

Adult-onset Still's disease: clinical presentation in a large cohort of Italian patients

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Abstract

Objective

To characterise the clinical phenotype of Italian patients with adult-onset Still's disease (AOSD).

Methods

Sixty-six subjects who received a definite diagnosis of AOSD were seen and followed-up at our institution from 1991 to 2009. The diagnosis was made by a senior rheumatologist and confirmed by Yamaguchi's criteria for AOSD. Data regarding clinical manifestations, laboratory and radiographic features, and disease course were collected and compared with those reported in other published series of different ethnicity.

Results

The most frequent features were: articular pain (100%), acute phase reactants elevation (100%), elevated serum ferritin (97%), high fever (95%), negative RF and ANA (92%), neutrophilia (82%), skin rash (79%), and overt arthritis (79%). Forty-percent of patients showed a chronic articular disease. Five subjects (8%) experienced severe, life-threatening complications, and 1 patient died. As compared to other North American, North European, Middle Eastern, and Far Eastern cohorts, Italian patients showed significant differences in several epidemiologic, clinical and laboratory features.

Conclusions

Our data show that AOSD is rare in the Italian population, and that its clinical presentation appears to be significantly influenced by the ethnicity of the affected patients. Given its broad differential diagnosis, early recognition of this condition is challenging, but it could become crucial in the setting of severe complications. Beyond the protean manifestations of this disease, a clinical picture of seronegative febrile arthritis and skin rash, concurrent with a marked elevation in serum ferritin should always be remindful of AOSD.

Key words

Adult-onset still's disease, historical cohort study, clinical presentation, disease onset, severe complications.

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Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory condition of unknown aetiology and pathogenesis. AOSD is characterised by spiking fever with an evanescent rash, arthritis and multi-organ involvement (1). It owes its name to George Still who published in 1897 his monograph, 'On a form of chronic joint disease in children' describing the features of 22 children with systemic-onset juvenile idiopathic arthritis (2). Following this initial description 'Still's disease' became the eponymous term for juvenile inflammatory arthritis. In 1971, Eric Bywaters described 14 adults with presentation similar to systemic-onset juvenile idiopathic arthritis, convincingly establishing the new disease entity of 'adult Still's disease', later denominated AOSD. It involved adult patients who did not meet the criteria for classic rheumatoid arthritis, but displayed features similar to those described in paediatric Still's disease (3). AOSD is a rare rheumatic condition with an annual incidence of approximately 0.16 per 100.000 population (4). Since it may have multiple clinical presentations and the spectrum of differential diagnoses is wide, case identification can be difficult and the numbers available on the frequency of this disease should be viewed with caution.

We describe a series of 66 patients with AOSD seen over an 18-year period at the Unit of Medicine and Clinical Immunology of San Raffaele Scientific Institute, a tertiary referral centre, in Milan, in Northern Italy. Our aim was to retrospectively characterise the clinical phenotype of Italian AOSD patients.

Patients and methods

A chart review was completed on patients diagnosed with AOSD followed at our Institution from January 1991 to February 2009. In all the patients the diagnosis of AOSD was made by a senior rheumatologist and confirmed by the diagnostic criteria proposed by Yamaguchi *et al.* (5).

Investigations were carried out in all patients in order to rule out infections, malignancies, and other rheumatic diseases. Radiographs of the involved joints were performed in all patients. A

complete general laboratory workup, comprehensive of rheumatoid factor (RF) and anti-nuclear autoantibodies (ANA), joint radiographs, ultrasound examination of the abdomen, and chest x-ray were performed on all patients. Other specific tests were implemented when appropriated. The clinical manifestations at and after disease onset and the laboratory features were reviewed and recorded for analysis. The 'onset' period was defined as the first 6 weeks after the occurrence of the initial symptom. The laboratory tests were always taken during the acute phase of the disease, and they were performed at the time of the diagnosis or during a disease flare. The clinical course was evaluated in the subjects followed-up for at least 12 months. Disease course was classified according to Cush *et al.* (6).

The data collected were compared with those obtained in 6 published series of different ethnic origin (6-11). Statistical analyses were performed using GraphPad Prism Version 4.0C for Macintosh, GraphPad Software, San Diego California USA, www.graphpad.com.

Results

Thirty-eight patients were female (female/male ratio=1.36). The median diagnostic delay in our series was 4 months, but with a wide range (1 month-20 years), due to a couple of patients with polycyclic disease course who were diagnosed with AOSD only after several disease recurrences.

The median age at the onset of disease manifestations was 37 years (39 years for women, and 32 years for men), within a range of 16 to 71 years. Thirty subjects (45%) had the onset of their disease when aged between 16 and 35 years. The median duration of the follow-up was 26 months (range 3 months to 15 years). Fifty-two patients (78%) were followed for at least 12 months.

Presenting symptoms

The symptoms which induced patients to seek medical attention at disease onset were: high fever ($>39^{\circ}\text{C}$ or 102.2°F) in 60 patients (91%); arthralgia in 59 (89%); cutaneous rash in 37 (56%); sore throat in 36 (54%); myalgias in 35 (53%); overt arthritis in 25 (36%); lymphadenopathy

Competing interests: none declared.

and abdominal pain in 6 (9%); ocular inflammation, included isolated conjunctivitis, in 4 (6%); urethritis symptoms and thoracic pain each in 2 subjects (3%). Thirteen subjects (20%) presented with a very aspecific triad of high fever, arthralgia and sore throat, lasting for at least one month before the appearance of other features.

In Figure 1 the frequencies of the major clinical manifestations at disease onset are compared to the overall frequencies, considering the entire disease course.

Clinical and laboratory features

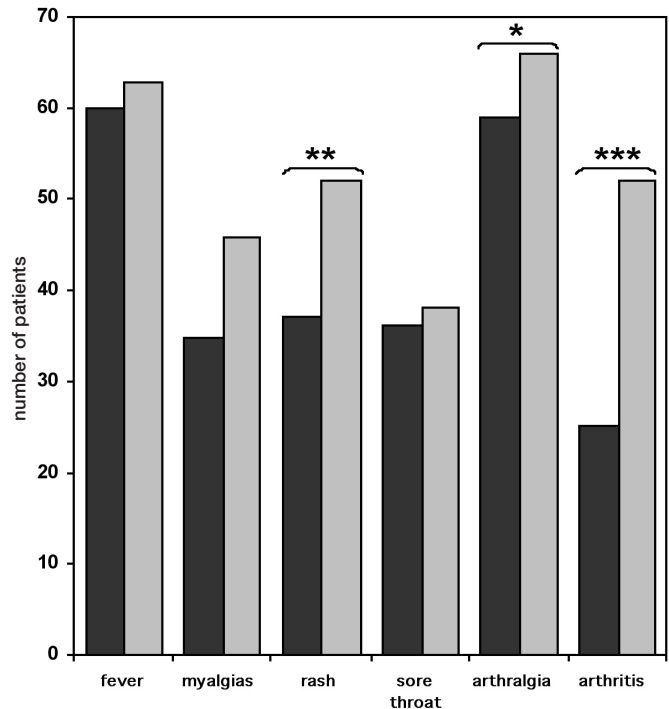
The epidemiological characteristics, clinical manifestations and laboratory features observed in our patients during the course of their disease are reported and compared to those of other series (6-11) in Table I and II.

All patients had been showing fever for more than two weeks before the diagnosis of AOSD was made. Sixty-three patients (95%) experienced quotidian fever $\geq 39.0^{\circ}\text{C}$ or 102.2°F at some point of the disease, while low fever was present in 3 cases. The pattern of fever was usually intermittent, but it was remittent in a few cases.

Involvement of musculoskeletal system was present in all patients. Persistent

Fig. 1. Frequency of AOSD manifestations during the first 6 weeks after the occurrence of the initial symptom (dark grey boxes), and during the subsequent course of the disease (light grey boxes). Some key clinical elements (skin rash and arthritis) were lacking at the time of the first medical evaluation in a significant quote of our patients and appeared only several weeks after the disease onset, making an early diagnosis of AOSD more challenging.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



myalgias were common (70%). Fourteen patients (21%) had arthralgia without evidence of arthritis during the entire course of the disease. The remaining 52 patients (79%) experienced joint inflammation during the follow-up period. Figure 2 shows the distribution and patterns of arthritis in these patients.

A diffuse macular or maculopapular rash characteristic of AOSD was seen in 52 patients (79%). It was associated with itching in 12% of patients and involved the face only in 15%. Koebner's phenomenon was frequently overlooked but, when evaluated, it was always positive. Two patients showed

Table I. Clinical manifestations of 66 Italian patients compared to 4 previously published series.

Clinical manifestations	Present study n=66	Cush (Ref. 6) n=21	Pouchot (Ref. 7) n=62	Wouters (Ref. 8) n=45	Ohta (Ref. 9) n=90	Catagay (Ref. 10) n=84	Zeng (Ref. 11) n=61
Country	Italy	USA	Canada	Netherlands	Japan	Turkey	China
Female	38/66 (58%)	13/21 (62%)	28/62 (45%)	27/45 (60%)	60/90 (67%)	59/84 (70%)	45/61 (74%)
Median age At onset (* = mean age at onset)	37 (mean 37)	21	24	25	32*	33*	37*
Onset Between 16 and 35 yrs	30/66 (45%)	17/21‡ (81%)	50/62§ (81%)	33/45‡ (73%)	48/90 (53%)	45/84 (54%)	29/61 (48%)
Arthralgia	66/66 (100%)	21/21 (100%)	62/62 (100%)	NS	90/90 (100%)	81/84 (96%)	NS
Fever $> 39^{\circ}\text{C}$	63/66 (95%)	21/21 (100%)	62/62 (100%)	45/45 (100%)	71/90‡ (81%)	80/84 (95%)	61/61 (100%)
Skin rash	52/66 (79%)	18/21 (86%)	54/62 (87%)	37/45 (82%)	72/83 (87%)	50/84† (60%)	54/61 (89%)
Arthritis	52/66 (79%)	21/21† (100%)	58/62† (94%)	44/45‡ (98%)	62/86 (72%)	58/84 (69%)	50/61 (82%)
Myalgias	46/66 (70%)	16/21 (76%)	52/62 (84%)	NS	50/89 (56%)	11/84§ (13%)	17/61§ (28%)
Sore throat	38/66 (58%)	19/21‡ (90%)	57/62§ (92%)	19/28 (68%)	58/83 (70%)	55/84 (65%)	44/61 (72%)
Lymphadenopathy	36/66 (54%)	19/21‡ (90%)	46/62† (74%)	32/45 (71%)	59/86 (69%)	28/84‡ (33%)	32/61 (52%)
Hepatomegaly	27/66 (41%)	8/21 (38%)	27/62 (44%)	NS	42/87 (48%)	32/84 (38%)	8/61§ (13%)
Splenomegaly	25/66 (38%)	11/21 (52%)	34/62 (55%)	16/45 (36%)	56/86‡ (65%)	24/84 (29%)	23/61 (38%)
Abdominal pain	16/66 (24%)	10/21 (48%)	30/62‡ (48%)	NS	NS	1/84§ (1%)	NS
Pleuritis	12/66 (18%)	9/21† (43%)	33/62§ (53%)	NS	11/89 (12%)	8/84 (10%)	11/61 (18%)
Pericarditis	9/66 (14%)	7/21 (33%)	23/62‡ (37%)	10/45 (22%)	9/87 (10%)	10/84 (12%)	15/61 (25%)
Pneumonitis	3/66 (5%)	2/21 (10%)	17/62§ (27%)	NS	5/90 (6%)	3/84 (4%)	0/61 (0%)

† $p < 0.05$ when compared to the present study; ‡ $p < 0.01$ when compared to the present study; § $p < 0.001$ when compared to the present study; NS: not stated.

Table II. Laboratory features of 66 Italian patients compared to 4 previously published series.

Laboratory features	Present study n=66	Cush (Ref. 6) n=21	Pouchot (Ref. 7) n=62	Wouters (Ref. 8) n=45	Ohta (Ref. 9) n=90	Catagay (Ref. 10) n=84	Zeng (Ref. 11) n=61
Country	Italy	USA	Canada	Netherlands	Japan	Turkey	China
Increased ESR	66/66 (100%)	21/21 (100%)	62/62 (100%)	45/45 (100%)	85/89 (96%)	79/84 (94%)	61/61 (100%)
Neutrophils >80% (*=>90%)	54/66 (82%)	NS	55/62 (88%)	17*/45 [§] (38%)	74/90 (82%)	35/63 [‡] (56%)	NS
WBC >10000	52/66 (79%)	NS	58/62 [†] (94%)	44/45 [‡] (98%)	80/90 (89%)	69/84 (84%)	51/61 (84%)
WBC >15000 (*=>18000)	41/66 (62%)	15/21 (71%)	50/62 [†] (81%)	24*/45 (53%)	NS	48/84 (57%)	31/61 (51%)
Liver disfunction	52/66 (79%)	15/19 (79%)	47/62 (76%)	38/45 (84%)	74/87 (85%)	30/84 [‡] (36%)	14/61 [§] (23%)
Ferritin >1000 ng/ml (* = 5-fold the upper normal limit)	43/61 (70%)	NS	NS	NS	22*/32 (69%)	32/84 [‡] (38%)	43/54 (80%)
Albumin <3.5mg/dl (*=<3.0 mg/dl)	43/66 (65%)	16/20 (80%)	51/62 [†] (85%)	NS	39*/88 [†] (44%)	35*/84 [‡] (42%)	NS
Haemoglobin <10mg/dl or haematocrit <35% (* = <7 mg/dl)	25/66 (38%)	16/21 [‡] (76%)	42/62 [§] (68%)	39*/45 [§] (87%)	53/90 [†] (59%)	30/84 (36%)	9/61 [‡] (15%)
Hypergammaglobulinemia	16/66 (24%)	NS	NS	NS	NS	NS	NS
Proteinuria	7/66 (11%)	6/21 (29%)	24/62 [§] (39%)	NS	9/90 (10%)	NS	NS
ANA >1:40	6/66 (9%)	0/21 (0%)	7/62 (11%)	2/45 (4%)	6/88 (7%)	NS	7/61 (11%)
Haematuria	3/66 (5%)	NS	NS	NS	5/90 (6%)	NS	NS
Haemophagocytic syndrome	2/66 (3%)	NS	NS	NS	NS	none	1/61 (2%)
RF positivity	0/66 (0%)	1/21 (5%)	4/62 (6%) [†]	2/45 (4%)	5/89 (6%)	exclusion criterion	7/61 [‡] (11%)

[†] $p < 0.05$ when compared to the present study; [‡] $p < 0.01$ when compared to the present study; [§] $p < 0.001$ when compared to the present study; NS: not stated.

livedo reticularis and one patient had erythema nodosum.

Coexistence of fever, rash, and arthritis was documented in 47 cases (71%).

Thirty-eight patients (58%) complained of sore throat, which usually appeared a few days before the spiking fever. In a minority of cases, pharyngodynia appeared weeks before all the other manifestations. The oro-pharynx was hyperaemic and the tonsils were variably enlarged. In 6 patients the pharyngodynia caused disabling dysphagia with significant weight loss. Nonetheless, pharyngeal or tonsillar exudates or other signs of bacterial infection were never noted. Lymphadenopathy was documented in 36 cases (54%). The neck and supraclavicular region were the most frequently involved areas. Lymph nodes were always soft and reactive in appearance.

A pleural and/or pericardial effusion was documented in 12 patients (18%). The serositis was always mild and never interfering per se with the cardiac or the respiratory function.

Two patients had severe myopericarditis with heart failure. Eight patients (12%) developed mild signs of left heart failure, but left ventricular dysfunction was documented only in 4 (6%).

The lung parenchyma was rarely involved: in one patient a lower left lobe opacity consistent with atelectasis was documented on CT scans. A subsequent bronchoscopy showed extrinsic distal

compression of the left main bronchus, due to an enlarged lymph node. One patient presented an inflammatory non-infective pneumonia with multiple bilateral lung opacities causing respiratory

Fig. 2. Frequency and patterns of articular involvement in the 52 patients who experienced clinical signs of arthritis.

DIPs: distal interphalangeal joints; MCPs: metacarpophalangeal joints; MTPs: metatarsophalangeal joints; PIPs: proximal interphalangeal joints; TMJ: temporomandibular joint. 'Polyarthritis' is defined as arthritis involving ≥ 5 joints.

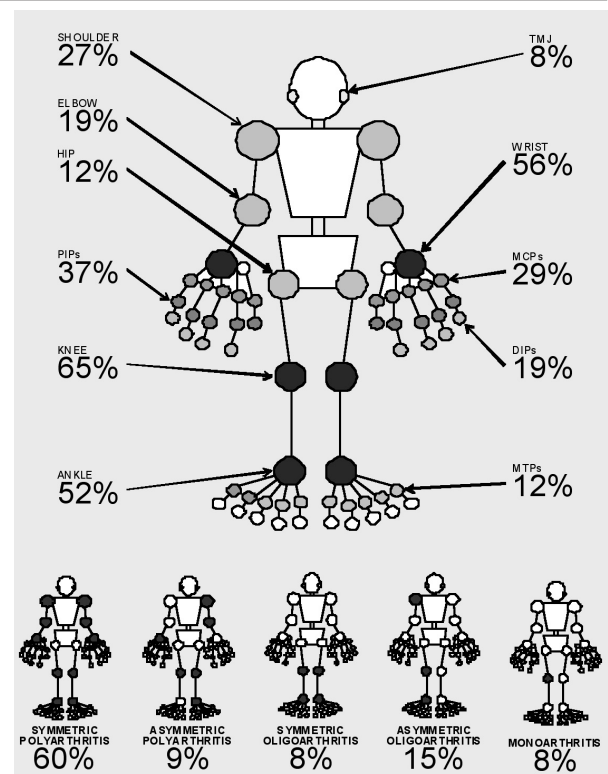


Table III. Disease course patterns of 54 Italian patients followed-up for at least 12 months, compared to 4 previously published series, according to Cush *et al.* (Ref. 6).

Pattern	Present study n=52	Cush (Ref. 6) n=21	Pouchot (Ref. 7) n=62	Wouters (Ref. 8) n=45	Ohta (Ref. 9) n=90	Catagay (Ref. 10) n=84	Zeng (Ref. 11) n=61
Country	Italy	USA	Canada	Netherlands	Japan	Turkey	China
Monocyclic	10/52 (20%)	4/21 (24%)	21/58 (36%)	15/45 (33%)	18/74 (24%)	28/84 (33%)	27/61 [‡] (44%)
Polycyclic	21/52 (40%)	1/21 [‡] (5%)	15/58 (26%)	8/45 [‡] (18%)	30/74 (41%)	28/84 (33%)	18/61 (29%)
Chronic articular	21/52 (40%)	15/21 [‡] (71%)	22/58 (38%)	22/45 (49%)	26/74 (35%)	24/84 (28%)	10/61 [‡] (16%)
Unclassified	0	0	4/62 (6%)	0	16/90 [§] (18%)	5/84 (6%)	6/61 [‡] (10%)

[†] $p < 0.05$ when compared to the present study; [‡] $p < 0.01$ when compared to the present study; [§] $p < 0.001$ when compared to the present study.

failure requiring mechanical ventilation. Sixteen patients (24%) complained of abdominal pain. One experienced post-prandial recurrent abdominal pain reminiscent of visceral arteritis, which improved after the initiation of steroid therapy. Excruciating abdominal pain was the first manifestation in one patient who presented with physical findings suggesting an 'acute abdomen'; diagnostic work-up ruled out any evident organic cause for the pain. Four patients (6%) experienced diarrhoea and abdominal pain during the disease flare-ups. Conjunctivitis was a feature in 3 cases; 2 patients presented monolateral episcleritis.

Twenty-five patients (38%) had serum haemoglobin lower than 10 g/dl. Leucocytosis (>10000 cell/mm³) was seen in 52 patients (79%). Forty-one (62%) had a leucocyte count greater than 15000 cell/mm³, and 25 (38%) greater than 18000 cells/mm³. Neutrophilia ($>80\%$) was noted in 54 cases (82%), thrombocytosis (>400000 /mm³) in 13 (20%), and thrombocytopenia (<150000 /mm³) in 6 (9%). Pancytopenia was seen in 4 patients (6%); two of them had marked pancytopenia associated with the haemophagocytic syndrome (HPS).

Elevation of hepatic enzymes was observed in 52 subjects (79%) but hepatitis with transient hepatic failure (defined as acute decrease in serum albumin and/or elevation of prothrombin time) was documented in only 5 (7%).

Serum ferritin above normal levels (normal levels 30–400 ng/ml in males, 15–150 ng/ml in females) was observed in 59/61 patients (97%). Serum ferritin was higher than 1000 ng/ml in 43/61 cases (70%), higher than 5000 ng/ml in 20 (33%), and higher than 8000 ng/ml in 14 (21%).

Renal manifestations were a feature in 6 patients (9%): all these 6 had proteinuria greater than 0.3 g/day, and 3 of them also showed macrohaematuria. One of the patients with proteinuria was subsequently diagnosed with renal amyloidosis. Of note, all the 4 subjects with multi-organ failure presented acute renal insufficiency with significant elevation in serum creatinine. Low-titer ($\leq 1:80$) positivity for ANA was present only in 5 subjects (8%). These subjects did not show any particular manifestation evocative for connective tissue diseases or any other peculiar feature as compared to the ANA-negative patients.

Radiographic features

Considering the 52 patients with a follow-up of at least 12 months, radiographic abnormalities on joint radiographs were documented in 14 out of 52 patients (27%).

Bone and joint alteration due to degenerative joint disease were not taken into account.

Periarticular osteopenia was evident in 12 cases. Eight patients presented joint space narrowing: carpal joints were involved in 4 cases, distal interphalangeal joints (DIPs) and metacarpophalangeal joints (MCPs) in 3 cases, proximal interphalangeal joints (PIPs) in 2 cases, metatarsophalangeal (MTPs) joints in 1 case, and the knees in 2 patients. One patient presented a Baker's cyst of the knee. Erosions were seen in 7/52 (13%) patients, involving carpal joints in 4 cases (with ankylosis of the wrist in one subject) and MCPs in 2. One patient had severe destructive arthropathy of both hips. MTPs, the knee and the shoulder were each involved in one case.

Disease course

The disease course pattern in the 52 patients followed-up for at least 12 months is shown in Table III. Although the frequency of overt arthritis and of root joint involvement was slightly higher in the group of patient with chronic articular disease as compared to the group without chronic joint involvement (respectively 78% vs. 68%, and 42% vs. 31%), no statistically significant differences were found in sex, age at onset, root joint involvement, number of involved joints, frequency of arthritis, cutaneous rash, or sore throat between the two groups.

Severe complications

Five cases of AOSD had life threatening complications. Four of them developed multi-organ failure, which, in 2 patients was associated with HPS and was lethal in one case.

A 63-year-old man presented with an acute systemic flare characterised by shock, severe anemia, striking granulocytosis, altered mental status and acute heart, hepatic and renal failure refractory to multiple large-spectrum antibiotics, high-dose iv steroids, immunosuppressants (cyclosporine and methotrexate). Extensive imaging and microbiologic work-up was negative for infection. He was then transferred to another hospital, closer to where he lived, but he eventually died shortly afterwards.

A 44-year-old female presented at onset with severe myopericarditis causing severe heart failure associated to disseminated intravascular coagulation, pancytopenia, hepatic and renal failure, extremely high serum ferritin levels (20700 ng/mL). The presence of HPS was confirmed by a bone marrow

biopsy. The patient was treated with high-dose iv methylprednisolone, and responded with a complete remission. A 16-year-old girl presented at diagnosis of AOSD with an inflammatory non-infective bilateral pneumonia and respiratory failure requiring mechanical ventilation, acute renal failure and hepatic insufficiency. She responded quite rapidly to high-dose oral prednisone.

The fourth case is a 58-year-old woman with a sudden onset of shock, acute renal failure, hepatitis, pancytopenia, and extremely high serum ferritin (53168 ng/mL) and triglyceride (505 mg/dL) levels. A diagnosis of AOSD was made and a bone marrow biopsy revealed HPS. She was treated with high-dose iv methylprednisolone followed by oral cyclosporine with prompt recovery.

The last case refers to a 63-year-old male with a disease onset characterised by chest pain and dyspnoea caused by acute myopericarditis. There was no evidence of any other organ involvement. The patient recovered rapidly after treatment with oral prednisone.

Discussion

We report 66 patients with AOSD consecutively diagnosed and followed-up in a 19-year period at the Clinical Immunology Unit of our Institute. Data on AOSD in Italy are largely lacking and this is the first large Italian AOSD series. Indeed, only 31 papers regarding Italian AOSD patients with a total of 55 patients are reported in the literature (12-16). The relatively small number of patients collected during such a long period probably reflects a low prevalence of AOSD in our country.

Due to the absence of pathognomonic diagnostic features, several authors have proposed different criteria for the diagnosis of AOSD (5, 6, 17-20). However, the lack of agreement on criteria for the diagnosis, together with the rarity of this disease, accounts for the extreme difficulty in comparing epidemiological data, clinical features, prognosis, treatment, and outcome from different studies.

We describe a well-defined population: all our patients were seen in a single centre and the diagnosis of AOSD was

made by a senior rheumatologist and confirmed by Yamaguchi's criteria (5). The most frequent clinical manifestation was arthralgia, which was invariably present in our patients, followed by: high fever, the typical Still's rash, and arthritis. The latter three symptoms constitute the classical triad mentioned in the description of AOSD since its first recognition as an independent nosological entity (3). Yet, while all our patients had arthralgia, only approximately three-fourths of them experienced overt arthritis. Overall, the classic triad of AOSD was completely manifested in 71% of patients.

The substantial diagnostic value of arthralgia in the absence of overt articular swelling was acknowledged by Yamaguchi's (5), Cush's (6) and Calabro's (17) criteria, which considered both arthralgia and arthritis as major diagnostic criteria. Indeed these 3 sets of criteria resulted to be more sensitive (21, 22) than the other proposed criteria for the diagnosis of AOSD, which either exclude arthralgia as a diagnostic criterion, or consider it only as a minor criterion (18-20).

A marked elevation in serum ferritin (≥ 1000 ng/mL) and the typical evanescent Still's rash, which are quite specific diagnostic clues (23-25), were present respectively in 70 and 79% of our patients. These features, given this fairly high sensitivity, could be useful in selecting patients with possible AOSD. Particular attention should be paid to the recognition of the evanescent rash, since it may be a very helpful diagnostic hint for AOSD, although in the setting of a fever of unknown origin it is easily mistaken for an allergic reaction to antibiotics (7).

The determination of RF and ANA is recommended, since it can be effective in narrowing the differential diagnosis (92% of our patients were seronegative). Notably, even if the majority of patients experienced a symmetrical polyarthritis resembling that of many other polyarticular arthritides, DIP joints were involved in about 20% of cases (Fig. 2). With the exception of psoriatic arthritis, this joint is spared in many common articular disorders of young adults (26).

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 a diagnosis of AOSD can be made (1). Furthermore, patients often develop the symptoms which characterise the disease over a period of several weeks or months (8, 22, 26), therefore making the diagnosis at the onset even more challenging. This observation was confirmed by our findings (Fig. 1): for example, although the vast majority of our patients developed a febrile seronegative arthritis and an evanescent rash at some time during the disease course, such signs were absent at the time of the first medical evaluation in a substantial number of cases.

Variable clinical and laboratory findings could be present in patients from different ethnic backgrounds (27, 28). Tables I, II and III confirm such wide variability in the frequencies of clinical and laboratory features in AOSD patients of different ethnic origin. Italian and Turkish patients, as well as Japanese and Chinese subjects, were generally older at disease onset than subjects from the other series. Interestingly, the median age for Italian male patients was somewhat lower than for female (respectively 32 and 39 years), suggesting that men might be more likely to have a younger onset, as reported by Otha *et al.* (9). Symptoms such as arthritis, pharyngitis, lymphadenopathy, and serositis appear to be less frequent in Italian, Turkish, and Far Eastern subjects.

Myalgias were more frequent among European and North American series. Turkish patients seem to differ for a lower frequency of abdominal pain, splenomegaly, granulocytosis, low serum albumin, liver dysfunction, elevation of serum ferritin. Chinese patients showed the lowest frequency of hepatomegaly and liver dysfunction, while the Japanese subjects had the highest frequency of splenomegaly. In the Canadian cohort a higher prevalence of abdominal pain, pneumonitis, neutrophilia, hypoalbuminaemia, and proteinuria was noted.

Significant anaemia (haemoglobin < 10 g/dL) was present in about one third of our patients – quite a small proportion

as compared to most of the older series. This could be also due to the NSAID-sparing effect of an early DMARDs treatment and to the prompt gastric protection with protonic pump inhibitors initiated in the vast majority of patients on NSAID therapy at our centre (data not shown).

We described some uncommon manifestations: two cases of episcleritis which has been previously reported only once in AOSD (30), and one case of renal amyloidosis, a condition rarely described in AOSD (31).

In earlier studies (32, 33), AOSD was thought to have a generally favourable prognosis and a benign course of articular disease as compared to rheumatoid arthritis. This view, which still endures in the conception of some non-rheumatologists, has been disputed when it was demonstrated that the course of AOSD is highly variable and that erosive, disabling arthritis, as well as life-threatening complications may occur in a substantial number of cases (8, 9). We observed five patients presenting with severe clinical situation characterised by life-threatening complications. Four of them had multi-organ failure and one eventually died, despite intensive treatments.

The reactive HPS (also termed macrophage activation syndrome) is a clinicopathological entity characterised by the activation of macrophages and/or histiocytes with prominent haemophagocytosis in bone marrow and other reticuloendothelial systems. It could be associated with AOSD in a minority of patients (34). Clinical features of HPS include fever, cytopoenia, liver enzyme elevation, hepatosplenomegaly, lymphadenopathy and coagulopathy with an overall mortality of 20-38.5%. A recent retrospective study from Japan reported HPS in 12% of AOSD patients (34). Although in our series we observed only two HPS cases (3), the ominous clinical significance of this condition was confirmed, as multi-organ failure was present in both cases.

One patient presented with fever, striking granulocytosis, multi-organ failure and refractory shock, closely resembling severe sepsis. Signs and symptoms

of acute AOSD are frequently wrongly attributed to an infectious aetiology. In severe cases, an early recognition of this condition is crucial because AOSD may be fatal if inappropriately and not promptly treated. Serum procalcitonin has proven to be more specific than CRP and white blood cell count for inflammatory processes due to bacterial or fungal infection and has therefore been proposed as a possibly useful tool in distinguishing between infectious and non-infectious aetiologies in acutely ill patients. However, Scirè *et al.* have recently demonstrated that the serum concentration of procalcitonin can dramatically increase in AOSD patients even in the absence of detectable infection (12). At the moment, no single biomarker appear adequate to guide the physician in discriminating between non-infectious inflammation and bacterial infection. Thus, AOSD should be always included in the differential diagnosis of a systemic inflammatory syndrome, in particular in the presence of repeatedly negative microbiological tests and when it appears to be refractory to multiple antibiotic regimens.

Conclusions

AOSD is rare in Italy. Significant differences exist in the clinical presentation between Italian patients and subjects of different ethnic origins, supporting the hypothesis that its phenotypical expression may at least partially be influenced by the patients' genetic background (35).

The diagnosis of AOSD is clinical and requires the exclusion of other conditions. In fact, due to its protean and non-specific clinical manifestations, a broad all-inclusive differential diagnosis should always be considered (1, 36). Furthermore, the frequent absence of key clinical features during the early phase of the disease could be deceptive in terms of early diagnosing or even suspecting AOSD.

Nonetheless, an early recognition of AOSD is crucial in patients with acute life-threatening symptoms, since the initiation of an appropriate immunosuppressive therapy frequently results in a rapid remission of its most severe manifestations.

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