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ORIGINAL ARTICLE

Adult-onset Still's disease: a report of 28 cases and review of the literature

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Abstract Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology. It is characterized by fever, skin rash, polyarthralgias or polyarthritis, sore throat, hepatosplenomegaly, lymphadenopathy, leukocytosis, liver enzyme elevation, and high serum level of ferritin. Several kinds of skin lesions have been reported in this condition. The aim of this study was to assess the clinical and laboratory aspects of 28 patients with AOSD in central Iran. According to the diagnostic criteria of AOSD, we identified 28 patients between 2002 and 2007. We intended to describe the clinical characteristics, treatment, and outcome of our patients with AOSD. Of 28 patients with AOSD, 21 (75%) were female, 7 (25%) were male. Fever (100%), sore throat (92%), Arthralgia (92%), dermatographism (92%), typical rash (85%) and arthritis (60%) were the most common findings. The mean values of laboratory findings were as follows; C-reactive protein (CRP) level of 14.4 mg/dl, erythrocyte sedimentation rate (ESR) of 91.5 mm/h, leukocyte count of 15744.4/μl. Abnormal levels of aspartate aminotransferase and alanine aminotransferase were observed in 25 (89%) patients. Twenty patients (71%) had high ferritin values (>500 ng/ml). The clinical characteristics were similar to previous series. A febrile polyarthritis was the most frequent presentation form. Dermatographism was frequently encountered phenomenon in our patients with AOSD. Being that dermatographism is a simple inducible skin reaction, along with its sensitivity in active disease, we suggest more controlled studies to validate accuracy and positive predictive value of it in convenient clinical setting in the diagnosis of AOSD and to consider including it in diagnostic criteria.

Keywords Adult-onset Still's disease (AOSD) · Dermatographism · FUO · Rheumatoid arthritis · Dermographism

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Introduction

The term adult-onset Still's disease (AOSD) was used to describe patients who had not fulfilled criteria for classic rheumatoid arthritis but had signs and symptoms similar to the children with systemic onset juvenile rheumatoid arthritis [1]. It is a rare systemic disorder of unknown etiology characterized by spiking fever, evanescent rash, arthritis and multi-organ involvement. The first description of an adult patient with signs and symptoms of AOSD, (erroneously labelled rheumatoid arthritis), was published in 1896. Then in 1897 it was described by George Still in 22 patients [2]. In 1971, Eric Bywaters described 14 adults with similar presentation, and termed it adult-onset Still's disease (AOSD) [1, 3, 4].

Because there is no pathogonomic test for the disease, diagnosis is based on a set of clinical and laboratory criteria

[5, 6]. Several sets of classification criteria have been published for AOSD (see Table 1).

The pathogenesis of AOSD is unknown, but genetic factors and various infectious agents have been considered as predisposing factors [6]. In one of the largest series of 62 patients, an association between HLA system and AOSD was reported [7].

The clinical presentation of AOSD is heterogeneous, and the spectrum of differential diagnoses is wide, including infectious, neoplastic, and autoimmune disorders, which should be ruled out before the diagnosis of AOSD can be made [6, 8].

Dermatographism (an exaggerated whealing tendency when the skin is stroked) is one of the objective findings in AOSD [5, 6, 9]. Herein, we describe clinical and laboratory manifestations of 28 patients with AOSD in central Iran.

Patients and methods

All of the patients with a diagnosis of AOSD who had been followed-up in our rheumatology center in Yazd (central Iran) between 2002 and 2007 were retrospectively evaluated. They fulfilled the diagnostic criteria of AOSD proposed by Yamaguchi. After a detailed history and physical examination, all patients underwent a series of laboratory tests including CBC and differentiated count, ESR (erythrocyte sedimentation rate, Westergren method), CRP (C-Reactive Protein), RF (rheumatoid factor, Bionik, Tehran, Iran), ANA (anti-nuclear antibody, AESKULISA Germany), Anti CCP (AESKULISA Germany), Ferritin, LFT (liver function test) and urinalysis. All of the clinical and laboratory characteristics were recorded by using a standardized form. Selected patients underwent bone marrow biopsy and other complementary diagnostic studies based on their clinical setting.

Table 1 Diagnostic criteria of adult-onset Still's disease

Yamaguchi	**Cush**
Major	2 points
Arthralgia >2 weeks	Quatidian fever >39
Fever >39 intermittent ≥1 week	Still's (evanescent) rash
Typical rash	Carpal ankylosis
WBC >10,000 (>80% granulocyte)	WBC >12,000 and ESR >40 mm/1st
	RF and ANA: Neg
Minor	
Sore throat	1 point
Lymphadenopathy and/or splenomegaly	Onset age <35 years
Abnormal LFT	Arthritis
RF and ANA: Neg	Prodromal sore throat
	Serositis
	RES involvement or abnormal LFTs
	Cervical or tarsal ankylosis

ANA antinuclear antibody, *RF* rheumatoid factor

LFT liver function test, *Neg* negative, *RES* reticuloendothelial system

Results

Of 28 patients, 21 (75%) were female and 7(25%) were male. The mean age of patients was 24.88 ± 11.64 year at the time of diagnosis.

The characteristics of clinical manifestations were found as follows: fever ($n = 28.100\%$), sore throat ($n = 26.92\%$), arthralgia ($n = 26.92\%$), rash ($n = 24.85\%$), arthritis ($n = 17.60\%$), lymphadenopathy ($n = 16.57\%$), splenomegaly ($n = 9.32\%$) and Pericardial effusion ($n = 8.28\%$). In 26 patients (92%) dermatographism was positive in active phase of disease and in nine patients (32%) persisted in remission phase.

ESR with mean value of 91.5 ± 35.5 mm/h and CRP with mean value of 14.4 mg/dl were prominent laboratory findings in our cases. Leukocytosis with a mean value of 15,744.4 ± 5,997.32/μl was present in 92% of the cases.

Twenty patients (71%) had high ferritin values (>500 ng/ml) and eight patients (33%) had a ferritin value within normal range. The mean value of ferritin was 1,200.94 ± 588.8 ng/ml.

In one patient, ANA was positive (1.3 ISR) and another one had positive RF (9 IU/ml), where their titers were considerably low.

Abnormal levels of aspartate aminotransferase and alanine aminotransferase were observed in 25 (89%) patients.

The clinical course of the patients was as follows: polycyclic pattern in 21 patients (75%), chronic pattern in three patients (10%) and monocyclic pattern in four patients (15%).

During follow-up, one patient developed a poor general condition, bleeding tendency, and thrombocytopenia, with impression of macrophage activation syndrome (MAS), bone marrow biopsy was done and the diagnosis was established. Six patients developed pericardial effusion (21%) (Comparison of clinical manifestation between our study and the others are shown in Table 2).

All of the patients received at least a course of prednisolone 10–30 mg/day (Aboureihan, Tehran, Iran) and oral methotrexate 7.5–25 mg/day (Ebewe, Austria).

Four patients were treated with cyclosporine 150–200 mg/day (Zahravi, Tabriz, Iran). For 24 patients, hydroxychloroquine 200 mg/day (Amin, Tehran, Iran) was used. Also, a biologic agent was administered in one of our patients: Rituximab 1,500 mg (MabThera, Novartis, Switzerland) and

Table 2 Clinical features of patients with AOSD

Clinical features (Number of patients)	Cagatay (84)	Chen (82)	Pouchot (62)	Mert (20)	Bambery (18)	Singh (14)	Present study (28)
F/M	59/25	59/23	28/34	12/8	10/8	5/9	21/7
Mean age (year)	33.33 ± 13.64	–	–	34	29	29.58	24.88 ± 11.64
Fever (%)	95.2	100	100	100	100	100	100
Arthralgia (%)	96.4	100	100	90	100	100	92
Arthritis (%)	69	100	94	65	–	100	60
Sore throat (%)	65.5	84	92	75	–	35	83
Rash (%)	59.5	87	87	85	50	57	85
Dermatographism (%)	26.2	59	–	–	–	–	92
Lymphadenopathy (%)	33.3	–	74	15	67	–	57
Splenomegaly (%)	28.6	–	55	40	56	–	32
Pericarditis (%)	11.9	–	37	–	0.05	–	21

Leflunomide 20 mg/day (Arava Aventis, Switzerland) were given in two other patients.

Discussion

AOSD is a rare inflammatory disease that characteristically affects young people [5, 8] and affects women slightly more often than men. This is the first study on AOSD in Iran and we do not have any published data on the prevalence of it in this country. In a retrospective review of 45 patients, 60% of the patients were women, and in Cagatay review of 84 patients 70.2% were female, [6, 10] which was comparable to our series that 75% of our patients were also women.

Fever, sore throat, skin rash, arthralgia, myalgia, lymphadenopathy, splenomegaly, and serositis were the main clinical observations. The onset of disease is usually heralded by a sore throat and constitutional manifestations [11]. In a review of 341 cases, sore throat was reported in 69% compared to 92% in our patients [12]. It is known as a cardinal sign of AOSD and may be associated with odynophagia [11]. Despite the presence of severe sore throat, physical examinations fail to show any abnormal findings. Throat cultures are negative and viral serological tests were non-diagnostic in all AOSD patients [11, 13]. Antibiotic therapy is ineffective [13]. Magnetic resonance imaging (MRI) of the larynx in six active AOSD patients showed crico-thyroid perichondritis [13]. The authors believe that sore throat with normal physical examination in the setting of fever and polyarthralgia is highly suggestive of AOSD.

The fever is classically described as quotidian, with temperature spiking once a day to 39°C or higher [4, 5, 14]. In the differential diagnosis of a patient with FUO (fever of unknown origin) AOSD should be considered, [15–18] and maculopapular rashes, arthralgia and sore throat should raise the suspicion of AOSD. Tabak reported AOSD in 11% of patients with FUO [16]. Low-grade fever is sometimes encountered in old patients [6].

The classic rash is an evanescent, salmon-pink, maculopapular eruption, which frequently appears during febrile attacks and is predominantly found on the proximal limbs and trunk with rare involvement of the face and distal limbs. The rash can be mildly pruritic or may be associated with burning [4, 5]. In some studies, dermatographism and Köebner phenomenon have been described as objective features of AOSD [5, 6, 9, 19]. Various atypical rashes have been reported in AOSD such as persistent dermal plaques, [20–23] urticaria [19, 24], and vesicolupustular lesions on the hands and feet [25].

Dermatographism has been reported in 59% in a series of patients in Taiwan and also in 26.2% of patients in Turkey [6, 9]. Dermatographism could be seen in 1.5–5% of the healthy population [26, 27]. Pathogenesis of dermatographism is unclear [19]. It is usually idiopathic, but it may be associated with systemic use of penicillin, famotidin, and atorvastatin [27, 28]. In a review of 40 patients, there is a close relationship between dermatographism and psychic factors, drug reactions, and scabies [27]. Superficial, perivascular leukocytic infiltrations are found in skin. Biopsy of the lesions reveals few infiltrating eosinophils and neutrophils associated with minimal extracellular major basic protein and neutrophil elastase deposition [27].

Although it is not a specific test (like fever or sore throat as included in the criteria), it can be considered as a sensitive diagnostic test in AOSD. The higher prevalence of dermatographism in our series may be due to racial differences or different patterns of AOSD in Iran. Even though in our series dermatographism was positive in 92% in acute phase of the disease, this percent decreased down to about 32% in remission phase. Unpublished data indicates that most of the other immune mediated disorders such as diabetes, asthma, and atopy also seem to be highly frequent in Iran.

Arthralgia and arthritis are found in AOSD, with incidences ranging from 64 to 100%. The joints most frequently affected are the knees, wrists, and ankles [7, 10, 29]. The pattern of arthritis is symmetric [7]. Arthritis is often found after constitutional and extra-articular manifestations [6]. Late diagnosis and treatment can lead to destruction of the joints. Destructive arthritis is found in 25% of patients, and carpal joints are the most affected joints [4, 5, 30]. Narrowing of the carpometacarpal and intercarpal joint spaces is said to be specific for AOSD (as compared to more radiocarpal involvement in RA) [30, 31].

AOSD could be seen as the first presentation in pregnancy [32].

The laboratory investigations show exaggerated systemic inflammatory responses such as polymorphonuclear leukocytosis, thrombocytosis, normochrom normocytic anemia, raised ESR, CRP and ferritin. Elevated LFT and LDH are also seen [3, 4, 6, 14]. High levels of ferritin seem to be characteristic of AOSD [3, 6, 11]. Nearly 70% of patients have hyper-ferritinemia [11]. In our study, 20 patients (71%) had high levels of ferritin. Cagatay reported very high levels of ferritin (>2,000) in 38% of patients [6]. High levels of ferritin can be seen in other diseases such as liver disease, infections, and malignancies and especially in the hemophagocytic syndrome. Ferritin levels in AOSD are usually higher than those found in other autoimmune or inflammatory diseases [3, 11]. Hyper-ferritinemia in AOSD is not related to iron metabolism and is likely to be a consequence of cytokine secretion induced by the reticuloendothelial system or hepatic damage [3, 6], but in some cases, ferritin levels are increased and LFT are normal [3]. Several cytokines—mainly, IL1b, IL18, TNFα, and IL6, seem to increase the production of ferritin [3]. A more specific diagnostic marker may be glycosylated ferritin. In AOSD, decreased glycosylated ferritin, an isoform of ferritin, was noted in comparison with other inflammatory diseases. In 50–80% of healthy individuals, ferritin is glycosylated while in inflammatory diseases it drops to 20–50%, and in AOSD less than 20% [3]. Recently in some studies hyper-ferritinemia was correlated to histiocyte hyperactivity, which can lead to association of AOSD and MAS [6]. In a review of 14 patients by Singh et al., MAS was reported in two patients, one after having had sulfasalazine therapy [33]. MAS was seen in one of our patients.

Hyper-ferritinemia with a value between 4,000–30,000 mg/dl has been reported in association with the onset and flare of disease activity [34].

The validity of hyprferritinemia as a diagnostic test was evaluated in a retrospective study, where a fivefold increase in serum ferritin had 41% specificity and 80% sensitivity [35]. Furthermore, serum ferritin levels correlate with disease activity and after the disease goes into remission, it is normalized [11]. Glycosylated ferritin cannot be used to monitor disease activity or response to treatment, because it remains low for many months even after the disease goes into remission [36].

The clinical course of AOSD can be divided into three main patterns:

1. The monocyclic pattern, which is often characterized by only one episode with systemic symptoms and remission is achieved within 1 year.
2. The intermittent or polycyclic systemic pattern, which is characterized by recurrent flares, with complete remission between the flares.
3. The chronic articular pattern, which is dominated by severe articular manifestations that can lead to joint destruction [6].

In the beginning, AOSD was considered as a benign disorder without any complications, the disease has a more ominous prognosis and has a serious complication such as amyloidosis, pericarditis, MAS, etc. [14, 37].

It is important that we know the lack of awareness of this disease is one of the major reasons for misdiagnosis [14].

The treatment of AOSD has centered around the use of NSAIDs, steroids, and disease-modifying antirheumatic drugs (DMARDs) [1]. Aspirin or NSAIDs are recommended in the initial treatment of AOSD [38]. LFT should be carefully monitored in patients in whom NSAIDs are used. Prednisolone should be used for the patients presenting with persistent anemia, pericarditis, serositis, and raised liver enzymes [5]. DMARDs such as methotrexate (MTX), azathioprine, cyclosporine, and cyclophophamide have been used for maintenance therapy and the control of disease [39]. Ulfasalazine should be avoided in AOSD [33].

MTX is a routine drug used in AOSD and arthritis is resolved completely in many cases treated with MTX. It is a useful option in elderly patients because they are at risk for corticosteroid-induced adverse effects and MTX has little adverse effect [40].

Whereas raised preinflammatory cytokines such as IL1α and TNFα are mainly factors in pathogenesis of AOSD, biologic agents are recommended for treatment of it [41–43]. Use of infliximab, the monoclonal chimeric anti-TNFα antibody, has been reported in various studies [39, 44–48]. Etanercept, the other TNF-blocking agent, has also been employed in studies [49–52]. Furthermore, etanercept was administered in a patient and nephrotic syndrome due to secondary renal amyloidosis, resulting in amelioration of proteinuria [53].

Most recently, IL1 blockade (Anakinra) has been used as a new therapeutic option [54–57].

Rituximab, a mono-clonal antibody against CD20 B-cells, is a new option in treatment. Ahmadi-Simab

reported useful effects of Rituximab in AOSD [58]. We also used it in treatment in one of our patients. The index case of AOSD in our study received Mabthera 2 years of the diagnosis due to persistent fever, rashes, abnormal laboratory tests, intolerance, and poor response to almost all DMARDs. She had remarkable improvement for more than 1 year (until the present time).

In conclusion, variable clinical features and laboratory findings could be seen in patients with AOSD. Fever, sore throat, arthralgia, dermatographism, typical rash, and arthritis were the most common findings. The clinical presentation of our patients was similar to that of the same series, but there were some differences. Dermatographism was found in 92% of our patients, which is more frequent than the others. The higher prevalence of dermatographism in our series may be due to racial difference or different patterns of AOSD in Iran. Dermatographism is a frequently encountered phenomenon in patients with AOSD, and along with its sensitivity in active disease, it can be considered as one criterion for diagnosis.

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Conflict of interest statement We declare that we have no conflicts of interest.

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