolone following pulsed methylprednisolone (1,000 mg/day for three consecutive days). His palpable purpura completely disappeared. Disease activity of AOSD remained high, so oral cyclosporin A (100 mg/day) was added and increased up to 200 mg/day. After this treatment, the patient's symptoms and laboratory test abnormalities including hyperferritinemia completely resolved (Fig. 4). Four weeks after admission, he was discharged from our hospital and prednisolone (PSL) doses were successfully tapered. One year later, PSL doses were decreased to 3 mg/day. However, AOSD was relapsed with pleurisy and hyperferritinemia two years after hospitalization. The increase to 30 mg of PSL relieved these symptoms. Finally, we diagnosed him multicyclic systemic type of AOSD complicated by IgA vasculitis and anti-CCP antibody positive arthritis.

Discussion

We described a Japanese patient with multicyclic systemic type of AOSD complicated by IgA vasculitis and anti-CCP antibody-positive arthritis. To the best of our knowledge, this is the first case report documenting the co-occurrence of AOSD and IgA vasculitis.

It is controversial whether this case is AOSD complicated with vasculitis, because AOSD is basically necessary to exclude other diseases including IgA vasculitis. However, this case should be considered as a complication with AOSD and IgA vasculitis for the following reasons. First, purpura in both lower legs was uncommon in AOSD and immunofluorescence staining on skin biopsy was characteristic to IgA vasculitis. The classic skin rash in AOSD is an evanescent, salmon pink, macular eruption that is usu-

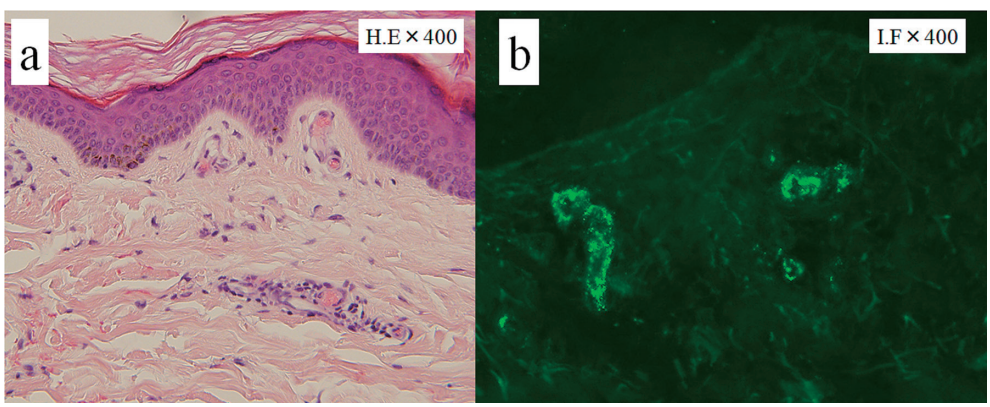

Fig. 3. Skin biopsy findings on the lower legs. (a) Concomitant angiocentric mixed neutrophilic and lymphocytic infiltrates in the upper dermis viewed by hematoxylin and eosin (H.E) staining. (b) IgA deposition in small vessels in the skin viewed by immunofluorescence (I.F) microscopy.

Fig. 4. The clinical course of a 38-year-old male Japanese patient with fever, palpable purpura of lower legs, and arthritis of the left shoulder.
After the administration of prednisolone, his symptoms and laboratory findings gradually improved.
BT, body temperature; CRP, C-reactive protein; mPSL, methylprednisolone; PSL, prednisolone.

ally non-pruritic and tends to occur with fever and disappear during afebrile episodes (Bagnari et al. 2010). The skin lesions in AOSD are characterized by perivascular inflammation of the superficial dermis (Yamamoto 2012), whereas leukocytoclastic vasculitis and nuclear dust have been observed in both IgA vasculitis and microscopic polyangiitis (MPA)/granulomatosis with polyangiitis (GPA) (Sunderkotter et al. 2005), not AOSD. Vasculitis can be observed as atypical skin manifestation in AOSD (Sozeri et al. 2009). However, there is no report of IgA-positive skin lesions by immunofluorescence staining in AOSD patient. The negative results of proteinase 3 and myeroperoxidase-antineutrophil cytoplasmic antibody testing, as well as the patient's clinical features, ruled out complications of MPA/GPA in our case. Second, the laboratory data, organ involvement and cytokine profile were typical for AOSD, but not IgA vasculitis. Hyperferritinemia and splenomegaly are common in AOSD, whereas uncommon in IgA vasculitis. Other diseases leading to hyperferrinemia were not found such as hemophagocytic syndrome and thrombotic thrombocytopenic purpura from his symptoms. The molecular pathways and cytokine profiles in the pathogenesis of AOSD are characterized by the inflammatory cytokines, IL-1, IL-6, IL-18, and tumor necrosis factor-α (TNF-α) (Gerfaud-Valentin et al. 2014). In particular, IL-18 is suggested to play a crucial role in activating macrophages, favoring Th1 type cytokine profiles in AOSD (Gerfaud-Valentin et al. 2014). On the other hand, an upregulation of IL-6, IL-8, TNF-α, and serum amyloid A have been reported in adult IgA vasculitis (Kuret et al. 2019). As the serum ferritin and serum IL-18 levels were elevated, it was more likely that systemic inflammation was derived from AOSD. In contrast, IgA vasculitis showed relatively small impact in our case.

The pathophysiology of complication with AOSD and IgA vasculitis is controversial. AOSD is one of the autoinflammatory disease (Gerfaud-Valentin et al. 2014). However, IgA vasculitis is classified to autoimmune disease (Sugino et al. 2021). While autoinflammatory diseases and autoimmune diseases are known to distinct disorders, immunogenic predisposition and environmental factors might be involved in this case. Innate and adaptive immune responses can be activated by various environmental factors (Turvey and Broide 2010; Chaplin 2010). For example, infectious agents, allergy, and agents with adjuvant activity, such as alum and silicon, activate both adaptive and innate immunity (Rose 2008; Turvey and Broide 2010). In these conditions, amplification of the immune responses consisting of macrophage activation and antigen presentation in the context of MHC class II molecules to CD4 positive cells might trigger both autoinflammatory and autoimmune diseases under environmental factor or genetic predisposition (Chaplin 2010; Ombrello et al. 2015). In fact, increased frequencies of IgA-related vasculitis or polyarteritis nodosa (PN) patients have been reported in Familial Mediterranean fever, an autoinflammatory disease (Abbara et al. 2019). Therefore, vasculitis can be accompanied by autoinflammatory disease. It might be reasonable to consider that coexistence of AOSD and IgA vasculitis may be incidental, however, the coexistence of these diseases may also be derived from common causes described above, environmental and genetic factors.

Furthermore, the patient also was diagnosed as having anti-CCP antibody and DR4-positive arthritis. The frequency of DR4 is significantly higher in rheumatoid arthritis (RA) patients (Wordsworth et al. 1989). Our case did

not fulfill the classification criteria for RA (Aletaha et al. 2010). However, AOSD patients with positive anti-CCP antibody testing are very rare. The most common arthritis in AOSD involves the wrist and knee joints, but shoulder arthritis is uncommon (Sanchez Loria et al. 1992). Ichida et al. (2014) classified AOSD patients who met the diagnostic criteria for rheumatoid arthritis as the RA subtype. They reported that one out of 16 RA subtype AOSD patients had positive anti-CCP antibody testing, whereas all non-RA patients were negative for this test (Ichida et al. 2014). Furthermore, Riera et al. (2011) tested for anti-CCP antibodies in 41 AOSD patients and reported that all were negative except for one patient who had a chronic articular pattern and severe erosive arthritis. Most AOSD patients do not have rheumatoid factor or anti-CCP antibodies. However, the presence of CCP-antibodies may affect the frequency and severity of arthritis in AOSD patients. More cases need to be studied to clarify the relationship between anti-CCP antibodies and AOSD.

In conclusion, this case represents an example of the complication of AOSD and IgA vasculitis with anti-CCP antibody. Since disease-specific antibody cannot rule out other rheumatic diseases, it is important to make a diagnosis based on clinical findings. Furthermore, clinicians need to consider the possibility of IgA vasculitis when they encounter unusual clinical manifestations such as purpura in a patient with AOSD.

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Conflict of Interest

The authors declare no conflict of interest.

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