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Review

New Markers for Adult-Onset Still's Disease

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ABSTRACT

Adult-onset Still's disease (AOSD) is a rare systemic auto-inflammatory disorder (SAID). Although the pathogenesis of the disease is complex and far from being fully understood, recent progresses in pathophysiological knowledge have paved the way to new diagnostic approaches. Indeed, AOSD diagnosis can be a real challenge, owing to its infrequency, and to the lack of specificity of the principal clinical features (high fever, arthralgia or arthritis, skin rash) and laboratory findings (elevated acute phase reactants, hyperleukocytosis $\geq$ 10,000 cells/mm^3 with neutrophils $\geq$ 80%). None of these manifestations is disease-specific, so clinicians must first rule out neoplastic, infectious or inflammatory conditions. Besides these diagnostic difficulties, several other challenges remain. AOSD is very heterogeneous in terms of clinical presentation, evolution and severity. Thus, new biomarkers are required to assess: (i) disease activity; (ii) disease severity (through the identification of patients at risk of severe organ failure, and eventually of life-threatening complications, such as reactive haemophagocytic lymphohistiocytosis); (iii) disease evolution (which can be monophasic, relapsing, or progressive, with either systemic inflammation or chronic erosive arthritis); (iv) and treatment efficacy. The identification of new markers can only be done through a better understanding of the pathogenesis of the disease. After a short focus on the current AOSD pathophysiological knowledge, this article reviews the main biomarkers that have been proposed in the literature over the last few years.

1. Introduction: a diagnostic challenge

Adult-onset Still's disease (AOSD) is a rare systemic auto-inflammatory disorder (SAID) that was first described in the early 1970s [1], about a century after the description of its childhood counterpart, the systemic form of juvenile inflammatory arthritis (sJIA). AOSD's incidence is estimated at 0.16 to 0.4 per 100,000 persons according to the countries [2,3], and reported prevalence rates range from 1 to 34 cases per 1 million persons in the Japanese and the European populations [3]. In most patients, AOSD is characterized by four cardinal symptoms: spiking fever, an evanescent salmon-pink maculopapular rash, arthralgia or arthritis and a white-blood-cell count (WBC) $\geq$ 10,000/mm^3, mainly neutrophilic polymorphonuclear cells (PMNs) [2]. Several other clinical and laboratory findings may occur [2,3] [Table S1; see the supplementary material associated with this article online]. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are common (90 to 100%). Increased serum ferritinaemia with glycosylated fraction $\leq$ 20% appears one of the most suggestive laboratory findings [2].

AOSD management offers several challenges. First, diagnosis of AOSD is difficult, due to the infrequency of the condition and because none of the clinical and biological features is disease specific. Hence, clinicians must first rule out neoplastic, infectious or inflammatory conditions [2,4] (Table 1). Diagnostic and therapeutic wavering is common; in one series of patients presenting with fever of unknown origin, 90% of those eventually diagnosed with AOSD also received antibiotics [5]. There are often delays in diagnosis: a recent retrospective series of 57 patients found a mean diagnosis delay of 4 months [6]. Yet, it has been shown that an early diagnosis may improve the prognosis [6,7]. Several sets of classification criteria have been proposed for research and may facilitate diagnosis [4,8] (Table 2). AOSD is heterogeneous in terms of clinical presentation, evolution and severity, suggesting different pathogenic mechanisms [2,3]. Different phenotypes have been suggested, ranging from very explosive systemic forms to more chronic articular subtypes [9–11]. Most of the patients have a favourable course, while some develop life-threatening complications, such as reactive haemophagocytic lymphohistiocytosis (RHL). AOSD prognosis has been dramatically improved by biological therapies, although some patients may be refractory to treatment [7].

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Table 1
Main differential diagnoses of adult-onset Still's disease (not exhaustive) (adapted from [2,3]).

Diseases	Helpful diagnostic tests
Infectious diseases	
Bacterial	
Pyogenic bacterial septicaemia	Blood cultures, PCT
Infectious endocarditis	Heart ultrasonography
Bilary, colic or urinary occult infections	CT scanner
Tuberculosis	IGRAs, PCR, CT scanner
Brucellosis, yersiniosis. . .	Serology, PCR
Viral infections	
HIV, viral hepatitis, parvovirus B19, Herpes viridae, measles, rubella. . .	Serology, PCR
Parasitological infections	
Toxoplasmosis, abscessed parasitosis	Serology, PCR
Malignant diseases	
Haematological disease	
Hodgkin disease or non-Hodgkin lymphoma	Lymph node biopsy
Angio-immunoblastic lymphadenopathy	Bone marrow examination
Castelman disease	CT scanner
Myeloproliferative disorders	PET/CT scanner
Solid cancers	
Kidney, colon, lung. . .	CT scanner, PET/CT scanner
Paraneoplastic syndroms	
Systemic diseases	
Autoimmune diseases	
Systemic lupus erythematosus	Antinuclear autoantibodies
Polymyositis, dermatopolymyositis	Idem, biopsy
Rheumatoid arthritis	RF, ACPA
Polyarteritis nodosa or other vasculitis	ANCA, arteriography
Auto-inflammatory diseases	
Post-streptococcal arthritis	ASLO
Reactive arthritis	HLA B27, magnetic resonance imaging
Hereditary auto-inflammatory syndromes	Familial history
Familial Mediterranean fever	MEFV gene analysis
Mevalonate kinase deficiency	Urinary mevalonic acid, mevalonate kinase analysis
TNF receptor-associated periodic syndrome	TNFRSF1A gene analysis
Cryopyrin-associated periodic syndromes	CIAS1 (NLRP3) gene analysis
Other	
Sarcoidosis	ACE, biopsy (granulomatosis)
Neutrophilic dermatosis, Sweet syndrome	Biopsy. . .
Drug-related hypersensitivity or other pseudo-lymphoma	
Schnitzler syndrome	
Kikuchi-Fujimoto disease	

PCT: procalcitonin; CT: computed tomography; IGRAs: interferon gamma release assays; PCR: polymerase chain reaction; PET: positron emission tomography; RF: rheumatoid factor; ACPA: anti-citrullinated antibody; ANCA: anti-neutrophil cytoplasmic antibodies; ASLO: anti-streptolysin O antibody; HLA: human leukocyte antigen; MEFV: Mediterranean fever; TNFRS1A: tumour necrosis factor receptor superfamily member 1A; ACE: angiotensin converting enzyme.

Table 2
Classification criteria for adult-onset Still's disease.

Yamaguchi et al. [4]	Fautrel et al. [8]
Major criteria	
Fever $\geq$ 39 °C lasting 1 week or more	Spiking fever $\geq$ 39 °C
Arthralgia lasting 2 weeks or more	Arthralgia
Typical skin rash: maculopapular, non-pruritic, salmon-pink rash with concomitant fever spikes	Transient erythema
Leukocytosis $\geq$ 10,000/mm^3 with neutrophil polymorphonuclear count $\geq$ 80%	Pharyngitis
	Neutrophil polymorphonuclear count $\geq$ 80%
	Glycosylated ferritin fraction $\leq$ 20%
Minor criteria	
Pharyngitis or sore throat	Typical rash
Lymphadenopathy and/or splenomegaly	Leukocytosis $\geq$ 10,000/mm^3
Liver enzyme abnormalities (aminotransferases)	
Negative for rheumatoid factor or antinuclear antibodies	
Exclusion criteria	
Absence of infection, especially sepsis and Epstein-Barr viral infection	None
Absence of malignant diseases, especially lymphomas	
Absence of inflammatory disease, especially polyarteritis nodosa	
Diagnostic requires	
At least 5 criteria, including 2 major criteria	At least 4 major criteria
and	or
No exclusion criteria	3 major and 2 minor criteria

Yamaguchi's criteria have the best sensitivity of 96.2%, and a specificity of 92.1%. They are the most widely cited criteria in the literature, and the most widely validated. Nevertheless, they require the exclusion of neoplasms, infections and autoimmune diseases that mimic AOSD. Using a 2002 retrospective analysis of 72 patients with AOSD and 130 controls, Fautrel et al. developed updated criteria with a sensitivity of 80.6%, but a higher specificity of 98.5%. These criteria do not require exclusions but include the glycosylated ferritin.

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