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Diagnosis and classification of adult Still's disease

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ABSTRACT

The cornerstone of adult onset Still's disease is the triad of daily fever, arthritis and rash. This syndrome remains enigmatic and most often a disease of exclusion. There are both musculoskeletal as well as systemic features. More importantly, reactive hemophagocytic syndrome may occur in patients. In this review we attempt to place this syndrome in perspective, including data on geoepidemiology, clinical and laboratory features.

1. Introduction

In 1896; George Still described for the first time a disease in children called after his name "Still's disease" characterized primarily by daily spiking fever, arthritis and rash [1]. Seventy-five years later, in 1971, Bywaters described a disease in adult patients resembling Still's disease in children which he termed "Adult onset Still Disease" (AOSD) [2]. Since then, AOSD has been widely studied and regarded as an inflammatory condition with autoimmune elements.

The exact mechanism of appearance of AOSD remains obscure, yet, many theories have been proposed including infectious triggers as triggers of the disease, mainly due to viral (rubella, echovirus 7, mumps, Epstein–Barr, cytomegalovirus, parainfluenza, parvovirus B19, coxackie, adneno, influenza, herpes, and hepatitis B and C viruses) and bacterial pathogens (Yersinia entercolitica and M. pneumonia) [3–5]. However, genetic factors with HLA linkage (HLA DRB1*1201 and 1501, B35, DR2 DR5) have also seemed to have a pathogenetic role in the disease emergence and progression [6]. Stressful life events during the year preceding the disease onset were also found to be associated with the onset of AOSD [7].

A retrospective study in France estimated an occurrence rate of 0.16 per 100.000 persons with an equal sex ratio and a bimodal age of distribution i.e. 15–25 and 36–45 years [8]. Though AOSD as the name indicates is adulthood disease; case reports were described in medical literature regarding late onset around the age of 70 [9,10].

2. Clinical features

The cornerstone of the disease is a triad of daily fever, arthritis and rash. These features are characterized as following:

- Fever – usually daily, exceeds 39°, can be bi-peaks (peaks twice daily), resolving within few hours, persisting up to 20% of cases even between spikes [11]. The clinical presentation is often reached by exclusion while investigating a patient with fever of unknown origin (FUO). [12]
- Musculoskeletal manifestations – though arthritis is the main representative of the musculoskeletal system; several other manifestations can be found such as arthralgia and myalgia [11]. Arthritis, at the beginning is mild and localized, aggravating through the course of the disease becoming more severe and polyarticular. Joints affected more often are knees, wrists, ankles and elbows. PIPs and shoulders may also be involved [11].
- Rash – the third component of the triad, typically macular or maculopapular, salmon-colored rash, involving mainly the trunk and extremities, occasionally the palms and soles, tends to accompany fever. Rash of AOSD can be misdiagnosed as drug eruption.

2.1. Other common manifestation

- Liver – slight elevation of liver enzymes is not uncommon [13]. Fulminant hepatic failure was described in 8 patients with AOSD; four died [14].

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- Splenomegaly – was described in AOSD patients in a range of 30–65% [15,16]. Lymphoma is always a differential diagnosis since fever is a part of both diseases in addition to splenomegaly.
- Lymphadenopathy and pharyngitis – mild enlargement of cervical lymph nodes is common, moreover; severe a characteristic non-suppurative pharyngitis is frequent.
- Heart and lungs – a variety of both systems manifestations can be seen including pericarditis, pleuritis, pleural effusions, and pulmonary infiltrates [17,18]. Rarely patients complain of pleuritic chest pain and dyspnea.
- Reactive hemophagocytic syndrome (RHS) – is a severe and fatal hematological disorder characterized by activation of differentiated macrophages to be involved in phagocytosis of hematopoietic cells. Pancytopenia and acute respiratory distress syndrome (ARDS) are common manifestations of the syndrome. This syndrome was described in 6 AOSD patients from a series of 50 patients presented by Arlet et al. [19].

3. Laboratory findings

Neutrophilic leukocytosis is common (98%), anemia of chronic disease is seen (69%), and it is reversible after the disease subsides. Reactive thromocytosis is commonly seen. Pancytopenia should alert the physician to haemophagocytic syndrome which necessitates prompt immunosuppressive treatment [11]. Hepatocellular enzymes are elevated in about 62% of patients, while cholestatic liver enzymes are elevated in about 40% of patients, Billirubin is mostly normal (88%) [13]. Inflammatory markers in blood tests are elevated including ESR (96%) and CRP (92%). Immunoglubolins are elevated in 46% of patients [13]. Coagulation abnormalities are rare and include prolongation of prothrombin time or partial thromboplastin time and disseminated intravascular coagulation [6]. Ferritin levels were found to be elevated in 99% of AOSD. With 51% of patients with serum ferritin levels of 1000–1500 ng/ml, and 32% of patients with serum ferritin levels of more than 1500 ng/ml [13]. It is not clear whether it represents an acute phase reactant or has a role in the pathogenesis of AOSD. Furthermore, serum ferritin levels correlate with disease activity and often normalize with remission of the disease [20]. In one retrospective study with 49 patients, it was found that fivefold increase in serum ferritin had 80% sensitivity and 41% specificity in diagnosing AOSD [21]. Some studies suggest the use of ferritin as predictive of progress to chronic disease [22].

Glycosylated ferritin is a more specific diagnostic marker than ferritin. In healthy subjects 50–80% of ferritin is glycosylated. In inflammatory diseases the fraction of glycosylated ferritin drops because of saturation of the glycosylation mechanism. In AOSD the phenomenon is particularly prevalent, where the glycosylation of ferritin is $<20\%$ [11]. The sensitivity of glycosylated ferritin test in the diagnosis of AOSD is 43% and the specificity is 93% [21].

Antinuclear antibodies (ANA) and Rheumatoid factor (RF) are mostly negative (in 100% and 95% of patients, respectively) [13].

Elevated serum levels of interleukin-6, tumor necrosis factor, interferon gamma and interleukin-18 are observed but these tests are not specific for AOSD [23].

It was observed that Germinal center kinase-like kinase (GLK) expressing T-cells and their products are significantly higher in patients with active AOSD. Testing their expression in patients was proposed as a disease activity biomarker [24].

4. Radiographic findings

Radiographs during the initial acute phase of AOSD are often not specific, being either normal or showing soft tissue swelling or mild joint effusion. Characteristic late finding in about 40% of patients is a nonerosive narrowing of the carpometacarpal and intercarpal joint spaces of the wrist, which often progresses to bony ankylosis, most marked in pericapitate region. Less common are radiographic intertarsal and tarsometatasal changes and ankylosis of the cervical spine and distal interphalangeal joints. Destruction of the hip joint, and less commonly the knee, has been described as a rare complication that often requires total joint replacement, as opposed to wrist and ankle involvement which only causes limited disability [11].

5. Pathological findings

The findings of biopsy of involved tissue in AOSD are not specific, yet it is usually performed in order to exclude other differential diagnosis. The most common biopsy performed is skin biopsy which shows perivascular inflammation of the superficial dermis with lymphocytes and histocytes. Direct immunofluorescent is usually negative for immunoglobulins and complement. Other tissues biopsies often reveal non specific inflammatory changes. Synovial fluids in AOSD are inflammatory with a polymorphonuclear predominance. Pleural and pericardial effusions are often sterile inflammatory exudates [25].

Liver biopsy typically shows mild periportal inflammation with monocyte infiltration [6].

6. Diagnosis

The diagnosis of AOSD is clinical, and in the absence of a definitive diagnostic test, often necessitates the arduous exclusion of potential mimickers, that is infectious, neoplasmatic, autoimmune, and other autoinflammatory diseases [11].

Infectious mimickers include viral syndromes. Cultures and serological tests are part of the workup before the diagnosis is made final. Neoplastic etiologies such as lymphoma and leukemia should be always ruled out. Sometimes the presentation defers widely and simple tests can help making the diagnosis, while in others cases the differentiation is difficult and may need tissue biopsy or bone smear examination.

Autoimmune and inflammatory diseases are part of the differential diagnosis. Periodic fever syndromes like familial Mediterranean fever and TNF receptor associated periodic syndromes should be considered.

Several diagnostic criteria have been proposed for the diagnosis of AOSD. These criteria are based on the combination of clinical and laboratory findings as discussed above. They all by nature are based on retrospective data and none of them are were compared and validated to a “gold standard” control group, which raises questions regarding their reported sensitivity and specificity [11]. The sensitivity of the Yamaguchi criteria is hampered by the large number of clinical conditions that should be excluded whereas Fautrel’s set of diagnostic criteria requires measurement of glycosylated-ferritin which is not available many health care facilities [27,28].

The work of Masson et al. from 1996 compared 6 types of criteria in AOSD. The Yamaguchi’s criteria are the most sensitive (93.5%), followed by Cush’s (80.6%) and Calabro’s (80.6%) [26].

Yamaguchi et al. [27] work conducted on a multicenter survey of 90 Japanese patients with AOSD and of 267 control patients to form a set of criteria consists of major and minor criteria (Table 1). Requiring 5 or more criteria including 2 or more major criteria yielded 96.2% sensitivity and 92.1% specificity.

Fautrel’s Criteria includes Serum ferritin and glycosylated ferritin fraction and it provides 80.6% sensitivity and 98.5% specificity [28].