Up to date

DIAGNOSTIC VALUE OF CUTANEOUS FINDINGS IN ADULT STILL DISEASE, A RARE AUTOINFLAMMATORY DISEASE

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Abstract

Adult onset Still disease (AOSD) is a rare autoinflammatory syndrome of unknown etiology, characterized by fever, arthralgia or arthritis, evanescent rash and systemic involvement. AOSD has variable clinical pictures, from mild symptoms to life-threatening complications, and variable disease course (self-limited, intermittent or chronic). The heterogeneous clinical presentation often makes the diagnosis difficult for an inexperienced clinician. Therefore, cutaneous manifestations are considered important clues for correct diagnosis. Besides the typical salmon-pink, macular or maculo-papular rash, which represents one of the major diagnosis criteria, AOSD can be associated with various types of skin lesions (e.g. persistent, erythematous, slightly scaly or crusted papules with linear configuration) with characteristic histological features. In this short review, we present a series of important diagnostic aspects in AOSD, insisting on cutaneous manifestations, according to available literature data.

Keywords:
Still disease, adult onset, rash, cutaneous manifestations

Autoinflammatory diseases: clues for diagnosis in patients with urticarial rashes

Urticarial skin reactions are one of the most frequent problems seen by dermatologists and allergists in daily practice. The most common reason for recurrent wheals is chronic spontaneous urticaria. Although it is much less common than acute urticaria, it is still a frequent condition, with a point prevalence of 0.5-1% in the European population(1). The underlying mechanisms of chronic urticaria are largely unknown, but being mast-cell mediator-mediated, the first line symptomatic treatment is based on non-sedating antihistamines.

Importantly, there are some much less common diseases that present with urticarial rash and thus mimic urticaria, such as autoinflammatory disorders. In contrast to autoimmune diseases (mediated by T and B cells and other key players of adaptive immunity), autoinflammatory diseases are disorders of the innate immune system(2). They include cryopirin-associated periodic syndrome (CAPS), Schnitzler’s syndrome and others disorders like Adult-onset Still’s disease (AOSD) (Table 1). They are characterized by episodic fever and chronic inflammation of the skin, joints and various other organs. Thus, the list of symptoms can also include inflammation of the anterior eye or uveitis.
resulting in eye redness and pain, periorbital edema, serositis, stomatitis, abdominal pain and diarrhea, myalgia, central nervous system (CNS) involvement, lymphadenopathy\(^2\). Importantly, when present separately, these symptoms do not raise the suspicion of an autoinflammatory disease. On the other hand, a characteristic association of symptoms (e.g. urticarial rash, recurrent fever and arthralgia or arthritis) should make the clinician take into consideration an autoinflammatory disorder.

Autoinflammatory disorders are rare and severely debilitating chronic diseases with limited awareness. Thus they are often underdiagnosed and recognized after many years of evolution. Patients frequently suffer from an impaired quality of life; delay in proper diagnosis may lead to long term complications such as amyloidosis and to serious side effects of immunosuppressive therapies including systemic glucocorticoids.

Therefore, clinicians should consider them as a potential differential diagnosis of urticarial rashes; in fact, urticarial eruptions are prototypic skin lesions of autoinflammatory conditions and cutaneous manifestations can help identify these diseases in early stages.

In this short review, we present a series of important diagnostic aspects in AOSD, a rare autoinflammatory disease, insisting on cutaneous manifestations, according to available literature data.

**AOSD - general data**

AOSD is a rare autoinflammatory syndrome of unknown etiology, characterized by fever, arthralgia or arthritis, evanescent rash and systemic involvement. AOSD has variable clinical pictures, from mild symptoms to life-threatening complications, and variable disease course (self-limited, intermittent or chronic)\(^3\).

It owns its name to George Still who published his monograph in 1897 describing 22 children with symptoms of the disease entity currently known as systemic onset of juvenile idiopathic arthritis. Only in 1971, Eric Bywaters described 14 adults with similar signs and symptoms as in pediatric presentations, thus establishing this new entity\(^4\). Later, in 1992, Yamaguchi et al. developed a set of diagnostic criteria for AOSD\(^5\). Its real incidence and prevalence in different populations is not known. Based on larger reviews from the 1980s it appears that it occurs worldwide and affects women slightly more often than men\(^5\). The disease affects young people, with three quarters of patients reporting disease onset between age 16 and 35 years\(^6, 7\). However, several cases of AOSD with onset after the age of 60 have been reported\(^8\).

Stress has been suggested to be an important risk factor for the development of the disease independent of age\(^9\).

A number of studies linked the condition to a series of HLA antigens e.g. HLA-B17, B18, B35, DR2\(^10\), but they were not confirmed later on, therefore a genetic component remains uncertain. Another hypothesis suggests that AOSD is triggered by various viral and bacterial infections: Epstein-Barr virus, cytomegalovirus, human herpes virus 6, parvovirus B19, coxsackie virus, rubella, echorrhovirus, human immunodeficiency virus, Hepatitis A, B, and C viruses, Mycoplasma pneumonia, Campylobacter jejuni, Chlamydia pneumonia, Yersinia enterocolitica 3 and 9 and Borrelia burgdorferi\(^11, 12\), in a pattern similar to reactive arthritis.

A more recent hypothesis is that alteration in cytokine production has an important pathophysiological role in AOSD; a predominant shift towards T helper (Th) 1 profile was shown in the peripheral blood and tissues of patients with active AOSD. Serum levels of interleukin (IL)-6, tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma are significantly higher than in healthy controls\(^13, 14\). Sustained macrophage activation may result in tissue inflammation,
production of ferritin and increased secretion of inflammatory cytokines such as IL-1, IL-6, IL-18, IFN-gamma and TNF-alpha. High serum levels of IL-18 were also detected in the acute phase of AOSD(15).

**AOSD- clinical manifestations**

AOSD is typically characterized by fever, arthralgia/arthritis, evanescent salmon-pink rash, lymphadenopathy. In some patients, myalgia, serositis and hepatosplenomegaly can be found. Fever is usually high (>39°C), transient, lasting typically under 4 hours, and usually appears in the early evening. Overall incidence of fever among AOSD patients across five of the largest retrospective studies was 95.7%(3).

The maculo-papular, transient eruption is predominantly found on the proximal limbs and trunk and appears in the evening, with the onset of fever and vanishes until the next day.

Arthralgia and arthritis are found in the majority of patients, with knees, ankles and wrists being the most commonly affected joints. The pattern is symmetric. These manifestations are also associated with fever spikes. Some patients may develop destructive polyarthritis(16).

The course of the disease is usually benign, but it can be complicated by acute liver failure, macrophage activation syndrome, pericarditis, pleuritis, respiratory failure and disseminated intravascular coagulation(17). Renal disease is rare and can manifest as interstitial nephritis, subacute glomerulitis, renal amyloidosis and the most recently described, collapsing glomerulopathy.

**Biological findings**

The biological profile of the disease mirrors the systemic inflammation: increased erythrocyte sedimentation rate and C reactive protein, high white blood cell count (>10,000 leukocytes/mm3 with >80% granulocytes), thrombocytosis, anemia, modified liver function tests, high lactate dehydrogenase levels and an increased serum ferritin with less than 20% glycosylated ferritin. Ferritin levels in AOSD are usually higher than those of patients with other autoimmune and autoinflammatory diseases. In most studies, a threshold for serum ferritin levels of 1,000 ng/ml, five times the upper normal limit (40-200 ng/ml) has been used to suggest AOSD(18). Rheumatoid factor and antinuclear antibodies (ANA) are both absent.

Joint radiographs are normal or show minimal changes in the initial phase of the disease (soft tissue swelling, joint effusion, mild periarticular demineralization). Patients suffering from the chronic articular disease pattern can develop ankylosis and present with joint erosions(19).

**Diagnosis**

The clinical presentation of AOSD is heterogeneous and consecutively, the diagnosis can be difficult for an inexperienced clinician. Differential diagnoses include viral/bacterial infections, neoplastic and autoimmune disorders, reactive arthritis, other spondyloarthropathies and the periodic fever syndromes (familial Mediterranean fever and TNF receptor associated periodic syndrome). A positive diagnosis can be made only by ruling out these conditions.

There are several sets of diagnostic criteria for AOSD, all of them having been developed based on retrospective data. Yamaguchi’s criteria (Table 2) are the most widely used and most sensitive (93.5%) (20). If the patient has 5 criteria (at least 2 major criteria) and infection and neoplasia have been ruled out, AOSD can be considered(5).

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>• Fever &gt; 39°C, intermittent, &gt; 1 week</td>
<td>• Sore throat</td>
</tr>
<tr>
<td>• Leukocytosis &gt; 10,000/mm3 (&gt;80% granulocytes)</td>
<td>• Lymphadenopathy</td>
</tr>
<tr>
<td>• Arthralgia &gt; 2 weeks</td>
<td>• Splenomegaly</td>
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<tr>
<td>• Typical rash</td>
<td>• Modified liver function tests</td>
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<td></td>
<td>• Negative rheumatoid factor and ANA</td>
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**Table 2.** Yamaguchi’s diagnostic criteria for AOSD(5)

Three clinical patterns have been described: self-limited or monocyclic pattern, intermittent or polycyclic systemic pattern and chronic articular pattern. The last one is dominated by joint manifestations that can lead to joint destruction. Patients with chronic joint disease have more disability and worse prognosis than patients with systemic symptoms(21).

**Skin manifestations: important diagnostic value**

Skin rash has a significant value for correct diagnosis. It is well known that the typical skin manifestation is a salmon-pink, macular or maculo-papular rash, appearing parallel with the onset of fever-up and disappearing in accordance with fever-down. The characteristic eruption (Figure 1) predominantly affects the extremities and trunk. The histopathologic exam of the skin biopsy most frequently reveals non-specific, modest infiltrates
of polymorphonuclear and mononuclear cells in the upper dermis (Figure 2).

However, unusual skin manifestations have been reported in patients with AOSD [22]. Among these are the so-called flagellate erythema: the lesions are persistent and consist of papules and erythematous plaques with scales and crusts with linear configuration, most commonly located on the chest, abdominal area and posterior torso, but also on the extremities.

Histopathologic exam of such lesions reveals a characteristic pattern [23-24] of dyskeratosis with a distinctive distribution in the upper epidermis and cornified layers and focal hyperkeratosis (Figure 3). A spare infiltrate containing neutrophils is seen in the upper dermis, but no feature of vasculitis was described in any of the mentioned papers.

Other types of eruptions like vesiculo-pustular eruption, generalized persistent erythema, prurigo pigmentosa-like eruption, and angioedema have been reported in AOSD patients [25-28].

**Conclusions**

AOSD is a rare autoinflammatory syndrome characterized by fever, arthralgia/arthritis and an evanescent salmon-pink rash. Diagnosis is usually established using Yamaguchi criteria. Early diagnosis is of great importance, enabling initiation of effective treatment and preventing long term complications of the disease, such as amyloidosis.

Therefore, cutaneous manifestations are considered important clues for correct diagnosis. Besides the typical rash, which represents one of the major diagnosis criteria, recent data clarify that AOSD can be associated with various types of skin lesions (e.g., persistent, erythematous, slightly scaly or crusted papules with linear configuration) with characteristic histological features. This suggests the importance of skin biopsy. It is therefore important to consider AOSD when diagnosing a patient with typical or atypical skin rash. However, further investigations regarding the mechanisms involved in the development of cutaneous manifestations in AOSD are necessary.