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Adult-onset Still's disease as a cutaneous marker of systemic disease

Katerina Damevska, MD, PhD[a,*], Katlein França, MD, PhD[b], Suzana Nikolovska, MD, PhD[a], Filip Gucev, MD[c]

[a]*University Clinic of Dermatology, Ss Cyril and Methodius University, Skopje, Macedonia*
[b]*Department of Dermatology and Cutaneous Surgery, Department of Psychiatry and Behavioral Sciences, Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, Florida, USA*
[c]*Univeristy Clinic of Rheumatology, Ss Cyriland Methodius University, Skopje, Macedonia*

Abstract Adult-onset Still's disease (AOSD) is a rare, systemic, inflammatory disorder characterized by spiking fevers, an evanescent eruption, arthritis, and multiorgan involvement. The disease has been recently classified as a polygenic autoinflammatory disorder at the "crossroads" of autoinflammatory and autoimmune diseases. The highly characteristic salmon-colored eruption is a cutaneous manifestation of a generalized inflammatory reaction and an important diagnostic criterion. In addition to the evanescent eruption, there are atypical persistent papules and plaques in many patients with AOSD. Emerging data suggest that AOSD with this typical evanescent eruption has a different clinicopathologic presentation and clinical course than AODS with atypical cutaneous manifestations.

It appears that there are two subtypes of AOSD with different immunologic profiles, including (1) a systemic disease with high fever, organ involvement, and elevated levels of ferritin, and (2) a chronic disease course with arthritis as the predominant finding. These observations provide novel insight into the disease pathogenesis, suggesting that the underlying mechanisms might differ between these two forms, partially explaining the reported differences in drug response.

Recent advances in the understanding of AOSD are summarized with a focus on the spectrum of cutaneous manifestations and its relationship to systemic inflammation.

Introduction

Adult-onset Still's disease (AOSD) is a rare, but clinically well-known, polygenic, systemic, autoinflammatory disease, characterized by the following four cardinal findings: (1) spiking fever, (2) evanescent eruption, (3) arthralgia or arthritis, and (4) neutrophilic leukocytosis.[1]

In many instances, the skin lesions can provide valuable diagnostic clues, leading directly to the diagnosis or limiting the list of diagnostic possibilities.[2]

From the first description of the disease,[3] there has been great progress in the understanding of macrophage and neutrophil activation that are key factors in the pathogenesis of AOSD.[1] The incidence ranges between 0.16 and 0.4 per

* Corresponding author. + 38975468676.
E-mail address: kate_damevska@yahoo.com (K. Damevska).

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100,000 persons, and estimated prevalence rates ranges from 1 to 39 cases per 1 million persons.[4,5] The peak age of onset occurs between 16 and 35 years, and women are more afflicted than men.[4–6] AOSD has evolved into a separate nosologic entity in recent years with well-defined clinical features and specific diagnostic criteria; however, the diagnosis of AOSD remains challenging, because many features overlap with other causes of severe illness, including infectious, neoplastic, autoimmune, and autoinflammatory diseases.

Corticosteroids remain the first-line treatment for AOSD; in the event of failure of corticosteroid treatment or steroid-dependence, disease-modifying antirheumatic drugs can be considered, including methotrexate, leflunomide, azathioprine, cyclosporine A, hydroxychloroquine, and tacrolimus.[1,6] Recent findings have highlighted the important role in the disease pathogenesis of certain cytokines, including interleukin (IL)-1, -6, -18, and tumor necrosis factor. Biologic agents that target these cytokines have yielded encouraging results, especially in treatment of refractory cases.[1]

Cutaneous manifestations

Although nonspecific, the presence of cutaneous lesions is essential for the diagnosis of AOSD. Their frequency varies from 60% to 80% in diagnosed patients, and the most common presentations are described next.[6–8]

Evanescent eruption

The characteristic eruption consists of discrete, nonpruritic, salmon-pink macules, or maculopapules, which are transient and most prominent during fever spikes (Figure 1). Typically, the eruption fades when the fever remits and reappears with the next spike. It is usually truncal but may involve the arms, with rare involvement of the face and legs (Figure 2).[6–8] Koebnerization is common.[7,8] This classic evanescent eruption typically occurs early in the course of disease,[9] and it may be difficult to identify in darker skins.[10]

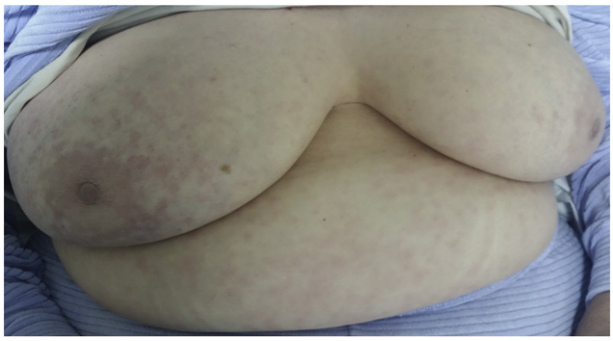

Fig. 1 Salmon-colored, nonpruritic, maculopapular eruption in a 48-year old patient with a 4-month history of recurrent fevers, polyarthralgia, and leukemoid reaction.

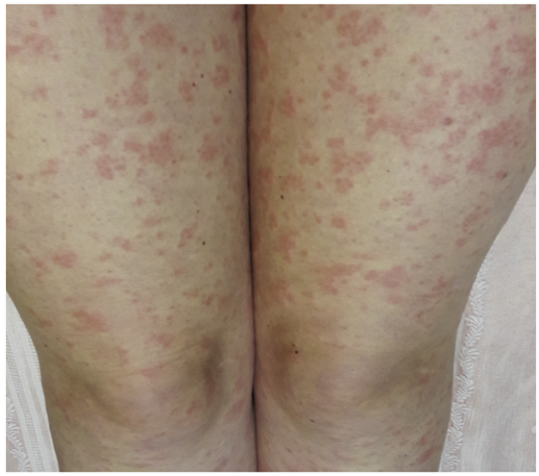

Fig. 2 Widespread macular eruption associated with a fever episode in a 33-year-old woman, who was a diagnostic dilemma for 6 months due to the nonspecific finding.

The histologic findings in the evanescent eruption are nonspecific, ranging from a predominantly lymphocytic infiltrate to predominantly neutrophilic, with both a perivascular and interstitial distribution. Focal vacuolar interface changes, neutrophilic eccrine hidradenitis, and epidermal neutrophils are also found. The lack of significant numbers of eosinophils may be helpful to distinguish it from a drug eruption.[11]

Atypical and rare cutaneous manifestations

In addition to the evanescent eruption, recent reports have described pruritic, persistent papules and plaques in 15% to 65% of patients with AOSD.[12,13] Persistent lesions may be an initial presentation of AOSD[14] or commonly appear weeks after disease onset.[12,13] In some patients, the persistent eruption may follow the typical evanescent lesion. Persistent papules and plaques of AOSD may be related to a poorer prognosis and more aggressive refractory disease.[14]

Atypical persistent eruptions in AOSD exhibit histologic heterogeneity.[15] The main dermal feature is an inflammatory infiltrate with variable intensity, more often perivascular than interstitial, with lymphocytes and neutrophils. Frank vasculitis is never found. Leukocytoclasia, a marker of degranulation and death of neutrophils,[12] and neutrophilic urticarial dermatosis-like dermal features[16] are also described.

The presentation of dyskeratotic keratinocytes in the upper one-third of the epidermal layer is a distinctive histopathologic reactive pattern for persistent pruritic eruptions. This pattern may be a useful histopathologic marker for the early diagnosis of AOSD.[12,15,16]

There are a small number of reports about other atypical or coexistent cutaneous lesions in AOSD patients. Among these are prurigo pigmentosa-like lesions,[17–22] linear pigmentation,[23] facial affection,[24,25] urticaria and dermographism,[26] angioedema,[27] erythematous-edematous plaques,[28] calcinosis

cutis,[29] vesiculopustules on the hands and feet,[30] eczematous plaques with pinpoint necrosis,[31] and lichen amyloidosis-like and dermatomyositis-like lesions.[32]

Another atypical presentation is a linear or flagellate configuration, more commonly involving scaly papules than macular erythema.[13,15,33] There is a report of an unusual presentation of the simultaneous occurrence of typical evanescent and an atypical persistent polymorphic cutaneous eruption.[34]

Systemic involvement

The common manifestations of AOSD include high-spiking fevers, leukocytosis, arthralgia, pharyngitis, myalgia, lymph node or spleen enlargement, liver dysfunction, and in rare cases, pleuritis or pericarditis, as well as abdominal pain secondary to deep lymphadenitis.[35]

Fever (≥39°C) occurs in 60% to 100% of AOSD patients, and usually precedes the onset of other manifestations. Classically, the fever follows a quotidian or double quotidian pattern and resolves spontaneously, resulting in daily temperature swings up to 4°C.[8]

Joint involvement may occur in 86% to 100% of the patients, mainly in the wrists, knees, ankles, and elbows. Joint fluid analysis often shows marked neutrophilic leukocytosis. At the onset of the disease, arthritis may be mild and transient, sometimes evolving into a chronic destructive symmetrical polyarthritis. A large percentage of AOSD patients experience generalized myalgias, usually associated with exacerbations of fever. Both splenomegaly and enlargement of cervical lymph nodes are prevalent findings associated with AOSD.[35,36]

Hepatomegaly and increased value of hepatic enzymes in AOSD are frequently observed and sometimes leads to acute liver failure, although liver dysfunction may be associated with nonsteroidal anti-inflammatory drug treatment.[35]

Less frequent manifestations may involve the ophthalmologic, neurologic, pulmonary, cardiac, hematologic, and renal systems. None of these signs is specific, constant, or simultaneously present at the onset of the disease.[36] Usually, 30% of AOSD patients develop a monocyclic pattern, characterized by a single systemic episode, 30% a polycyclic pattern with multiple flares lasting for 1 year or more but alternating with remissions, and 40% with a chronic pattern that is persistently active and associated with polyarthritis.[35,37] A predictor of a systemic, particularly monocyclic, disease course is a high fever.[8] Multiorgan involvement and the presence of comorbidities at the time of diagnosis is also predictive of a more severe outcome and increased mortality.[8,38]

Laboratory analysis typically reflects the unspecific systemic inflammatory state, with increased erythrocyte sedimentation rate, high levels of C-reactive protein, and increased numbers of neutrophils, usually associated with anemia, thrombocytosis, and elevated liver enzymes. Exceptional high ferritin levels are found in AOSD patients, associated with a low glycosylated ferritin fraction. This parameter appears to be more a marker of activity rather than a reliable diagnostic tool due to its poor specificity[35,39]; however, one report[38] did not find any correlation between the ferritin levels and patient outcomes.

A small subgroup of patients with AOSD may develop life-threatening organ complications,[40] reactive hemophagocytic syndrome, also known as macrophage activation syndrome, cardiac complications, including tamponades, multiple organ failure, disseminated intravascular coagulopathy, pancytopenia, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, and fulminant hepatitis.[35,40] Uncontrollable macrophage activation syndrome, the most frequent complication associated with death,[38] includes a nonremitting fever, abdominal pain, hepatosplenomegaly, neurologic findings, cytopenia affecting two2 or more lineages, and hemophagocytosis in the bone marrow, spleen, or lymph node.[38–40]

Diseases associated with AOSD

Limited knowledge about the potential comorbidities of AOSD is based on case series and results from small studies (Table 1).[41–70]

AOSD and other autoinflammatory and autoimmune disorders

Ten cases of Kikuchi-Fujimoto's disease—a necrotizing lymphadenitis—have been described in association with AOSD; these patients showed manifestations of both diseases.[25,46,47] The rarity of each of the diseases individually makes it unlikely that their co-occurrence is a random event; this may offer a window into the potential pathophysiologic mechanisms that they share.[46]

A link with defective apoptosis may be further suggested by the association of macrophage activation syndrome and Kikuchi's disease, in patients with AOSD. AOSD has been reported in association with other autoimmune diseases, including autoimmune hepatitis,[48,49] autoimmune hemolytic anemia,[50] Sjögren's syndrome,[51] polymyositis,[52] irritable bowel disease,[53–56] and Sweet's syndrome.[57]

Dermatologic diseases

A few isolated case reports in the medical literature have described the coexistence of AOSD with dermatologic diseases.[58–61] Urticaria has been associated with approximately 25 cases of AOSD.[70] Recently, there has been a report of psoriasis with AOSD, but with an inverse correlation.[59]

Table 1 Reported associations among adult-onset Still's disease and malignances, autoinflammatory and autoimmune disorders, and dermatologic diseases

Hematopoietic malignancies and solid tumors[41–45]
Hodgkin's disease
Large B-cell lymphoma
Marginal zone lymphoma
T-cell lymphoma
Chronic myeloid leukemia
Myelodysplastic syndrome
Breast carcinoma
Lung carcinoma
Esophageal squamous cell carcinoma
Rectal adenocarcinoma
Liver angiosarcoma
Liver cholangiocarcinoma
Papillary thyroid carcinoma
Squamous cell carcinoma of the larynx
Malignant melanoma
Sarcomatoid renal cell carcinoma
Thymic epithelial tumor
Autoinflammatory and autoimmune disorders
Kikuchi-Fujimoto's disease[25,46,47]
Autoimmune hepatitis[48,49]
Autoimmune hemolytic anemia[50]
Sjögren's syndrome[51]
Polymyositis[52]
IBD[53–56]
Sweet syndrome[57]
Dermatologic diseases
Psoriasis/psoriatic arthritis[58,59]
Palisaded neutrophilic granulomatous dermatitis[60,61]
Urticaria[70]
Miscellaneous
Bilateral trochleitis[62]
Basedow's disease[63]
Sarkoidosis[64]
Polyarteritis nodosa[65]
Erythema nodosum[66]
Miller Fisher syndrome[67]
G6PD deficiency[68]
Celiac disease[69]

IBD, irritable bowel disease.

Paraneoplastic syndrome

Both solid tumors and hematologic malignancies have been reported in association with AOSD, with a prevalence of approximately 2%.[41,44,45] In 72% of all cases of malignancy-associated AOSD, clinical manifestations preceded the diagnosis of a malignancy by a median of 9 months. In the majority of patients with solid tumors, metastasis had already occurred at the time of diagnosis, with the most common malignancies involving the breast and lung cancers,[41,45] not unexpected as they are the most common cancers.

There is an ongoing debate whether malignancy-associated AOSD is a true paraneoplastic syndrome or just a coincidence. Misinterpretation of tumor findings for AOSD[44] and the possibility for an AOSD-like drug reaction cannot be eliminated. There is a report of paraneoplastic syndrome being caused adenocarcinoma of the lung after the first cycle of chemotherapy with paclitaxel plus carboplatin, indistinguishable from AOSD.[71] Another patient with metastatic non–small-cell lung carcinoma developed AOSD after the administration of the first cycle of pemetrexed-gemcitabine regimen.[72]

Chronic inflammation and autoimmunity are associated with the development of malignancy[73]; however, proinflammatory cytokines that are produced in cancer cells may play an important role in the development of malignancy-associated AOSD. The levels of IL-18 were increased in patients with breast cancer exhibiting AOSD-like clinical manifestations. IL-18 stimulates macrophages excessively, which may lead to macrophage activation syndrome.[74]

In terms of differentiation of idiopathic AOSD and AOSD-like paraneoplastic syndrome, key features that point toward the latter include an onset of AOSD after the age of 40 years, the presence of atypical clinical, biologic, or immunologic features, and a poor response to nonsteroidal anti-inflammatory drugs or systemic glucocorticoids.[41,44,45,71] In the absence of a diagnostic gold standard method, the differentiation of idiopathic AOSD from malignancy-associated AOSD, and from drug-induced AOSD-like reactions should be based on the appropriate interpretation of the results of the workup. There is no clear information regarding the clinical course of AOSD when the associated malignancy is treated.

A historic perspective

In 1897, Sir George Frederick Still (1868-1941) described several types of juvenile rheumatoid arthritis while still a registrar at the Great Ormond Street Hospital, London and introduced a previously unrecognizable disease, now referred to as Still's disease or systemic-onset juvenile idiopathic arthritis.[75] He did not describe any dermatologic findings, but in 1933, Sir Harold E.A. Boldero (1889-1960) of Middlesex Hospital, London,[76] noted a "rheumatoid rash" or "Still's rash."

During the 1940s in Europe, patients suffering from a spiking fever, polyarthritis, an eruption, and lymphadenopathy, would be diagnosed with Wissler–Fanconi syndrome.[75] In 1971, an English rheumatologist Eric Bywaters (1910-2003)[3] described a series of 14 adults with a clinical presentation identical to the systemic-onset juvenile idiopathic arthritis and coined the term "adult Still's disease." Subsequent to Bywaters' paper,[3] adult Still's disease has been widely recognized as a clinical entity. By the1980s,[77] many rheumatologists had concluded that adult Still's disease might be more disabling than as originally reported, describing cases that require long-term anti-inflammatory, or cytotoxic, therapy.

More recently, there have been efforts to classify AOSD within the popular nosologic identities, such as seronegative

inflammatory polyarthritis or autoimmune and autoinflammatory diseases,[72] as well as within the so-called "hyperferritinemic syndrome,"[78]a common umbrella gathering different diseases in which the increased ferritin levels might not only reflect an acute-phase response but be directly involved in inflammation.[39]

AOSD is now categorized as a multigenic autoinflammatory disease, at the 'crossroads' of autoinflammatory and autoimmune diseases, due to the involvement of innate and acquired immune systems.[38] The interplay of viral infections, genetic factors, and immune deregulation, may also contribute to the development of the AOSD.[1,72,79]

Regarding the genetic background, AOSD could be associated with some human leukocyte antigens, such as human leukocyte antigen–DR4, –Bw35, and –DRB1, although familial cases have not been reported. Polymorphisms have been described in genes encoding innate immunity-associated factors such as IL-18, or macrophage migration inhibitory factor (MIF) in patients with AOSD; however, their contribution to AOSD pathogenesis remains elusive.[79]

From the very early days of the description of the entity, infections have been proposed to be the underlying causes of disease initiation; both viruses (rubella, measles, Echovirus 7, Coxsackievirus B4, Cytomegalovirus (CMV), Epstein–Barr virus (EBV), Human Herpesvirus 6 (HHV-6), Parainfluenza, Influenza A, Adenovirus, hepatitis B and C, and Parvovirus B19) and bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Yersinia enterocolitica*, *Brucellaabortus*, and *Borreliaburgdorferi*) have been implicated, but a unique and defining trigger has not been identified.[38,79]

Autoinflammation and immune dysregulation

Autoinflammation involves aberrant control of the innate immune response, often through IL-1–mediated pathways, and macrophages are most often the effector cells.[80] In contrast to autoimmune diseases, specific autoantibodies or autoreactive T cell are usually absent; however, autoinflammation and autoimmunity are not mutually exclusive. As a result, the role of CD4+ T helper cells in the pathogenesis of AOSD has been recently considered, with Th1 subset predominating over that of Th2 CD4+ cells and being associated with disease activity.[81]

The uncontrolled inflammation in AOSD may result not only from the unchained activation of proinflammatory mechanisms but also from defects in the immunoregulation.

An early event in immune responses is the release of endogenous danger signals or damage-associated molecular pattern molecules that activate other immune cells, resulting in an inflammatory cascade. Such danger signals set fire to a dysregulated NLRP3 inflammasome, which triggers the secretion of proinflammatory cytokines. At the same time, upon Toll-like receptor-7 activation, dendritic cells induce Th17 response and neutrophil recruitment. Downstream of IL-1b, -18, -8, 6, and tumor necrosis factor-α, along with IL-17, are responsible for the clinical manifestations observed in AOSD.[79]

IL-6 is responsible for the liver synthesis and fast release of ferritin. In addition, skin biopsies from characteristic salmon-colored eruptions have revealed heightened IL-6 levels.[82]

IL-18 triggers a natural killer cell–mediated interferon-γ production, which in turn increases macrophage activation. The pivotal role of IL-1β in AOSD is confirmed by a number of works showing the efficacy of anti–IL-1 drugs in the management of these patients.[83]

Two subsets of AOSD

Emerging data suggest that AOSD with a typical evanescent eruption differs from AODS with atypical cutaneous manifestations, in both, its clinicopathologic presentation and clinical course. In addition, recent findings concerning the patients' cytokine profiles has led to the assumption that there exist two subtypes of AOSD with different immunologic profile:

1. A systemic course with high levels of IL-18, -6, and -1β, interferon-γ, high fever, organ involvement, and exaggerate levels of ferritin, with a greater risk of severe complications
2. A chronic disease course with high levels of IL-8, -17, -6, -23, and tumor necrosis factor-α, and arthritis as the predominant indicators[75]

These findings provide novel insight into disease pathogenesis, suggesting that the underlying mechanisms might be different between these forms and could partially explain the reported differences in drug response.[72] In the light of this new concept, the type of cutaneous lesions can be helpful diagnostic clues and provide insight about the subtypes of AOSD.

Conclusions

Although significant advances have been made in the areas of immunopathology, genetics, and therapeutics, Bywaters'[3] first clinical description of AOSD in 1971 encompasses most of what we know about this disease today. Good clinical and laboratory prognostic markers are still lacking. Because AOSD may first appear with skin findings, we suggest that dermatologists should be familiar with the typical and atypical cutaneous manifestations of the AOSD. Although not common, the presentation of a transient or persistent eruption and systemic signs of unknown origin, may indicate AOSD and should be explored as a rare differential diagnosis.

Conflict of interest

The authors declare no conflict of interest.

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