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Adult-onset Still's disease: Advances in the treatment

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A B S T R A C T

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder mainly characterized by persistent high spiking fevers, evanescent rash, and joint involvement. The pathogenesis of AOSD is only partially known, but pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-18, and IFN-γ seem to play a major role in this disorder. AOSD is at the crossroad of auto-inflammatory syndromes and autoimmune diseases. It is diagnosed by exclusion to determine the presence of high serum ferritin levels, which is usually >1000 μg/L. AOSD is generally treated with non-steroidal anti-inflammatory drugs, corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs). Although information on biologic therapy in the management of AOSD is scarce, these drugs represent a major breakthrough in the management of patients with AOSD refractory to corticosteroids or conventional DMARDs or in patients presenting life-threatening manifestations. In this regard, TNF-α, IL-1, and IL-6 antagonists had been proved effective in patients with AOSD.

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Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown etiology characterized by persistent high spiking fevers, evanescent rash, and joint involvement. It was described in 1971 by Bywaters [1] in a series of 14 young women presenting with similar clinical features to those of systemic onset juvenile idiopathic arthritis (JIA) reported by Sir George F Still in children in 1897 [2]. AOSD is characterized by high daily spiking fever, polyarthritis, skin rash, myalgia, lymphadenopathy, sore throat, hepatosplenomegaly, serositis, myocarditis, marked leukocytosis with neutrophilia, and elevated acute phase reactants (APRs) such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

AOSD is a very uncommon disease. Its annual incidence has been estimated between 0.16 and 0.4 per 100,000 persons worldwide, independent of ethnic group [3–5]. The reported prevalence rates range from 1 to 34 cases per 1 million people [5]. Women seem to be slightly more commonly affected than men [6,7]. There is a bimodal age distribution, with one peak between 15 and 25 years and the second between 35 and 45 years of age [3].

The precise etiology of AOSD is unknown. Currently, AOSD is considered a complex auto-inflammatory syndrome in which genetic factors, infectious agents, and other environmental factors trigger an auto-inflammatory systemic response leading to a dysregulation of the inflammasome complex with the overproduction of several proinflammatory cytokines such as IL-1, IL-6, IL-18, IFN-γ, and TNF-α. Besides, there are some cases of AOSD associated with malignancies including solid cancer and hematological disorders [8–10].

The clinical course is marked by sporadic exacerbations of systemic inflammation and/or chronic inflammatory arthritis. Nevertheless, the evolution varies considerably from one individual to another, ranging from benign and self-limited clinical forms to severe forms with life-threatening manifestations.

Clinical picture

The major clinical features of AOSD include quotidian (daily) high spiking fever with temperature often exceeding 39 °C, arthralgia or true arthritis, and an evanescent salmon-colored skin rash that mainly appears on the trunk and proximal limbs and usually coincides with fever spikes. The joints more commonly affected are the knee, wrist, ankle, and hand. The involvement of the hip and shoulder at the onset of the disease implies a worse prognosis. Other common manifestations of AOSD include myalgia, pharyngitis, lymphadenopathy, organomegaly, pulmonary infiltrates, pleuritis, pericarditis, myocarditis, and abdominal pain [11,12]. AOSD presents in some patients as persistent fever of unknown etiology. The frequency of the most relevant clinical features is shown in Table 1.

Laboratory findings are nonspecific and reflect the systemic inflammatory nature of the disease [8,11,12]. Marked elevation of ESR and CRP is seen in the majority of the patients. Leukocytosis with neutrophilia (>80% polymorphonuclear cells) is found in about 80% of patients. Anemia and thrombocytosis are also frequently found. Elevations in the serum liver enzyme levels, especially alanine and aspartate aminotransferases, are seen in 75% of patients. Serum ferritin level is particularly increased in AOSD, and it may be a good marker of disease activity. AOSD is also associated with a reduction in the glycosylated ferritin fraction, so that the combination of serum ferritin levels higher than 1000 μg/L with a glycosylated fraction under 20% has been found to have a high specificity for the diagnosis of AOSD [13,14]. In contrast, rheumatoid factor, anti-citrullinated protein autoantibodies, antinuclear antibodies, and other immunologic studies typical of autoimmune diseases are present in <10% of patients and only at low titers (Table 2).

The clinical course of the disease can be ranked in three main patterns: monophasic or monocyclic AOSD, characterized by a unique and self-limited flare lasting several weeks to months with subsequent resolution (~30% of patients); systemic intermittent pattern characterized by recurrence of multiple flares with or without joint symptoms (~30%); and a chronic pattern, characterized by