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【 CASE REPORT 】

A Recurrent Case of Adult-onset Still's Disease with Concurrent Acalculous Cholecystitis and Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis Successfully Treated with Combination Immunosuppressive Therapy

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Abstract:

We herein report the case of 21-year-old female diagnosed with adult-onset Still's disease (AOSD) three years earlier who presented with fever and right upper abdominal pain. She was diagnosed with acute acalculous cholecystitis (AAC) based on hepatic dysfunction, elevated C-reactive protein, and gallbladder wall thickening on abdominal ultrasound. Based on the presence of pancytopenia, hyperferritinemia, and hemophagocytosis by a bone marrow examination, she was diagnosed with macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) which was refractory to glucocorticoid pulse therapy. The combination of intravenous cyclosporine A with glucocorticoids was able to successfully control the disease activity of AOSD-related AAC and MAS/HLH.

Key words: adult-onset Still's disease, macrophage activation syndrome, hemophagocytic lymphohistiocytosis, acalculous cholecystitis, cyclosporine A

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Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of unknown etiology that is characterized by fever, arthritis, characteristic rash, hepatosplenomegaly, and hyperferritinemia. The pathogenesis of AOSD is considered to involve various inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, IL-18, and interferon-γ (1). Some cases might be complicated by macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), a fatal condition caused by hypercytokinemia which can lead to multi-organ failure (2). Conversely, acute acalculous cholecystitis (AAC), a relatively rare organ complication of AOSD (3, 4), has been reported to be complicated by connective tissue diseases including systemic lupus erythematosus (SLE). Since it is a rare complication of AOSD, there is no consensus on the course of treatment for AOSD related AAC, partly because it can be observed as AOSD-related organ failure following surgical cholecystectomy (4, 5). We herein report the case of a patient presenting with concurrent MAS/HLH and AAC at the time of AOSD relapse who was successfully treated only with glucocorticoids and cyclosporine A (CsA).

Case Report

A 21-year-old female patient was diagnosed with AOSD three years prior to the present admission based on the findings of fever, erythema of the extremities and trunk, polyarthritis, hepatic dysfunction, hyperferritinemia, elevated inflammatory response, and splenomegaly. She was treated

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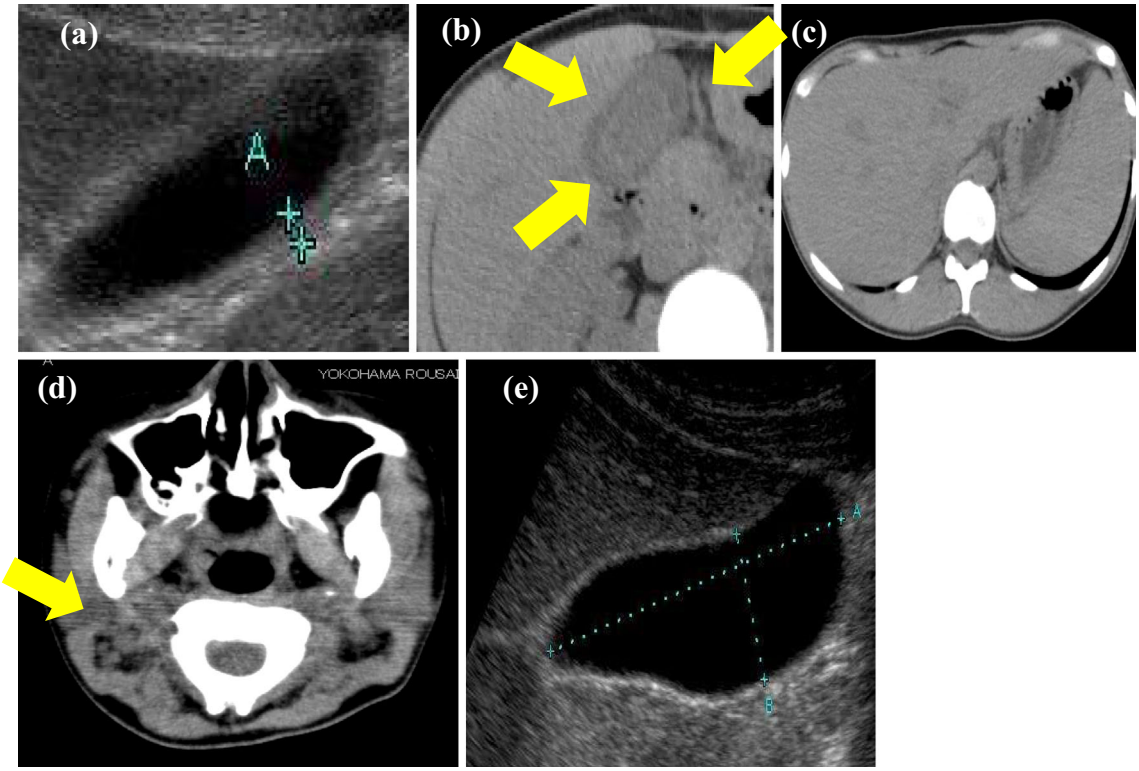

Figure 1. **Ultrasonography and computed tomography (CT) images on admission. (a) Ultrasonography images of the gallbladder. (b, c) CT images of the gallbladder (arrows), liver, and spleen. (d) CT images of the cervical lymph nodes (arrow). (e) Changes in the gallbladder ultrasonography findings on day 26.**

with 30 mg/day prednisolone, which was tapered off after achieving an improvement of the disease activity. Eleven months before hospitalization, she developed arthritis in her right knee and was diagnosed with a minor flare of AOSD. She was initiated on 7.5 mg/day prednisolone and 8 mg/week methotrexate the following month. After obtaining an improvement of the arthritis in the right knee, prednisolone was tapered off and discontinued three months prior to the current admission and remission was maintained with a methotrexate dose of 8 mg/week thereafter. She had a history of paroxysmal supraventricular tachycardia, no allergies, and no family history of rheumatic disease.

Two months before the hospitalization, a urticaria-like rash with itching appeared on her extremities. A week before this hospitalization, she also developed a fever ranging between 39℃ and 40℃ and pain in both shoulders and knees. In mid-April, she developed nausea, vomiting, and right hypochondriac pain. At the time of examination, she had fever, right hypochondralgia, and tenderness in both shoulder and knee joints. Laboratory tests showed elevated hepatobiliary enzymes (aspartate aminotransferase, 734 U/L; alanine aminotransferase, 429 U/L; lactate dehydrogenase, 2,941 U/L; gamma-glutamyl transferase, 272 U/L) and C-reactive protein (CRP, 5.34 mg/dL). Abdominal ultrasonography (Fig. 1a) and abdominal computed tomography scans (Fig. 1b) showed gallbladder enlargement and wall thickening without any biliary stones.

She was admitted to the hospital with the diagnosis of AAC because the common bile duct was not obstructed and the possibility of obstructive cholangitis was considered unlikely. She was managed by fasting and antibiotic treatment with tazobactam/piperacillin. However, pancytopenia (WBC, 2,300/μL; hemoglobin, 11.0 g/dL; platelet count, 7.9×10^4/μL) developed on the second day with no improvement in hepatic dysfunction. The laboratory findings on the second day before the initiation of immunosuppressive therapy including glucocorticoids are presented in Table 1.

The patient was diagnosed with AOSD recurrence based on a fever ≥39°C lasting more than one week, arthralgia lasting more than two weeks, typical rash, splenomegaly (Fig. 1c), cervical lymphadenopathy (Fig. 1d), hepatic dysfunction, and negative rheumatoid factor and antinuclear antibodies, according to the AOSD diagnostic criteria by Yamaguchi et al. (6). In addition, she was diagnosed with MAS/HLH based on fever, splenomegaly, cytopenia of two or more lineages, hepatitis-like findings, and pathological changes in myeloid markers by bone marrow biopsy examination (Fig. 2), including hemophagocytosis, elevated serum ferritin, and elevated soluble IL-2 receptor, which fulfilled the criteria of the MAS/HLH diagnosis (7). There were no findings suggesting active viral infection and a viral etiology was ruled out for MAS/HLH, which was therefore considered to be due to AOSD recurrence. AAC was diagnosed as an organ complication associated with AOSD recurrence as it was associated with an exacerbated disease activity including MAS/HLH. Because of her poor general condition and

Table 1. Laboratory Findings at the Time of Hospitalization before the Start of Immunosuppressive Therapy.

Complete blood count		LDH	2,549 U/L	Rheumatoid factor	3 U/mL
WBC	2,300 /μL	γ-GTP	272 U/L	anti-CCP Ab	0.5 U/mL
Neutro	93.0 %	CK	113 U/L	MPO-ANCA	<1.0 U/mL
Lympho	3.5 %	TG	142 mg/dL	PR3-ANCA	<1.0 U/mL
Mono	3.0 %	T-Cho	93 mg/dL	anti-U1 RNP Ab	<2.0 U/mL
Baso	0.5 %	HDL-Cho	23 mg/dL	**Infection**	
Eosino	0.0 %	BUN	5.5 mg/dL	HBs Ag	negative
RBC	365.0 ×10⁴/μL	Cre	0.61 mg/dL	HBs Ab	negative
Hb	11.0 g/dL	Na	130 mEq/L	HBc Ab	negative
HCT	31.1 %	K	4.1 mEq/L	HCV Ab	negative
MCV	85.2 Fl	glucose	84 mg/dL	Cytomegalovirus antigenemia	negative
PLT	7.9 ×10⁴/μL	HbA1c	5.5 %	EBVCA IgG	positive
Coagulation		Ferritin	20,811 ng/mL	EBVCA IgM	negative
PT-INR	1.09	sIL-2R	5,421 U/mL	Parvo B19 IgM	negative
APTT	40.9 sec	CRP	6.11 mg/dL	T-spot	negative
Fibrinogen	194 mg/dL			β-glucan	15.0 pg/mL
D-dimer	6.28 μg/mL	Erythrocyte sedimentation ratio		Procalcitonin	1.99 ng/mL
FDP	16.6 μg/mL		18 mm/h	Blood culture	negative
AT-3	98 %	**Immunology**		Urine culture	negative
Biochemistry		IgG	1,162 mg/dL	**Urine**	
TP	5.3 g/dL	IgA	228 mg/dL	pH	6.5
ALB	2.5 g/dL	IgM	266 mg/dL	Occult blood	negative
T-Bil	2.15 mg/dL	C3	77 mg/dL	Protein	negative
D-Bil	1.56 mg/dL	C4	33.5 mg/dL	Cast	negative
AST	763 U/L	anti-nuclear Ab	<1:40	WBC	negative
ALT	469 U/L	anti-ds-DNA Ab	1.99 U/mL		
ALP	1,586 U/L	anti-Smith Ab	<1.0 U/mL		

Neutro: neutrophil, Lympho: lymphocyte, Mono: monocyte, Baso: basophil, Eosino: eosinophil, RBC: red blood cell, HCT: hematocrit, MCV: mean cell volume, PLT: platelet, PT-INR: prothrombin-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin degradation product, AT-3: antithrombin 3, TP: total protein, ALB: albumin, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate transaminase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, CK: creatine kinase, TG: triglyceride, T-Cho: total cholesterol, HDL-Cho: high-density lipoprotein cholesterol, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, sIL-2R: soluble interleukin-2 receptor, CRP: C-reactive protein, anti-CCP Ab: anti-cyclic citrullinated peptides antibodies, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase3 anti-neutrophil cytoplasmic antibody, anti U1-RNP Ab: anti U1-ribonucleoprotein antibody, HCV: hepatitis C virus, EBV: Epstein-Barr virus

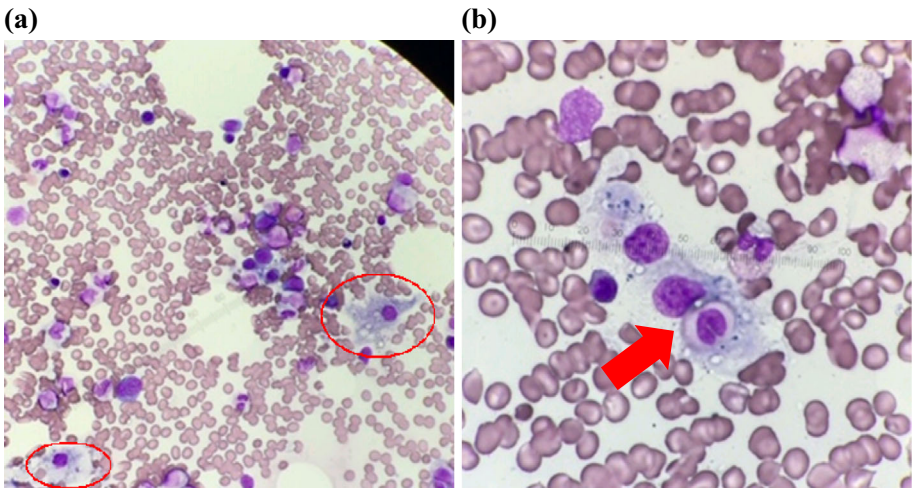

Figure 2. Histopathological findings of a bone marrow biopsy sample. (a) Hematopoiesis in the bone marrow is preserved. Histiocytes are shown (red circles) (magnification: 400×). (b) Activated macrophages exhibiting phagocytosis (red arrow) (magnification: 1,000×).

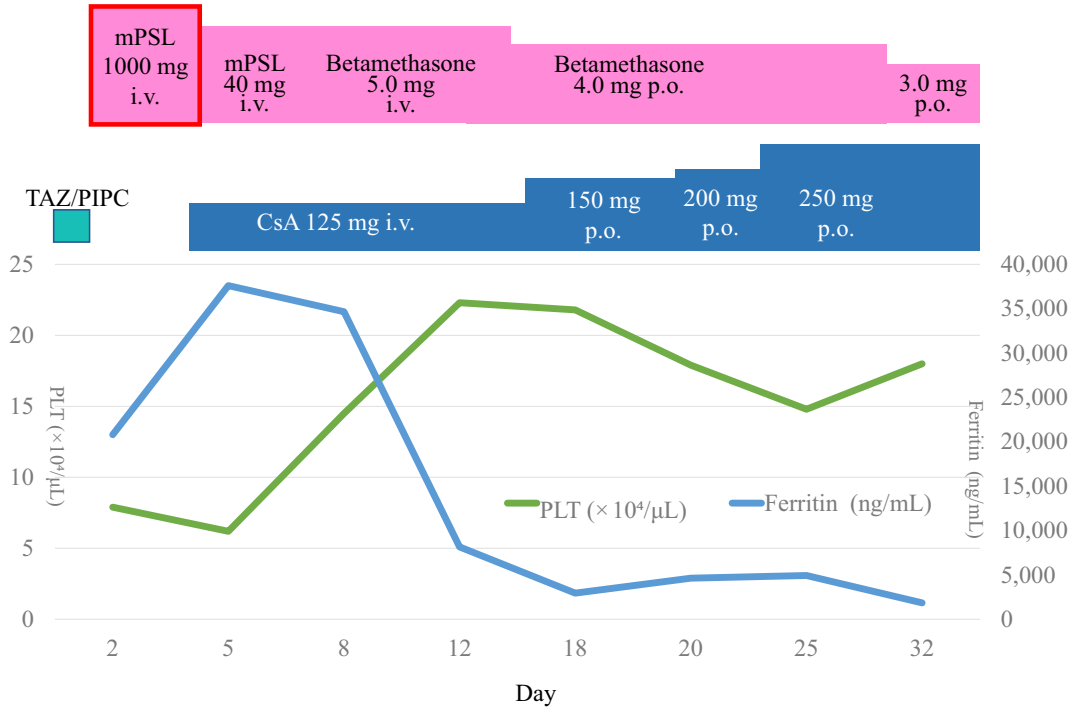

Figure 3. Clinical course of the patient. CsA: cyclosporine A, i.v.: intravenous, mPSL: methylprednisolone, PLT: platelet count, p.o.: per os, TAZ/PIPC: tazobactam/piperacillin

severe thrombocytopenia associated with MAS/HLH, the patient was not considered to be a good candidate for invasive procedures such as cholecystectomy and percutaneous transhepatic gallbladder drainage for AAC, and therefore immunosuppressive therapy for AOSD was prioritized. Glucocorticoid pulse therapy with methylprednisolone (1 g/day) on days 2-4 of hospitalization was initiated for AOSD with a high disease activity, AAC, and MAS/HLH. After the initiation of glucocorticoid pulse therapy, the platelet count continued to decrease and the serum ferritin level tended to increase; therefore, the glucocorticoid therapy alone was considered to be insufficient for controlling the disease activity. After obtaining approval from the institutional ethics committee and informed consent from the patient, 125 mg continuous intravenous CsA was initiated on day four (Fig. 3). With the combination of glucocorticoids and intravenous CsA, the disease activity improved. Therefore, the glucocorticoid dose was reduced on day 15 with a switch to 4.0 mg/day oral betamethasone; the patient was also switched to 150 mg oral CsA the same day. Betamethasone was reduced from 4.0 to 3.0 mg on day 30. There was no recurrence of the disease activity after the initiation of the glucocorticoid taper, and abdominal ultrasound on day 26 showed an improvement in the gallbladder enlargement and gallbladder wall thickening observed at the time of admission (Fig. 1e). Pancytopenia, hepatic dysfunction, and hyperferritinemia also improved (platelet count, $20.4\times10^4/\mu L$ on day 44; aspartate aminotransferase, 43 U/L on day 44; alanine aminotransferase, 32 U/L on day 44; ferritin, 20,811 and 185 ng/mL on days 2 and 43, respectively), and she was discharged on day 47.

Discussion

The risk factors for AAC, which accounts for 5-15% of all acute cholecystitis cases, include surgery, trauma, prolonged intensive care unit stay, infection, burn, intravenous feeding, vasculitis, and collagen diseases such as SLE (4, 8-11). Bile stasis, ischemia, and infection have also been suggested to be involved in the pathogenesis of AAC (12, 13). The present patient neither had these typical risk factors for AAC nor any severe thrombogenic tendency that could cause organ ischemia. Moreover, there were no findings (anti-neutrophil cytoplasmic antibody positivity, rapidly progressive glomerulonephritis, interstitial lung disease, multiple mononeuropathy, etc.) that would lead to a suspicion of vasculitis, which led us to consider the possibility of AAC associated with AOSD. The present patient had hepatic dysfunction with aspartate aminotransferase elevation as well as the elevated levels of total bilirubin and and biliary enzymes including alkaline phosphatase and gamma-glutamyl transferase. Although cholecystectomy and liver biopsy were not performed and there was no histopathological examination, the recurrence of AOSD and hepatocellular damage caused by MAS/HLH might have had an adverse effect in the biliary system, resulting in secondary biliary stasis and AAC. Serositis has been proposed to be associated with the pathogenesis of AAC in patients with SLE complicated by AAC (5). Albeit less frequent, AOSD has been reported to be associated with serositis such as pleurisy and pericarditis (14, 15). In the present case, there were no signs of advanced ascites or extensive peritoneal irritation.

Table 2. Case Summaries of AAC Associated with AOSD.

	Age	Sex	Abdominal findings other than AAC	HPS/HLH	DIC	Antibiotics	Treatment
Present case	21	Female	Hepatosplenomegaly	+	-	TAZ/PIPC	High-dose glucocorticoids, CsA
(3)	49	Female	Hepatosplenomegaly Serositis (a small amount of right pleural effusion and ascites) Enterocolitis	+	+	CTRX	High-dose glucocorticoids, CsA, IVIG
(4)	28	Female	Peritonitis	Unknown	+	MNZ, MEPM, CPFX	Prednisone, naproxen, cholecystectomy

DIC: disseminated intravascular coagulation, TAZ/PIPC: tazobactam/piperacillin, CTRX: ceftriaxone, MNZ: metronidazole, MEPM: meropenem, CPFX: ciprofloxacin, IVIG: intravenous immunoglobulin

Although extensive peritonitis was unlikely, the present patient might have had AAC as a result of localized serositis in the gallbladder associated with a severe systemic inflammatory response. AAC complicated with AOSD is relatively rare and it has also been less frequently reported. One possible explanation for the paucity of studies is that some cases of AAC complicated with AOSD may be asymptomatic. Although the background disease is different, asymptomatic AAC cases have been reported (5, 16, 17). A certain number of cases of AAC associated with autoimmune diseases may be asymptomatic because high-dose glucocorticoid treatment may be initiated before performing imaging studies, such as abdominal ultrasonography and computed tomography. Therefore, AAC may remain asymptomatic and improve with immunosupressive treatment. Previously reported cases of AAC associated with AOSD are summarized in Table 2 (3, 4). All patients, including the present patient, were female, with relapsing or recurrent cases of AOSD with high disease activity, complicated with HPS or DIC. The results of infectious disease examinations, such as blood culture, were negative, and antibiotic treatment did not improve the disease condition. The findings in the previous two cases-suggested complications of serositis (peritonitis). Therefore, serositis may have been involved in the development of AAC. In terms of treatment, cholecystectomy was performed in one patient, but all patients showed an improvement with immunosuppressive therapy, including steroids. In the case reported by Vallianou et al., cholecystectomy was performed (4). However, after cholecystectomy, the patient presented with high fever associated with increased disease activity of AOSD and was eventually treated with steroids and naproxen, which improved the patient's condition. Since cholecystectomy did not improve the disease activity, Vallianou et al. suggested that immunosuppressive therapy, including steroids, may be more beneficial than surgical treatment for AAC complicated with AOSD. Similar to calculous cholecystitis, the treatment of AAC is often surgical, including cholecystectomy; however, conservative treatment may be an alternative approach in high-risk cases. In the 2018 Tokyo guidelines for the management of acute cholecystitis, patients with a Charlson comorbidity index score of ≤5 and an American Society of Anesthesiologists-Physical Status score of ≤2 are considered to be in a sufficently good general condition to safely undergo surgery (18). The present patient had a Charlson comorbidity index score of 1, but surgery was not recommended as she was in American Society of Anesthesiologists-Physical Status class IV. In addition, because of the severe thrombocytopenia caused by MAS/HLH associated with AOSD, invasive treatment approaches such as surgical cholecystectomy and percutaneous transhepatic gallbladder drainage were considered to be risky and conservative treatment was therefore prioritized. Although the patient's general condition was poor, she did not harbor any risk factors for AAC and the disease activity was very high based on the presence of MAS/HLH. In the present case, the early clinical diagnosis of AOSD-related AAC led to the prompt initiation of immunosuppressive therapy, which might have been a factor in the favorable outcome in the current case.

The treatment with glucocorticoids and CsA resulted in an improvement in both MAS/HLH and AAC, suggesting that AAC might be caused by a common pathophysiology shared with AOSD-related MAS/HLH. Because the patient was refractory to glucocorticoids, we initiated concomitant treatment with CsA. CsA inhibits the production of cytokines such as IL-2, IL-5, IL-6, interferon-γ, and tumor necrosis factor-α, thereby inhibiting lymphocyte proliferation and differentiation (19, 20). Park et al. reported the successful treatment of refractory AOSD complicated by MAS/HLH, desseminated intravascular coagulation, and AAC with glucocorticoids or oral CsA (3); therefore, CsA was chosen as a concomitant immunosuppressive agent in the present case. In a study by Park et al., glucocorticoids and CsA were started simultaneously, and improvement was achieved. Although it is unknown whether glucocorticoids alone are sufficient, the concomitant use of glucocorticoids and CsA is recommended to achieve an early therapeutic effect in severe cases of AOSD, such as those complicated with MAS and/or DIC. Although CsA was administered orally in the previous report, intravenous CsA administration was chosen in the present case to achieve a rapid effect and improve fever and laboratory abnormalities within 12-24 hours after treatment initiation (21). Intravenous CsA might be a useful immunosuppressant to achieve a rapid effect in AOSD with fatal or-

gan complications such as MAS/HLH or AAC, for which immediate treatment is essential.

Tocilizumab has been reported to be effective for the treatment of AOSD (22). In the present case, tocilizumab was also considered prior to the administration of CsA. AAC is a rapidly worsening condition with a high risk of gallbladder perforation and secondary infection (23). In the present case, surgery remained a potential treatment direction due to the possibility of gallbladder perforation as a complication. In general, biologics are often discontinued for several weeks during the perioperative period due to the risk of infection. Tocilizumab was not initiated in the present case and treatment including immunosuppressive agents with a short half-life was desired because of the potential for surgery in the near future. In addition, cytopenia is a relatively common adverse event associated with tocilizumab and the patient had severe thrombocytopenia, which would be difficult to treat if it persisted or worsened after the introduction of tocilizumab (24). In the present case, the treatment with CsA was successful without any significant adverse events. However, CsA has been reported to cause drug-induced thrombotic microangiopathy (TMA) as a serious adverse event (25). While CsA is expected to have an immediate effect in patients with MAS/HLH and severe thrombocytopenia, CsA can cause TMA with severe thrombocytopenia and critical organ damage such as renal impairment as an adverse event. Therefore, CsA should be used with care and should be promptly discontinued if TMA is suspected for reconsideration of the treatment strategy.

Conclusion

AAC complicated by AOSD reccurence or exacerbated disease activity requires careful consideration when making a diagnosis, as it may be a manifestation of AOSD-related organ dysfunction. Immunosuppressive therapy with glucocorticoids or CsA might be a useful therapeutic option for AAC complicated by increased disease activity in patients with refractory AOSD.

For this case report, informed consent was obtained in writing from the patient.

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

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