

Adult-onset Still's disease evolving with multiple organ failure and death: A case report and review of the literature

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Abstract

BACKGROUND

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease, which is characterized by daily fever and arthritis, with an evanescent rash and neutrophilic leukocytosis. To date, there has been no definite laboratory or imaging test available for diagnosing AOSD; the diagnosis is one of exclusion, which can be very challenging. In particular, AOSD patients may experience different complications affecting their clinical picture, management, and prognosis. The treatment of AOSD remains largely empirical and involves therapeutic agents.

CASE SUMMARY

We report the case of a 36-year-old woman who presented with fever, red rash, arthralgia, and sore throat. Her serum ferritin level and white blood cell count were markedly elevated, and the first diagnosis 22 years prior was "juvenile rheumatoid arthritis of systemic type". The patient was treated with prednisone, sulfasalazine, methotrexate, and leflunomide. After remission of her symptoms, the patient stopped taking the medications, and the disease recurred. Ultimately, the patient was diagnosed with adult-onset Still's disease. Relapse occurred several times due to self-medication withdrawal, and an interleukin-6 antagonist (tocilizumab/Actemra) was administered to control the disease. Recently, she was hospitalized because an incision did not heal, and the patient suddenly developed high fever and diarrhea during hospitalization. The patient's disease progressed

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violently and quickly developed into macrophage activation syndrome, disseminated intravascular coagulation, shock, and multiple organ failure. The patient had sudden cardiac arrest, and she died despite emergency rescue efforts.

CONCLUSION

AOSD patients need regular follow-up in the long-term treatment process, and must press formulary standard medication, and do not voluntarily withdraw or reduce the dose. Otherwise it may cause disease back-and-forth or serious life-threatening complications. Meanwhile, strict management of trauma, infections, tumors, and other diseases may contribute to improved outcomes in patients with complications.

Key Words: Adult-onset Still's disease; Macrophage activation syndrome; Disseminated intravascular coagulopathy; Multiple organ failure; Death; Case report

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Core Tip: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease, and the lack of disease-specific symptoms and laboratory markers hinders the diagnosis and assessment of its progression. More importantly, the treatment of AOSD remains largely empirical, with a lack of controlled clinical trials. Few cases of the disease with multiple complications have been reported. The present case highlights the characteristics of AOSD and severe complications and shares our experience in its diagnosis and treatment to provide experience for the effective recognition and treatment of this disease. The authors also note the link between the biopsychosocial model and autoimmune diseases.

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INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease, which is characterized by fever, arthritis, an evanescent rash, and neutrophilic leukocytosis. Other nonspecific symptoms may be observed in AOSD, such as sore throat, cardiopulmonary features, kidney disease, and neurological manifestations^[1,2]. AOSD was definitively described in 1971 by Eric Bywaters, who named the disease on account of its close resemblance to the pediatric syndrome systemic-onset juvenile idiopathic arthritis (SoJIA), which was formerly called "Still's disease" for the reason that it was described by Dr George Still in 1897^[3,4]. The etiology is unknown, and both infectious triggers and genetic factors have been suggested, but there is no clear evidence of an infectious etiology^[5].

Available epidemiologic results show that the incidence of AOSD ranges between 0.16 and 0.4/100000 people, with an estimated prevalence rate between 1 and 34 cases/1 million people^[2,6,7]. Based on some reports, females seem to be more affected than males; however, AOSD is considered to be evenly distributed between the sexes. AOSD usually afflicts young people, with a bimodal peak at ages 15-25 and 36-46 years^[2,8]. Diagnosis is based on clinical grounds, following the exclusion of mimickers of autoimmune, infectious, and neoplastic disorders, with the additional consideration of nonspecific laboratory abnormalities such as elevation of serum ferritin (SF), peripheral leukocytosis, and other acute-phase reactants^[9]. In general, the absence of disease-specific symptoms and laboratory markers hinders its diagnosis, and the lack of established disease activity markers makes the determination of treatment efficacy problematic. More importantly, AOSD-related complications are significantly associated with mortality. These patients may also experience different complications that affect their clinical symptoms, management, and prognosis. Moreover, clinical

progression is also unpredictable, with 60%-70% of those patients developing a chronic form of the disease^[2].

CASE PRESENTATION

Chief complaints

A 36-year-old woman presented to the Outpatient Department of our hospital complaining of poor wound healing of an incision in her right hip and AOSD.

History of present illness

She had developed steroid-induced femoral head osteonecrosis caused by long-term prednisone therapy for AOSD, and the incision had not healed by 2 mo after bilateral prosthetic replacement. She was hospitalized for treatment in a stable condition. During hospitalization, the patient suddenly developed high fever and diarrhea, with the highest temperature reaching 38.2 °C, accompanied by nausea, vomiting, poor appetite, and mild dehydration. The patient was transferred to the intensive care unit (ICU) after refusing fluid rehydration therapy with deep-vein puncture. After further inquiry about the patient's history, her husband said that her AOSD was greatly affected by her mood, and the patient had a high fever of 41 °C lasting for 1 mo due to depression". The next day, her condition suddenly deteriorated, blood pressure decreased, and her dyspnea, oliguria, and disease rapidly worsened.

History of past illness

Twenty-two years prior (at 14 years old, 1998), fever occurred due to overflight, with the highest body temperature reaching 40 °C; her body temperature often increased in the morning. This was accompanied by a red rash on her back, sore throat, migratory swelling, and pain of multiple joints and muscle in the whole body, mainly affecting the proximal interphalangeal joint of both hands, metacarpophalangeal joint, double wrist joint, double elbow joint, and bilateral temporomandibular joint. Her symptoms associated with morning stiffness eased slightly after 1 h of activity. Test results showed that SF was increased and white blood cells (WBCs) obviously increased. The first diagnosis was "juvenile rheumatoid arthritis of systemic type", and the patient was treated with prednisone up to 30 mg/d, sulfasalazine, methotrexate, and leflunomide. After her symptoms improved, the patient stopped taking the medicines. The disease then recurred, and she was diagnosed with "AOSD" and was treated with prednisone at a dose up to 60 mg (1 mg/kg), methotrexate, and traditional Chinese medicine, resulting in short-term improvement of symptoms. In 2002, bilateral alternating hip pain began to appear. After that, movement of both hip joints and knee joints was limited, with overflexion of the proximal interphalangeal joints of fingers and feet. In 2015, X-ray of her hands was performed, showing a narrow joint space of the hands and wrists. X-ray of the hip joint revealed a flattened femoral head on both sides, with multiple transparent shadows and hyperosteoecy and sclerosis, and the acetabular bone on both sides was obviously thinner; some bones were discontinuous, with hyperosteoecy and cystic shadow, and the joint space of both hips became obviously narrow. During this period, the disease recurred many times, and the patient took oral prednisone, lothorofan, and leflumide intermittently. Methotrexate, iguratimod, and Tripterygium wilfordii were discontinued due to adverse effects. In April 2016, the patient began treatment with etanercept. After that, due to frequent recurrence of the disease, the patient began to receive regular monthly intravenous administration of an interleukin (IL)-6 antagonist (Actemra) at 320 mg, and the dose of prednisone was reduced to 10 mg/d. In April 2020, she was hospitalized with the aggravation of pain in both hip joints and a limp. The test results showed that WBC count, C-reactive protein (CRP), and SF were normal. Bilateral femoral head necrosis was definitively diagnosed, and bilateral prosthetic replacement was performed. Two months after the surgery, the patient did withdrawal of Actemra and immunosuppressive agents on her own.

Physical examination

After her second day in the ICU, the patient's temperature was 36.5 °C, her heart rate was 96 bpm, her respiratory rate was 26 breaths per minute, her blood pressure was 80/41 mmHg, and her oxygen saturation in room air was 88%-96%. The patient was under some type of sedation but responded to painful stimuli. A 1 cm unhealed incision was seen on the right hip, with seepage of a reddish fluid. Other physical

examinations showed no abnormal signs.

Laboratory examinations

On the first day in the ICU, laboratory parameters showed abnormalities of routine blood examination, coagulation function, hepatic function, and serum electrolytes (Table 1, Day 1).

Imaging examinations

Abdominal B-ultrasonography revealed splenomegaly. X-ray of the hip joints showed that the shape and position of bilateral prosthesis were normal, and there were no signs of infection.

Further diagnostic work-up

Over the next 3 d in the ICU, the laboratory parameters of routine blood examination, coagulation function, hepatic function, and serum electrolyte deteriorated further (Table 1, Day 2, 3 and 4).

The level of SF was more than 10000 ng/mL (normal range: 13-150 ng/mL). The level of general cortisol was more than 1649.9 mmol/L (101.2-535.7 mmol/L), and that of adrenocorticotrophic hormone was less than 1.54 mL/L (7.2-63.6 mL/L). Serum κ and λ light chain levels were 60.9 mg/L (6.7-22.4 mg/L) and 1.62 (0.31-1.56 mg/L), respectively, and the ratio of κ/λ was 1.62 (0.31-1.56). Other immunological tests were almost within the normal range, including anti-phospholipid antibodies, immunoglobulin, complement, rheumatoid factor (RF), antistreptolysin O test, anti-CCP antibody, autoimmune antibody tests, and Coombs test (MGCT). No bacteria or fungi were found in blood culture, sputum culture, or secretions of surgical wound. Routine urine tests indicated urine protein 2+, occult blood 2+, and WBCs 188.5 mL/L, with no other abnormality found. Fecal flora analysis indicated 100% *Enterobacter spp.* The examination of lymphocyte subpopulations and cytokines was ongoing.

MULTIDISCIPLINARY EXPERT CONSULTATION

Given the multiple organ involvement and high SF and WBC levels, and the patient's history of stopping Actemra and immunosuppressive agents on her own for 2 mo, the diagnosis of active AOSD was confirmed by multidisciplinary expert consultation. It was discussed whether the diarrhea was a second hit. Diarrhea may trigger a pathologic process in genetically susceptible patients, finally leading to an uncontrollable increase in proinflammatory cytokines, with a severe systemic inflammatory reaction, which is responsible for AOSD development. It was agreed that the large dose of cortisol impulse therapy up to 200 mg per day was a reasonable treatment and that immunomodulatory and inflammatory suppression should be continued. Hemodialysis should also be performed to remove metabolic wastes and inflammatory factors from the blood. Furthermore, the examination of lymphocyte subpopulations and cytokines should be carried out to detect disease activity. If necessary, the patient should undergo bone marrow biopsy, flow cytometry, and chromosome testing. Treatment with cortisol at a dose of 200 mg/d was recommended, and hemodialysis was performed. In the case of nonresponse, it was decided to consider treatment with Actemra and cyclosporine.

FINAL DIAGNOSIS

The final diagnoses of the presented case were shock, multiple organ dysfunction syndrome (acute heart failure, acute liver failure, acute respiratory dysfunction, and abnormal coagulation function), AOSD, acute gastroenteritis, postoperative nonunion of the right hip, electrolyte disorder, anemia, and hypoproteinemia.

TREATMENT

After comprehensive treatment, such as anti-shock, blood transfusion, auxiliary ventilation, plasma exchange, and cortisol impulse treatment, the patient's body temperature returned to normal, but her diarrhea was not relieved.

Table 1 Main laboratory findings (Day 1 to Day 4)

Main laboratory finding	Value				Normal range
	Day 1	Day 2	Day 3	Day 4	
White blood cell count	5.0	5.6	20.5	28.3	(3.5-9.5) × 10 ⁹ /L
Lymphocyte percentage	6.6	10.1	8.9	15.6	20%-50%
Neutrophil percentage	90	86.7	90.1	81	40%-75%
Hemoglobin	80	99	112	98	(115-150) g/L
Platelets	30	32	52	35	(125-350) × 10 ⁹ /L
Prothrombin time	18.1	18.8	18.2	16.4	(9-14) s
International normalized ratio	1.6	1.68	1.62	1.42	
Prothrombin activity	54.9	51.8	54.2	63	%
Activated partial thromboplastin time standardization	61	55.3	54.1	56.8	(20-40) s
Thrombin time	39.7	37.1	50.6	Chyle blood, no test	(14-21) s
Fibrinogen	1.37	1.0	0.77	Chyle blood, no test	(2-4) g/L
D-Dimer		4.88		5.96	(0-0.5) µg/L
Fibrinogen degradation products		272.9		90.6	(0-5) µg/L
Erythrocyte sedimentation rate			10		(0-20) mm/L
C-reactive protein		121.01	111.7	104.2	(0-10) mg/L
Hemolytic index	15	15	60	55	0-15
Blood lipid index	2	2	2	225	0-2
Total protein	57.1	53.5	46.8	55.7	(65-85) g/L
Albumin	28.8	26.3	26.3	23.2	(40-55) g/L
Globin	28.3	27.3	26.2	24.4	(20-40) g/L
Total bilirubin	35.9	42.9	49.6	62.1	(0-21) µmol/L
Conjugated bilirubin	14.6	19.5	27.3	35.2	(0-5) µmol/L
Unconjugated hyperbilirubinemia	3.5	3.5	2.6	4.2	(0-19) µmol/L
Glutamic-pyruvic transaminase	84.9	90.9	139.8	153.8	(0-40) U/L
Aspartate aminotransferase	295	329	593	589	(0-40) U/L
Alkaline phosphatase	366	510	508	453	(38-126) U/L
γ-Glutamyl transpeptidase	118	161	185	183	(6-35) U/L
Cholinesterase	3584.3	3395.1	3476.1	4351.8	(4650-12220) U/L
Lactate dehydrogenase	5292	5616	9299	8746	(313-618) U/L
K ⁺	4.9	4.57	4.42	5.3	(3.6-5) mm/L
Na ⁺	127.8	128.9	142.6	146.2	(137-145) mm/L
Cl ⁻	102	103.9	111.8	106.7	(98-107) mm/L
Creatinine	288.1	299.2	298.8	311.5	(41-73) µmol/L
Carbamide	16.19	17.79	22.38	28.01	(2.6-7.5) mm/L
Uric acid	683	706.4	487.4	510.4	(155-357) µmol/L
Hypersensitive troponin	0.012	0.138	13	52	(0-0.034) ng/L
NT-ProBNP	4120	9910	35000	35000	(0-125) pg/L
Myoglobin		145.7		936.4	(0-110) ng/moL
Procalcitonin		10.479		24.025	(0-0.05) ng/mL

This table shows the main laboratory findings of the patient during the intensive care unit.

OUTCOME AND FOLLOW-UP

On the third day in the ICU, the patient's condition worsened; her blood pressure suddenly dropped to 50/30 mmHg, and she did not respond to increased epinephrine and dopamine doses or intravenous epinephrine. In the end, the patient had sudden cardiac arrest, and she died despite emergency rescue efforts.

DISCUSSION

AOSD is classified as a multigenic autoinflammatory disease because of its complex pathogenesis, involving both the innate and adaptive immune systems. It is generally considered that some unknown factors, playing as second hits, may startup a pathologic procedure in genetically susceptible patients, eventually leading to the activation of an aberrant inflammatory response, which leads to the development of AOSD. Although the pathogenesis is mostly unknown, the pivotal role of proinflammatory cytokines, including IL-1 β , IL-6, IL-8, IL-10, IL-17, IL-18, interferon- γ , tumor necrosis factor, and ferritin in developing the inflammatory vicious circle has been reported^[10-13]. There are six sets of criteria for the diagnosis of AOSD currently, and Yamaguchi's criteria are the most sensitive as well as the most widely used. The criteria include fever evanescent rash, arthralgia, and leukocytosis as major items and other nonspecific symptoms, such as sore throat, lymphadenopathy, splenomegaly, deterioration of liver function, negative rheumatoid factor, and antinuclear antibody as minor items; more than five items including at least two major criteria are necessary for the diagnosis and to exclude malignancy or infectious disease^[14].

AOSD typically manifests with a symptomatic triad characterized by fever (60%-100%), red rash (60%-80%), and arthralgia and arthritis (70%-100%) which may develop to destructive symmetric polyarthritis^[1]. In AOSD, fever always precedes other manifestations' onset, and the fever shows an abrupt onset usually, commonly once or twice the quotidian pattern, with the highest temperature detected in the early evening or late afternoon. The temperature may sometimes return to a normal value without any antipyretic treatment. The rash is usually observed on the proximal trunk and limbs, appearing during the febrile attacks, and its typically histopathology shows a mixed inflammatory infiltrate, surrounding the perivascular areas without epidermal changes. Joint disease is also a common sign. Arthritis and arthralgia mostly affect knees, wrists, and ankles. Some patients may gradually develop chronic destructive symmetrical polyarthritis and ankylosis in subsequent years. Laboratory test of joint fluid may show an inflammatory fluid with neutrophil predominance. Other nonspecific symptoms may be found in AOSD, such as sore throat, cardiopulmonary features, kidney disease, neurological manifestations, enlargement of cervical lymph nodes (LNs), splenomegaly, hepatomegaly, liver dysfunction, and increased hepatic enzymes^[15].

Laboratory tests commonly show increased SF, CRP, and erythrocyte sedimentation rate (ESR), neutrophilic leukocytosis, anemia, and thrombocytopenia. The levels of SF are higher than those observed in other autoimmune, infectious, inflammatory, or neoplastic diseases. It has been reported that SF is an acute-phase protein released from impaired hepatocytes; the levels may be elevated in inflammatory disorders, alcohol abuse, liver disease, infectious diseases such as HIV infection, or malignancy^[16]. Eighty percent of AOSD patients were reported to have increased ferritin levels, 70% of which were more than five times the normal upper limit^[17]. The median level of SF in AOSD patients is reportedly 4752 ng/mL. A SF level higher than 10000 ng/mL can be a specific marker for AOSD if there is no severe liver dysfunction or history of multiple blood transfusions, but the SF level itself is only a nonspecific marker for inflammation^[18-20]. Due to its low specificity, elevated SF is not included in this disease's diagnostic criteria, but we consider that this association is worth highlighting, given that younger age and the nonspecific nature of most presentations often lead to delayed diagnosis^[21-23]. It has been reported that proinflammatory cytokine levels are significantly increased in both the pathological tissues and sera of patients with active or untreated AOSD, and that ferritin synthesis is regulated by proinflammatory cytokines at various levels during cellular differentiation, proliferation, and inflammation. Cytokines may also have an effect on ferritin

translation indirectly by their ability to increase inducible nitric oxide synthase (iNOS) and hence increase the levels of NO. NO in turn induces ferritin expression. These reports suggest that the level of ferritin might be a good biomarker to monitor the disease activity of AOSD^[10,24]. Furthermore, thrombocytopenia and leukocytosis are reportedly promoted along with rises in SF levels, which is associated with AOSD's disease activity strongly and may also be a biomarker of AOSD^[25,26]. Some studies have confirmed that SF and heme oxygenase 1 can serve as highly sensitive and specific biomarkers for AOSD^[27].

AOSD patients may experience different complications affecting their clinical manifestations, management, and prognosis. The major cause of death is infection, followed by severe complications. Important systemic complications of AOSD reported until now include macrophage activation syndrome (MAS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulopathy (DIC), thrombotic microangiopathy, diffuse alveolar hemorrhage, respiratory distress syndrome, pulmonary arterial hypertension, shock, multiple organ failure, myocarditis, tamponade, constrictive endocarditis, pericarditis, fulminant hepatitis, and amyloidosis^[9,15,28].

MAS or reactive hemophagocytic syndrome (HPS) is a potentially life-threatening complication characterized by excessive macrophage activity and cytokine production leading to multiple organ failure^[29,30]. Primary MAS commonly occurs in children with MAS-associated genetic defects or a family history of MAS, while secondary MAS occurs after exposure to immunological trigger factors of underlying autoimmune diseases, infections, malignancies, or flares of AOSD^[31]. It is reported that the incidence of MAS is up to 15% among those AOSD patients and it is considered the most severe complication, with a high mortality rate ranging from 10% to 41%^[9,32]. The criteria for diagnosing MAS according to the 2004 guidelines are as follows: (1) Fever > 38.5 °C or lasting more than 7 d; (2) Cytopenia affecting at least two of three lineages in the peripheral blood (Hb < 90 g/L, absolute neutrophil count < 1.0 × 10⁹/L, platelet < 100 × 10⁹/L); (3) Splenomegaly; (4) Hypofibrinogenemia or hypertriglyceridemia; (5) Hyperferritinemia (SF ≥ 500 µg/L); (6) Hemophagocytosis in bone marrow, lymph nodes, or the spleen; (7) High levels of sIL-2r (s-CD25 ≥ 500 µg/L); and (8) Low or absent NK-cell activity. MAS can be diagnosed if five of the eight criteria are fulfilled^[33]. However, the diagnosis of MAS is often delayed due to possible differential diagnoses. These include conditions that can present with similar clinical manifestations and laboratory abnormalities, such as systemic inflammatory response syndromes or sepsis. However, the level of SF is usually obviously higher in MAS patients and considered a highly characteristic feature of MAS by most scholars^[34]. Bone marrow aspiration is considered the gold standard and is usually required in some untypical cases where there may be a diagnostic dilemma. In the present case, the patient presented a high fever with a body temperature of 38.3 °C, splenomegaly, hemopenia, hypertriglyceride, hypofibrinemia, and SF greater than 10000 µg/L. Inflammatory factors and bone marrow puncture were not examined, and the patient died. Although her body temperature did not meet the diagnostic criteria, the continued increase in SF and hypofibrinogenemia reflected worsening of the disease.

DIC is also a lethal complication characterized by uninhibited activation of the coagulation system. Some reports suggest that its diagnosis can be challenging, even for some experienced clinicians^[35]. A precipitous decrease in ESR in the context of persistent hyperferritinemia and worsening clinical condition may be a danger sign and raise the index of suspicion for the presence of DIC. Some specialists have suggested that anakinra may be recommended for patients with severe flares of AOSD and DIC^[36,37].

The treatment of AOSD remains largely empirical, and therapeutic agents for AOSD include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate, and biological disease-modifying anti-rheumatic drugs (bDMARDs). Some studies have shown that NSAIDs may fail to control the symptoms of AOSD, and a large percentage of patients may afflict drug adverse reactions. According to some reports, only 15%-20% of AOSD patients respond to NSAIDs treatment, and a corticosteroid is required to control disease manifestations in most cases. Corticosteroids have been suggested as the first-line treatment for AOSD, producing a clinical response in approximately 60% of cases. Corticosteroids should be started at a dosage of 0.51 mg/kg per day, but intravenous high-dose corticosteroids may be considered if MAS and/or severe visceral involvement occur. Some cases may relapse over chronic treatment or tapering of the corticosteroid dosage^[38]. High-dose corticosteroids seem to be more efficient in controlling those disease, but the maintenance of long-term corticosteroids can induce many potential adverse reactions^[15,39]. In the present case,

the patient developed femoral head necrosis due to long-term glucocorticoid use, and she experienced relapse due to repeated spontaneous reduction or withdrawal of the drug. Cyclosporine and methotrexate (MTX) are the most frequently administered sDMARDs in AOSD, mainly owing to their steroid-sparing effects. Other agents, such as azathioprine, leflunomide, cyclophosphamide, tacrolimus, hydroxychloroquine sulfate, and intravenous immunoglobulin, have also been widely applied, producing various response rates. In a study, after adding MTX, 70% of patients achieved complete remission, and 39% of patients discontinued corticosteroids. Thus, csDMARDs have been used to prevent AOSD relapse and allow for reduction of the corticosteroid dosage simultaneously^[39-41]. Some researchers also have found that cyclosporine can be used in patients with severe MAS as well as AOSD^[42,43]. Biologic agents or biologic DMARDs (bDMARDs) targeting specific cytokines are suggested for the treatment of those cases that are refractory to csDMARDs and corticosteroids. Some studies have revealed a key role of proinflammatory cytokines such as IL-1, IL-6, IL-8, IL-18 and tumor necrosis factor- α (TNF- α) in disease pathogenesis, promoting the development of novel targeted therapies aimed at the optimum method of disease control^[44]. It has been reported that bDMARDs are an important option for relapsed patients or as a first-line regimen, which may help to reduce the dosage in terms of glucocorticoid and other cDMARD exposure^[45,46]. Some researchers have shown that most patients (84.4%) are able to achieve clinical remission initially by using bDMARDs^[47]. It has also been reported that a case of glucocorticoid and cyclosporine refractory AOSD complicated by DIC was successfully managed with a humanized anti-IL-6 receptor monoclonal antibody. IL-6 inhibition can lead to a rapid response, symptomatic improvement, and corticosteroid sparing^[48]. Wang *et al.*^[49] have found that anti-IL-6 antibody combined with MTX have significant therapeutic effects for refractory AOSD, is conducive to the reduction and discontinuation of prednisone, and may allow stabilization of the patient's condition after reducing the dosage of anti-IL-6 antibody, with good safety.

In this case, the patient experienced relapse of the disease due to voluntary drug withdrawal or dosage reduction several times, and her WBC and SF levels were significantly increased. Because of the frequent recurrence of the disease, the patient received anti-IL-6 antibody, and the frequency of disease recurrence was significantly reduced; glucocorticoid dosage was also reduced. The recurrence of her disease was caused by the spontaneous cessation of Actemra and leflunomide at 2 mo after surgery. Diarrhea was the main factor that caused the rapid progression of the disease. The most frequently implicated triggering factors include infections, medications, and disease flares^[50]. This may induce T cell activation and proliferation with cytokine secretion (interferon-gamma and granulocyte macrophage colony-stimulating factor) and macrophage hyperactivation. The final result is an uncontrollable increase in IL-1, TNF α , and IL-6 production, with a severe systemic inflammatory reaction^[51]. Rituximab may suppress the triggering factor effectively, but the severe AOSD flare and subsequent cytokine release required more T-cell-specific immunosuppression (*i.e.*, cyclosporine) for effective control^[52]. Furthermore, the diarrhea resulted in a large amount of fluid loss, electrolyte disturbance, and malnutrition, which aggravated the development of the disease and eventually resulted in DIC and MODS. The mortality rate of MODS patients with two-organ failure is 50%-60%, and the mortality rate of MODS patients with failure of more than four organs is 100%. In addition, a large prospective study identified an increased risk of death in patients with continued platelet depletion and poor response to treatment^[53]. Our patient simultaneously developed five-organ failure, and glucocorticoid shock therapy and blood purification failed; the disease progressed violently, and the patient died before the use of cyclosporine and Actemra. In particular, attention should be paid to the signature value of the biopsychosocial model in the process of patient management, which may have great potential value, and mental health may be related to the occurrence, progression, and prognosis of the disease. The patient experienced a high fever lasting 1 mo due to bad mood. Some scholars have found the levels of ESR, CRP, and PLT in patients with rheumatoid arthritis combined with depression to be significantly higher than those in patients with no depression. Psychological intervention for rheumatoid arthritis with depression has obvious effects in improving patients' treatment compliance, as well as improving their primary symptoms and depressive state^[54]. Several cross-sectional studies have revealed that those exhibiting depressive manifestations have increased levels of IL-1, IL-6, IL-2, TNF- α , and CRP, which are associated with depression in patients being treated for clinical depression^[55,56]. Figueiredo-Braga *et al.* reported that anxiety and depression in lupus are influenced by a complicated mix of biological, social, and psychological factors. Their study also found that IL-6 and IL-10 correlated with increased Hospital Anxiety and Depression

Scale (HADS) depression scores in depressed patients. IL-10 is responsible for helping drive the Th2-mediated response that results in increased B cell activation, immunoglobulin G class switching, and increased antibody production. It is also strongly associated with disease activity in patients with systemic lupus erythematosus (SLE)^[57]. Overall, the relationship between AOSD and psychology remains to be further studied.

CONCLUSION

AOSD is an exclusionary diagnosis that can be very challenging. It requires an extensive workup and multidisciplinary evaluation. Despite access to many imaging technologies and medical tests, a detailed history and good physical examination are still two powerful tools that can guide an accurate diagnosis. Importantly, more clinical studies will be useful to increase our knowledge about AOSD and complications and offer tailoring for more effective therapies. The biopsychosocial model has great potential value and should also be taken seriously.

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