Adult-onset Still's disease with secondary macrophage activation syndrome: a case report

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ABSTRACT

We describe a case of adult-onset Still's disease (AOSD) with secondary macrophage activation syndrome. AOSD is a rare disease with unknown origin. Rarely it's complicated by secondary macrophage activation syndrome, which is a life-threatening disorder. Because the diagnosis of AOSD is essential for exclusion and complications are life-threatening, it is mandatory for a prompt and extensive diagnostic workup and treatment.

Introduction

We describe a case of adult-onset Still disease (AOSD) with secondary macrophage activation syndrome in a 66 years old woman. AOSD is a rare disease with unknown origin. The annual incidence of AOSD is estimated to be between 0.16 and 0.62 per 100000 people,[1] the prevalence is approximately 1-24 per million.[2] Rarely, it's complicated by secondary macrophage activation syndrome (MAS), which is a life-threatening disorder.

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Case report

A 66 years old woman was admitted to the internal medicine department with a 15 days history of spiking fever of up to 39°C, myalgias, night sweats, and sore throat. The patient was before evaluated by his primary care physician, that administered nonsteroidal anti-inflammatory drugs and empirical antibiotic therapy without being relieved of the clinical picture. The medical history of the patient was unremarkable, except for a minimal congenital interventricular defect. No travel and animal exposure were referred.

The temperature was 39°C, the blood pressure was 140/80 mmHg, the respiratory rate was 16, and oxygen saturation was 97%, while the patient was breathing room air. Her neck was supple, and oropharynx was erythematous without exudate. No lymph nodes were palpable. The chest, cardiovascular, and abdominal examinations were normal. Blood and urine tests revealed no bacterial, fungal, or viral infection. Blood cultures performed repeatedly over time were negative. Basic laboratory test results showed leukocytosis with neutrophilia, elevated liver enzymes (alanine transaminase 64 U/L, aspartase transaminase 50 U/L), C-reactive protein (CRP) 100 mg/dL and erythrocyte sedimentation rate (ESR) 90 mm/h. There were markedly elevated ferritin levels (6000 ng/mL). Tests for rheumatologic disorders were negative. Chest radiography and abdomen echo were normal. A tuberculin skin test was negative. Transthoracic and transesophageal echocardiography were normal. A

computed tomographic scan of the chest, abdomen and pelvis was unremarkable. PET's total body was normal. On the ninth hospital day, a transient salmon-pink maculopapular rash appeared (Figures 1 and 2).

A diagnosis of adult-onset Still's disease was made. A therapy with methylprednisolone 1 mg/pro/kg die was started. There was a rapid improvement of symptoms until a fourth day after the beginning of the steroid therapy when a spiking fever appeared, a salmon-like rush, and night sweats. Overnight the oxygen saturation decreased to 85%, the auscultation of the lungs revealed rales in all lung fields, and a chest tomography showed signs of pericardial effusion and pulmonary edema that, with prompt treatment, gradually improved. Laboratory tests showed ferritin 9000, a very high level of CRP and ESR. Interleukin 6 was 119 pg/mL (v.n.0-5.6), interleukin 8 was 71.6 pg/mL (v.n.1.9-17.4), Interleukin 10 was 49.6 pg/mL (v.n.0-6.3), Tumor necrosis Factor (TNF-alfa) 37.3 pg/mL (v.n.0-13.3), interferon gamma >1289 (v.n.0-13.6), Monocyte Chem. Prot. -1 >14788 (v.n. 70.5-209.3). Therapy with methotrexate and high doses of methylprednisolone (500 mg bid) was started without improvement of the clinical picture. Anakinra was started. The patient improved, but on the fourth day after, there was a sudden worsening. The patient became dyspnoic; the oxygen saturation decreased to 91%, laboratory findings showed pancytopenia with severe neutrophenia, very high level of ferritinemia 42457 ug/L (v.n.10-291), LDH 955 UI/L (v.n. 0-248) and triglyceridemia 670 mg/dl (v.n.35-170). The fever was very high and changed from intermittent to non-remittent. There was a prolongation of the PT, a decrease of fibrinogen levels, and an elevation of the Dimer levels without bleeding. The oxygen saturation decreased to 88%. A diagnosis of MAS was made. Supplemental oxygen through a nasal cannula at a rate of 2 liters per minute and fresh frozen plasma were administered, no bleeding occurred. Anakinra was stopped. Methylprednisolone (500 mg bid) was started for 5 days. The patient and laboratory findings improved. A tapering of the corticosteroid dose was started. The patient's symptoms did not recur after the corticosteroid therapy was discontinued.

Discussion

This case highlights two important rare disorders: AOSD and secondary macrophage activation syndrome. Adult's Still disease is a rare inflammatory disease of unknown etiology. The diagnosis is difficult, essentially of exclusion of other possible disorders because no laboratory tests are specific for AOSD. There are three patterns described in AOSD disease. The chronic articular pattern is characterized by long-lasting polyarthritis; the polycyclic pattern is characterized by one or more disease flares, and the monocyclic

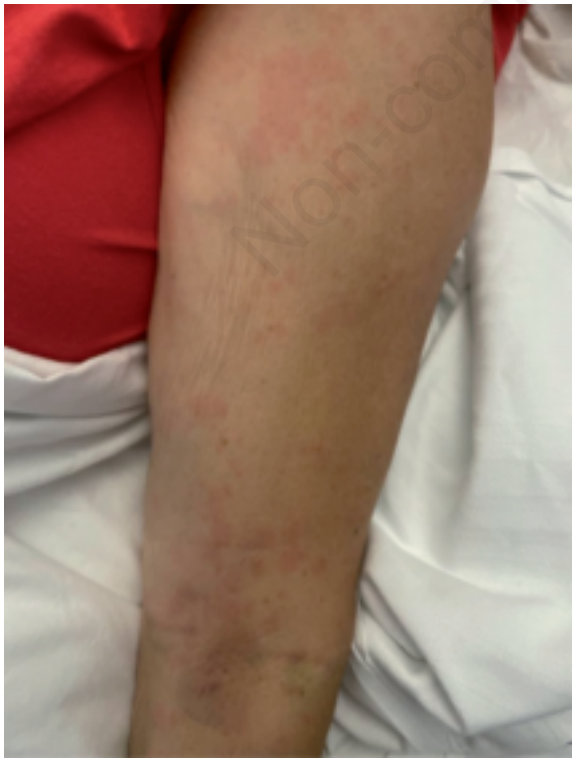

Figure 1. Salmon-like rush.

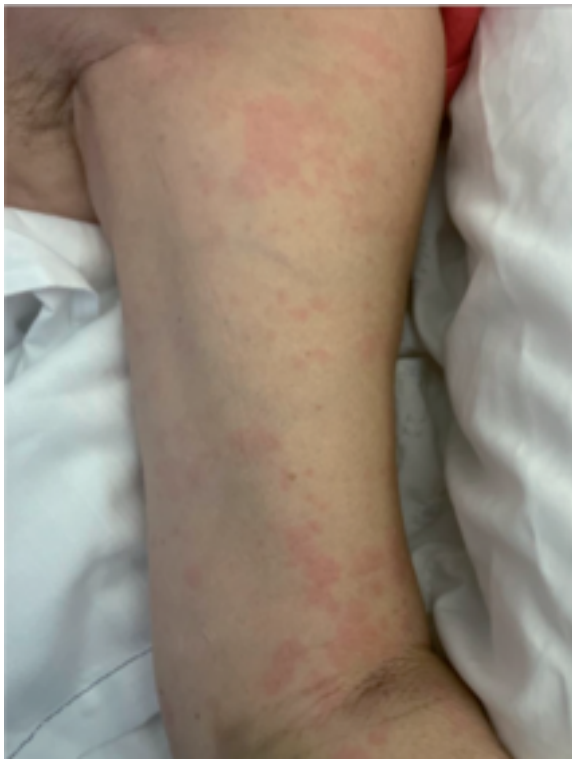

Figure 2. Salmon-like rush.

Table 1. Diagnosis of adult-onset Still's disease: 5 or more criteria of which at least 2 major (Yamaguky criteria).

Major criteria	Minor criteria	Exclusion
Fever >39° lasting 7 days or longer	Sore throat	Infections
Arthralgias or arthritis for 14 days or longer	Hepatomegaly or splenomegaly	Malignancies
Typical rash	Lymphadenopaty	Other rheumatic disease
WBC counts >10000 with 80% neutrophils	Abnormal liver function tests	
	Negative antinuclear antibody and rheumatoid factor tests	

pattern is characterized by a single systemic episode completely resolving.[3] The patient often presents with high intermittent fever, fugax salmon rash, sore throat, arthralgia, and a very high level of ferritin, ESR, and CRP. Leukocytosis with neutrophilia and elevated liver enzymes are also frequent. The Yamaguchi criteria are the most commonly used classification criteria for AOSD (sensitivity 96.2%, specificity 92.1%).[4] For diagnosis of AOSD, patients should meet 5 or more criteria, of which at least 2 should be major. Major criteria are: fever ≥39°C lasting at least 1 week; arthralgia or arthritis for ≥2 weeks; typical nonpruritic salmon-pink skin rash; leukocytosis ≥10.000 with ≥80 polymorphonuclear cells. Minor criteria are: sore throat; lymph node enlargement; hepatomegaly or splenomegaly; abnormal liver function tests; negative antinuclear antibody and rheumatoid factor tests. It is mandatory the exclusion of infections, malignancy, and other rheumatic disorders (Table 1).

Secondary macrophage activation syndrome (MAS) is a rare, life-threatening complication of hematologic cancer, infection, exposure to immunomodulatory drugs, and autoimmune disease caused by a dysregulation of the immune response. It is considered to be a form of secondary hemophagocytic lymphohistiocytosis.[5] Experimental models showed that in the MAS, T cells are drivers of the cytokine storm.[6-8] A prolonged activation of T cells leads to a cytokine storm with high circulating cytokine levels, acute systemic inflammatory symptoms, and secondary organ dysfunction. Typical is hemophagocytosis in the bone marrow and other reticuloendothelial cells. Sometimes MAS is associated with heterozygous mutations and polymorphisms in the genes responsible for familial hemophagocytic lymphohistiocytosis.[9] In the hemophagocytic lymphohistiocytosis, there is impaired cytotoxic capacity of T cells with dysregulation of the immune response, and thus a cytokine storm may occur. AOSD is responsible for 10 to 15% of cases of MAS.[10,11] MAS has been associated with a significant increase in mortality in patients with AOSD.[12]

The diagnosis is difficult, although a score has been proposed.[13] In 2007, guidelines for the diagnosis of hemophagocytic lymphohistiocytosis stated that the diagnosis could be made in the presence of five to eight of the following criteria: high fever, cytopenia affecting at least two of three lineages, splenomegaly, hypofibrinogenemia, very high level of triglyceridemia and ferritin, hemophagocytosis in bone marrow, spleen or lymph nodes, low NK cell activity and high level of interleukin -2.[14]

Severe pancytopenia is the most important cause of death in this syndrome. Not too long ago, the treatment of a patient with AOSD and MAS was a cause of considerable uncertainty. Nowadays, it is clear that the treatment should be guided by control of the cytokine storm, limiting the damage of the activated immune system, and supportive care if necessary. Sometimes, it may be completely worthless to neutralize a high level of cytokine if another cytokine with a low or normal level is the key to the hyperinflammatory circuit.[15] Considering that during anakinra treatment, MAS occurred, we chose to shift toward high doses of methylprednisolone (500 mg bid) empirically. We think trials should be performed to select the right drugs for the right patients in these rare and life-threatening diseases.

Conclusions

This case highlights the importance of rapid recognition of a rare disease, such as AOSD, that sometimes may be complicated by a life-threatening disease, such as MAS. AOSD and MAS being rare diseases, are a diagnostic and therapeutic challenge for the physician. It is important for the clinical to keep in mind these disorders because only prompt recognition can permit aggressive management and thus result in a good clinical outcome. Although the therapy should be targeted in managing cytokine storm by blocking the cytokine, which is responsible for the hyperinflammatory circuit, non-specific immunosuppression may be useful to limit the activated immune system. To our knowledge, no controlled studies on the therapy of MAS exist. Even today, therapy is based on expert opinion, case series, and personal experience. Randomized controlled trials should be performed to find the right drug for the right patient to improve the prognosis of these diseases.

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