Adult onset Stills disease: Not so rare neither so benign.

NG Vallianou¹, A Kollas¹

Abstract
Introduction
Adult onset still’s disease (AOSD), is an inflammatory disease characterized by fever, arthritis or arthralgias, muscle pain, pharyngitis, lymphadenopathy, rash, splenomegaly, pleuritic and pericarditis.

Discussion
Fever together with arthralgias and myalgias are reported in > 90% of patients with AOSD. Fever is present every day and sometimes it may occur with two spikes daily, (double quotidian), the latter being characteristic of AOSD and visceral leishmaniasis. It is usually high (>39°C), with dramatic changes within only a few hours and it may proceed even for a year before the other symptoms develop.

Conclusion
In fact, AOSD has been suggested to be among the most common causes of fever of unknown origin, especially in younger age groups. Complete defervescence does not always occur, as fever may persist among spikes in about 20% of the patients.

Introduction
Arthralgias, arthritis and myalgias are universal features of AOSD. During the first stages of the disease, arthritis may be mild and oligoarticular, but later on it can become severe to destructive polyarthritis. Fusion of the wrist is a characteristic feature of AOSD, although it may develop in a minority of patients. Arthritis occurs in the knees, the wrist, the tarsal, the elbows, the proximal interphalangeal joints and the shoulders. Synovial fluid is inflammatory with a leukocyte count between 100 and 48.000 cells/ml. Myalgias may be severe, especially during fever spikes. Muscle weakness is not present, but aldolase and creatinine kinase serum levels may be elevated. Electromyography and muscle biopsy are usually normal or show a non-specific inflammatory myopathy.

Rash
Rash develops in approximately in 80% of the patients. It is an evanescent, salmon-like colored rash, which usually becomes evident during fever spikes, macular or maculopapular rash, which typically develops in the trunk or the extremities, but may spread to the palms, soles and occasionally the face (Figure 1). Skin biopsy shows non-specific results, but it may be important in differentiating AOSD from vasculitis. It usually depicts dermal edema together mild perivascular inflammation of the dermis, consisting mainly of lymphocytes and histiocytes. Immunofluorescence may show mild deposition of C3 in the blood vessel walls.

Pharyngitis
Pharyngitis, non-suppurative occurs in approximately 70% of the patients. Hepatomegaly with or without elevation in liver aminotransferases frequently occurs. Eight cases of fulminant hepatitis have been described in association with AOSD, with four fatalities. All of them were associated with treatment with NSAIDs.

Lymphadenopathy
Lymphadenopathy with slightly tender lymph nodes develops in about half the cases. Splenomegaly may also occur. Due to the presence of fever, lymphadenopathy and splenomegaly AOSD must be differentiated from lymphoma. Lymph node biopsy reveals intense paracortical immunoblastic hyperplasia, which is different from the findings in Sjogren’s disease, systemic lupus erythematosus, rheumatic arthritis and Kikuchi’s disease. However, these changes may resemble those of a lymphoma. Nevertheless, immunohistochemistry shows a benign, polyclonal hyperplasia and differentiates it from the monoclonal changes found in lymphoma.

Pleuritis
Pleuritis, transient pulmonary infiltrates and pericarditis have been described in 30% to 53% of cases with AOSD. Severe pulmonary involvement, such as pleuritic or interstitial pneumonia in AOSD is related to poor prognosis. Patients may complain of dyspnea, pleuritic pain or cough. Furthermore, severe cases of interstitial pulmonary disease have been reported, some of which have progressed to acute respiratory distress syndrome. Nowadays, nineteen cases of acute respiratory distress syndrome associated with AOSD have been documented. It is important to recognize these cases early, as corticosteroids and/or other immunosuppressive agents may be mandatory for their treatment. Myocarditis occurs very rarely and may cause arrhythmias or heart failure and may lead to death. Currently, there are reports suggesting an improved survival among patients with AOSD and myocarditis, taking newer immunosuppressive regimens, such as tocilizumab and anakinra as well as intravenous immunoglobulin.

¹ Evangelismos General Hospital, Athens, Greece

*Corresponding author
Email: natalia.vallianou@hotmail.com


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Apart from the above-mentioned clinical manifestations of AOSD, hematological implications, such as the reactive hemophagocytic syndrome must not be overlooked. The reactive hemophagocytic syndrome in the context of AOSD has also been termed macrophage activation syndrome (MAS). The hallmark of MAS is the presence of well-differentiated macrophages (histiocytes) in the bone marrow specimen21. MAS may develop at any time in the history of AOSD, and simultaneous presence of MAS and AOSD are not unusual22. As hyperferritinemia does occur in both syndromes and isolated cytopenias may also be present in both syndromes, too, sometimes a bone marrow biopsy is indispensable to distinguish between them. MAS is related with poor prognosis and may become fatal. Therefore, its recognition is of great importance, as it demands special treatment with immunosuppressive regimens, such as cyclosporine 23.

Laboratory findings

Common laboratory findings include leukocytosis with polymorphonuclear domination in 90% of the cases, an elevated CRP and ERS in >90% of the patients, anemia in 75%, a mild elevation of the aminotransferases in 75% and an elevated serum ferritin in 70% of the patients, the latter being sometimes extremely elevated, above 10.000 ng/ml. It is noteworthy that some rheumatologists use serum ferritin levels to monitor treatment of AOSD24,25. Besides, glycosylated ferritin levels are low in patients with AOSD, usually <20% and this combination of elevated serum ferritin and low glycosylated ferritin has high specificity for AOSD26,27.

Diagnosing AOSD

As no specific test exists for diagnosing AOSD, there are several criteria that have been proposed, amongst which the Yamaguchi criteria have been most widely used. In order to diagnose AOSD, at least five criteria must be present, among which at least two must belong to the major Yamaguchi criteria28.

Major criteria

- Fever ≥ 39 º C for more than a week
- Arthralgias or arthritis for more than two weeks
- A non-pruritic macular or maculopapular salmon-like rash in the trunk or the extremities during fever spikes
- Leukocytosis (>10.000/mm³) with at least 80% polymorphonuclear leukocytes present

Minor criteria

- Pharyngitis
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal liver enzymes (mostly ALT, AST, LDH)
- Negative ANA and RF

References