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Case Report

Clinical manifestation, pathologic findings and genotyping of adult-onset Still's disease: report of a fatal case

Lin Zhang, Wenhe Li, Yue Liang, Fang Tong, Hongmei Dong, Yiwu Zhou

Department of Forensic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, PR China

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Abstract: Adult-onset Still's disease (AOSD) is a rare kind of autoimmune diseases (AID). Since firstly reported in 1887, it has been widely concerned in clinics on account of its difficult diagnosis and fatal complications. However, there are no systematically autopsy literatures except a few reports of tissue biopsies. Here we report a 39-year-old woman who was repeatedly attacked by skin rashes, high fever and painful joints after a loop electrosurgical excision procedure (LEEP), and finally died of cardiac arrhythmias. Scarlet spots and erythema can be seen on her head, face, chest and abdomen. Microscopically, lymphocytes were perivascularly infiltrated in subcutaneous tissues. Severe edema, fibrinous exudate, inflammatory infiltration and focal hemorrhages were evident in multiple organs, particularly in sinuatrial node and pulmonary alveoli. Immunoprofile reflected high expression of CD68 and positive for CD3 and CD20, but negative for CD1α and IgG4. Genotype of HLA were HLA-A*0207/HLA-A*1101, HLA-B*1502/HLA-B*4601, HLA-C*0102/HLA-C*0801, HLA-DRB1*0803/HLA-DRB1*1501 and HLA-DQB1*0601. Histopathologic and laboratory examination demonstrated the woman once suffered and died from AOSD.

Keywords: Adult-onset Still's disease, autoimmune disease, monocyte-macrophage activation, fatal complications

Introduction

Adult onset Still's disease (AOSD) is a rare type of chronic autoimmune disease (AID) with multi-organs involvement that revolves around the monocyte-macrophage activation [1]. The clinical manifestations mainly include the evanescent eruption, spiking fever, arthritis, sore throat, lymphadenopathy and hepatosplenomegaly. Laboratory tests reveal an elevated WBC count and ferritin level. Tumors, infections and other AIDs must be excluded before AOSD confirmation. As a benignly self-limited disease, the lethal mechanisms are mostly attributed to its life-threatening complications [2].

Pathologic studies about AOSD and its severe complications, namely the macrophage activation syndrome (MAS), disseminated intravascular coagulopathy (DIC), diffuse alveolar hemorrhage, liver involvement, thrombotic thrombocytopenic purpura and pulmonary arterial hypertension are common. But reports of unexpected death due to AOSD have not been found by now.

Here, we report a rare case of AOSD in a 39-year-old woman with immunohistochemical and genotyping studies.

Case report

A 39-year-old woman was hospitalized for chronic cervicitis and received a loop electrosurgical excision procedure (LEEP) operation intraday. After one day she complained of skin pruritus. Physical examination revealed blotchy rashes were scattered over her body. Promethazine hydrochloride and dexamethasone were prescribed then the symptoms were relieved half an hour later. The patient was discharged that day.

Ten days later she was readmitted to hospital for skin erythema, fever and arthralgia. Her body temperature was 39.7°C. Small spots of

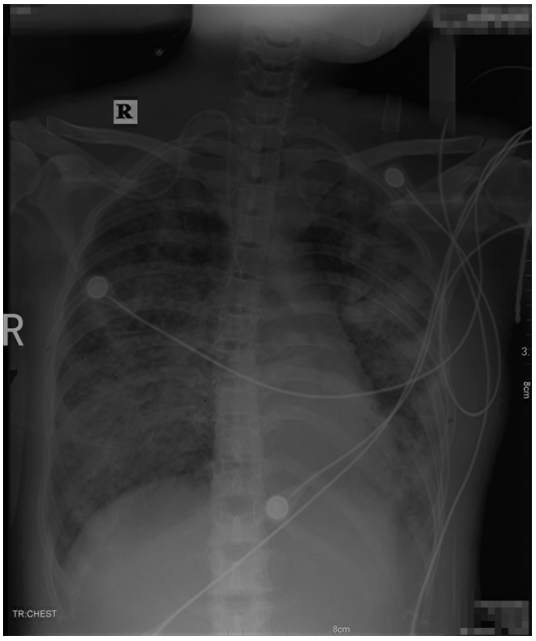

Figure 1. Chest X-ray showed an exudative change of lungs.

erythema were symmetrically distributed in her face and hands, and there was tender pain in her shoulder, elbow, wrist, finger, knee and ankle joints. Blood routine indicated very high white blood cell (WBC) count (21.12×10^9/L), polymorphonuclear leukocyte (PMN) ratio (88.90%) and platelet (PLT) count (544×10^9/L); serum biochemistry was shown that lactate dehydrogenase (LDH) of 430.6 U/L and C-reaction protein (CRP) of 114.0 mg/L; serum ferritin (SF) of 1417.0 ng/mL but glycosylated hemoglobin (GH) was normal. A type I immunoglobulin G of herpes simplex virus (HSV-I-IgG) was positive but the antinuclear antibody (ANA) and rheumatoid factor (RF) displayed negative results. Chest X-ray showed an exudative change of lungs (**Figure 1**). An admitting diagnosis was fever and rash of unknown. Methylprednisolone, teicoplanin, epinastine and desloratadine citrate disodium were given then she obviously made an improvement and was discharged after 5 days.

After thirty days, the patient was third admitted due to the same but greatly aggravated symptoms as the second. The body temperature was 39.5°C and blood pressure was 90/56 mmHg. A large area of diffused erythema was observed in her head, face and trunk which blanched on pressure, also found erratically in both upper limbs. The WBC count (18.88×10^9/L), PMN (86.60%), CRP (94.60 mg/L) and LDH (2369.7 U/L) were steadily maintained. Her SF was over 40000.00 ng/ml, but GH was still normal. Overnight she felt rather tired with cold extremities, the 24 hours urine volume (UV) was 50 ml. WBC counts zoomed to 45.72×10^9/L and PMN was 87.74%. Occult blood test (OBT) of gastric juice, urine and feces indicated a positive result. Two days later, her oxygen saturation was decreased to 75~78%, then cardiac arrhythmias and atrial fibrillation occurred. The woman was pronounced dead after hospital invalid.

On gross examination, there were scarlet spots and erythema on her head, face, chest and abdomen. Microscopically, large amounts of lymphocytes were perivascularly infiltrated in subcutaneous tissues (**Figure 2**) where microthrombi and hyaline thrombi were formed. Demyelination in brain tissues was obvious, accompanying with encephaledema, neuronal necrosis, encephalomalacia and microglial hyperplasia. Granular cells and Purkinje cells of cerebellum were decreased. Coagulative necrosis of the adenohypophysis was seen. There are two ulcer foci as small as 1 cm in diameter on her laryngeal vestibule with edema and hemorrhages. Moderate amount of pleural, peritoneal and pericardial effusion was noted. Multiple hemorrhages were also found on epicardium and endocardium. And, more remarkable, severe edema, fibrinous exudate, inflammatory infiltration and focal hemorrhages were evident in myocardium, particularly sinuatrial node, and pulmonary alveoli. Structure of lymph nodes was disappeared while histocyte and immunoblast proliferation was obvious in the cortex. Splenomegaly and fibrinoid necrosis of central arteries were concomitant. Kidneys, paranephroi and alimentary tract revealed a character of hemorrhagic inflammation and hyaline thrombus formation. Different degrees of hemorrhages, hyaline thrombi and inflammatory infiltration were observed in other organs.

There were focal hemorrhages, interstitial fibrosis and inflammatory infiltration in the sinuatrial node by Masson trichrome stain (**Figure 3**). By Giemsa-Wright stain, blood smear revealed the monocyte activation (**Figure 4**) and bone marrow smear indicated a proliferative myelogram.

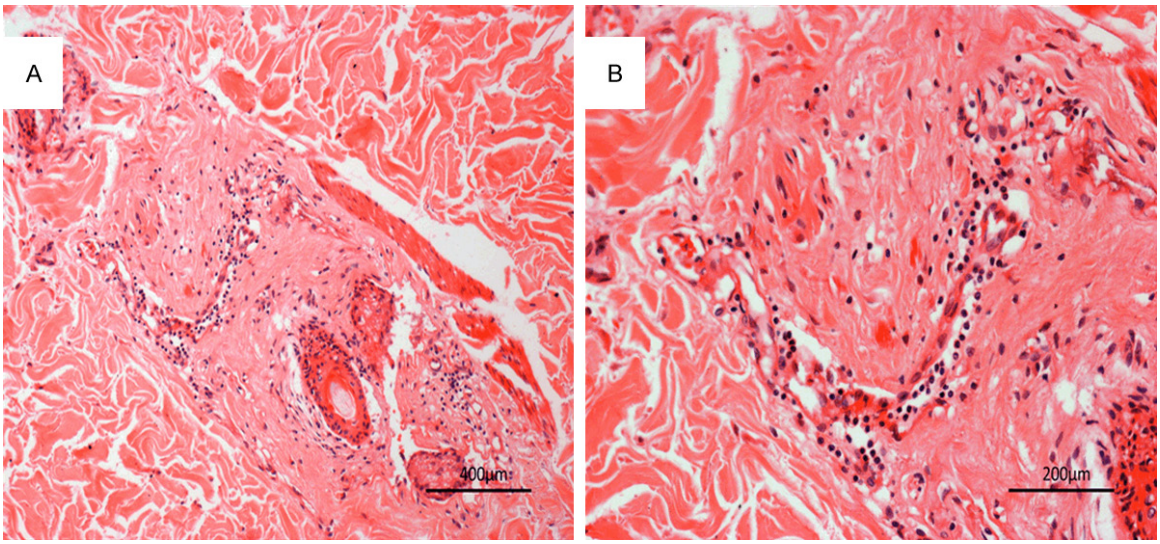

Figure 2. Large amounts of lymphocytes were perivascularly infiltrated in subcutaneous tissue (A: HE stain, ×100; B: HE stain, ×200).

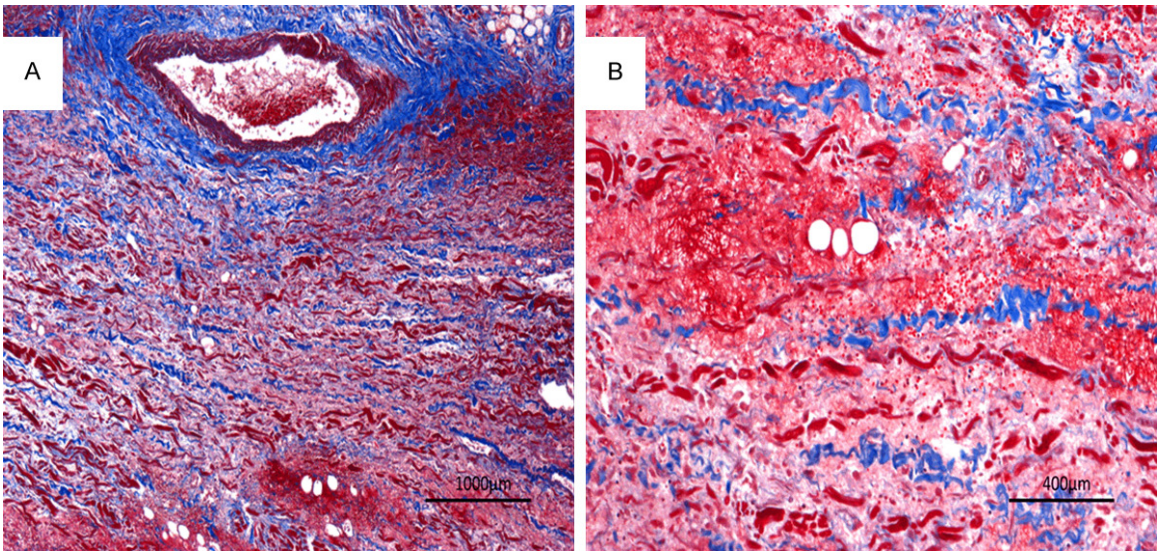

Figure 3. Interstitial fibrosis, lymphocytes infiltration and focal hemorrhages in sinuatrial node (A: Masson trichrome stain, ×40; B: Masson trichrome stain, ×100).

Immunohistochemical staining of lymph nodes demonstrated that CD68 was highly expressed in histocytes. Both CD3 and CD20 were positive in immunoblasts. CD1α and IgG4 were negative (**Figure 5**).

The genotype of HLA were HLA-A*0207/HLA-A*1101, HLA-B*1502/HLA-B*4601, HLA-C*0102/HLA-C*0801, HLA-DRB1*0803/HLA-DRB1*1501 and HLA-DQB1*0601.

According to the clinical data, autopsy, histopathological and laboratory examination, the primary cause of death was ascertained as cardiac arrhythmias secondary to adult-onset Still's disease.

Discussion

The incidence of AOSD is approximately 0.16 to 0.40 per 100,000 persons [3-6]. It usually occurs in young and middle-aged adults and sex ratios are basically flat [3, 5] or slightly skewed against male [4, 6]. Its causes and pathogenesis remain unclear until now. While epidemiological and pedigree investigation do

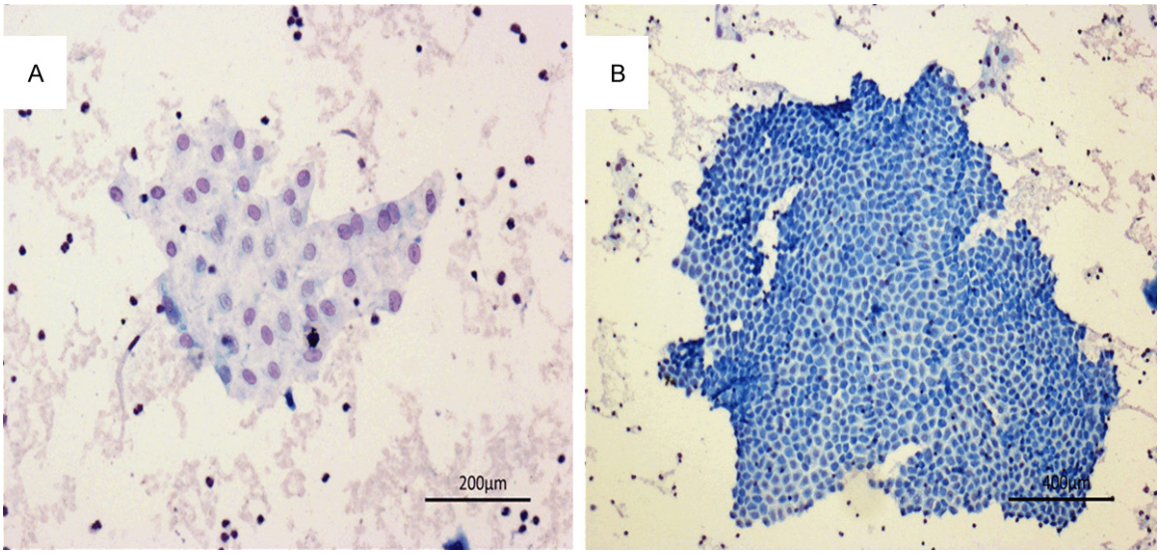

Figure 4. Monocyte proliferation and activation in blood (A: Giemsa-Wright stain, ×200; B: Giemsa-Wright stain, ×100).

not indicate an apparent genetic link in most cases, AOSD is still a polygenic disease that it was largely associated with the genetic susceptibility of human leucocyte antigens (HLAs). In a Japan study, HLA-DRB1*1501 has been found to be associated with chronic articular AOSD [7]. In this case, HLA-DRB1*1501 was positive from a Chinese woman with a long-term course of joint pain, which performed a distinct immunogenetic profile. Moreover, activation of the mononuclear phagocyte system can be exogenously triggered by factors such as previous infection of viruses (mumps virus, parainfluenza virus, rubella virus, echovirus, adenovirus, influenza virus, human herpes virus, hepatitis B virus, human parvovirus, Epstein-Barr virus and cytomegalovirus) [8] and bacteria [9], drugs and chemical substances, which leads to a huge release of tumor necrosis factors (TNFs) and interleukins (ILs) where there are interactions that induce the onset and clinical signs of the disease. Serological test of this woman indicated a previous infection of HSV, which we tended to consider as an inducing factor.

Non-specific systemic inflammation, as main pathologic change of AOSD, may appear in any part of the body and incur subsequent local ischemia and dysfunction owing to concurrent thrombogenesis. Skin biopsy contains epidermal edema, perivascular infiltration of lymphocytes, monocytes and histocytes [10]; central nervous system reveals a demyelinating change [11]; focal endocardial thickening, myocardial hypertrophy, fibrosis and interstitial inflammation may be detected [12]; renal damage is properly reflected in glomerular hypertrophy, mesentery proliferation, tubular atrophy and angiosclerosis [13]; sometimes, leukoplakia, superficial ulcer and Crohn's disease can be seen in the digestive tract [14, 15]; paracortical areas expand with proliferation of histocyte, vascular and large immunoblasts, also with follicular hyperplasia [16]. In this case, furthermore, fibrinous inflammation in myocardial interstitium where there were large amounts of fibrin exudation in the sinuatrial node might probably induce an arrhythmia. Besides, exudation had led to an outpouring of inflammatory fluid with fibrin into the alveolar spaces coupled with fibrinous pleuritis indicated radiographically, which in some degree, endorsed autoimmunity as an essential trait of AOSD.

Meanwhile, except using CD68, CD3 and CD20 in lymph nodes for observing the histocyte and immunoblast proliferation, CD1α is appropriate for whether a Langerhans cell histiocytosis exists. In addition, a negative expression of IgG4 is applied to exclude some AIDs, for instance, Mikulicz disease (MD), autoimmune pancreatitis (AIMP), inflammatory pseudotumor, retroperitoneal fibrosis, autoimmune hepatitis and sclerosing cholangitis, etc.

Hyperthermia, evanescent rashes and arthritis/arthralgia are clinical trial of AOSD. There-

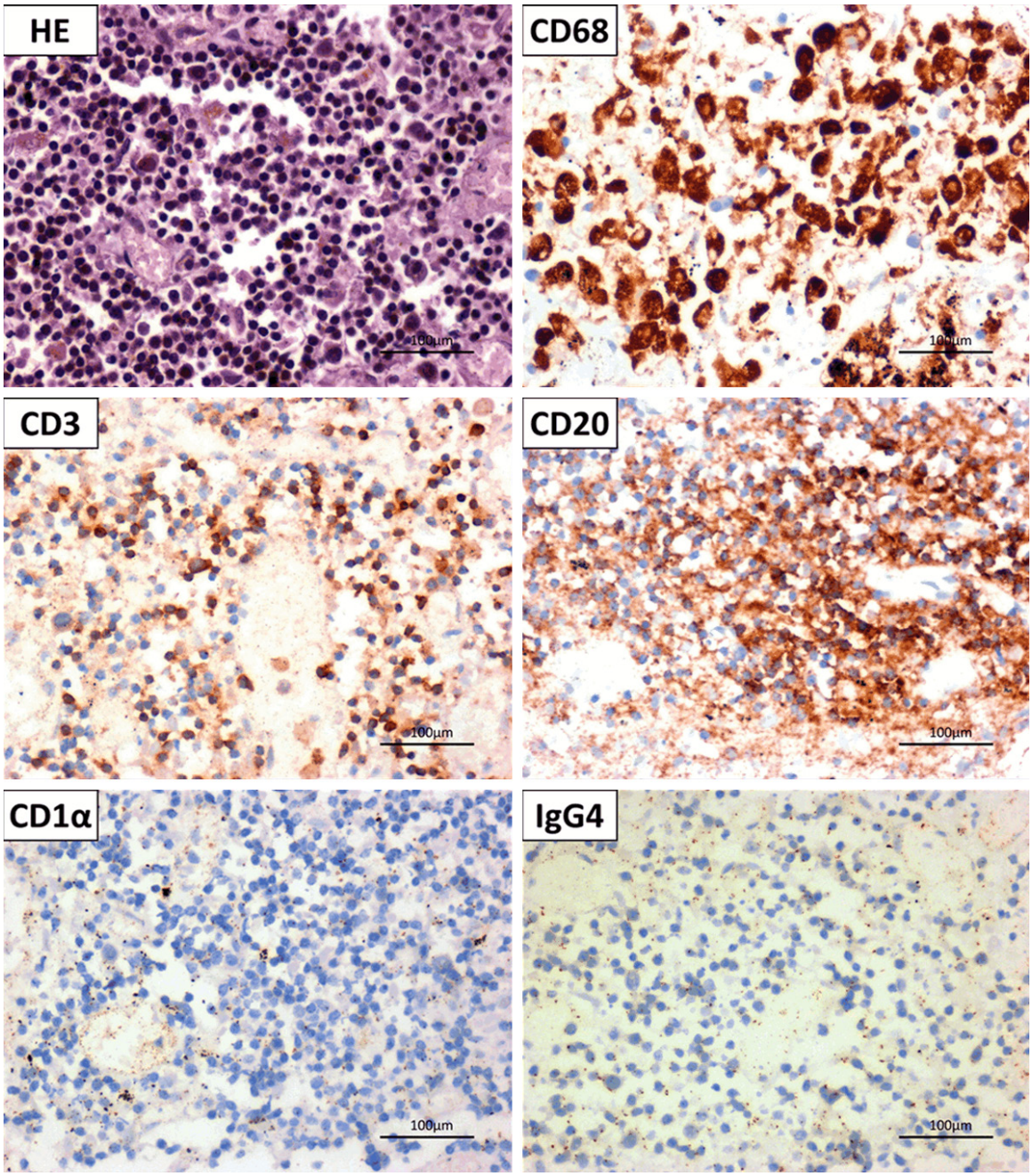

Figure 5. Immunohistochemistry showed positive results of CD68 in histocytes, CD3 and CD20 in immunoblasts but negative results of CD1α and IgG4 in lymph nodes.

into, the body temperature includes a fever of more than 39°C and occurs frequently in a single or two peak, with some voluntary return to normal. Typical rash, that is evanescent orange, red or blush maculopapule, may be mechanical stimulus-induced and then fades after the fever drops. On account of the general manifestations, most articular symptoms are coverage-prone and assume the style of an asymptomatic, uncertain, migratory and non-specific involvement with muscle pain. Moreover, angina, lymphadenectasis, hepatosplenomegaly, serositis, bellyache, interstitial pneumonia, pleuritis and pericarditis were often observed [17].

Laboratory examination gradually represents a general trend of the diagnosis and differentia-

Table 1. Yamaguchi classification criteria [22]

Major criteria	Minor criteria	Exclusion criteria
Fever ≥39°C	Sore throat	Infections
Lasting 1 week or longer		
Arthralgia or arthritis	Recent development of significant lymphadenopathy	Malignancies (mainly malignant lymphoma)
Lasting 2 weeks or longer		
Typical rash	Hepatomegaly or splenomegaly	Other rheumatic disease (mainly systemic vasculitides)
Leucocytosis ≥10,000/mm^3 with ≥80% polymorphonuclear cells	Abnormal liver function tests	
	Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)	

Five or more criteria required, of whom 2 or more must be major.

tion of AOSD. An increase of WBC count coupled with a PMN ratio more than 80% but negative outcomes of ANA and RF should attract attention, and other blood routine index plays an accessorial role at different degrees. Bone marrow smear reveals an infectious status where the granulocytic cells were actively proliferated with reactive histocytosis, hemophagocytosis and plasmacytosis. The usage of joint detection of SF and GH has greatly increased the sensibility and accuracy [18]. These two were paralleled to the activity of disease, and also used to exclude the infection, tumor and drug reaction when SF is greater than 1000 ng/ml but GH less than 20%. Synovial and serosal fluid reveals sterile exudate. Interleukins (IL-1β or IL-18) detection was available for definition and observation [19, 20]. In spite of being induced by multiple microorganisms, etiological examinations tend to be negative or previous infection. Imaging tests, in the early stage, perform non-specific results or only soft tissue swelling and osteopenia, while bone and cartilage destruction even joint space narrowing can be seen until later period.

Several standards were multi-perceptively proposed in the diagnosis of AOSD [21], but a Yamaguchi classification criteria was broadly adopted in clinics (**Table 1**) [22]. In addition, laboratory tests including autoantibody detection, polymerase chain reaction (PCR) and blood culture for pathogen testing, skin biopsy, imaging and gene screening perform an essential role in exclusion of infectious, tumorous, AIDs, drug reaction and idiopathic inflammatory [17]. In this case, blood smear for monocyte counts was of particular interest, since we know monocyte-macrophage activation usually played a key role in symptoms onset of rheumatic diseases, and furthermore, no other articles focused on the pathologic application of this detection.

Generally speaking, potential fatality due to complications of AOSD is extremely perilous that mainly contain MAS, DIC, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, pulmonary arterial hypertension and liver involvement [2]. In these, the mortality rate of MAS is approximately 10~22% [23, 24], which activates the form of reticuloendothelial system (RES) that brings about quickly high fever, lymphadenectasis and hepatosplenomegaly. Laboratory inspection reminds a pancytopenia with increased levels of SF, triglyceride and aminotransferase. Respiratory involvement is about 30%~53% [2, 25] and commonly seen in pleuritis, respiratory distress syndrome (RDS), diffuse alveolar hemorrhage, organizing pneumonia and interstitial lung disease [22]. All the above-mentioned could lead to pulmonary arterial hypertension. Liver dysfunction is up to 92% [26] and may induce liver failure and MAS [27].

AOSD have the characteristics of rarity and complexity in pathologic practice. Attention should be paid when hyperthermia, arthralgia, rashes and increased WBC count are mentioned in medical records. During the autopsy and pathologic examination, fibrinous inflammation in multiple organs combined with mononuclear macrophage activation from the blood and bone marrow smear have contributed to the diagnosis of AOSD. Besides, accessory examinations, for instance, genotyping, cytokines detection, special stain and immunohistochemistry are necessary to eliminate the probability of other organic diseases. After a confirmed diagnosis, comprehensive analysis and consultation may be used to determine

those fatal complications and the analysis on the cause of death.

Ethics statement

The informed and written consent have been obtained. This study has been performed according to the Declaration of Helsinki. However, approval from a local ethics committee of necropsy was not acquired in China so we did not have this kind of paper. Thank you for your understanding.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yiwu Zhou, Department of Forensic Medicine, Tongji Medical College of Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan 430030, Hubei, PR China. Tel: +86 27 83657925; Fax: +86 27 83692638; E-mail: yiwuzhou@yahoo.com

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