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Cardiac involvement in adult-onset Still's disease: Manifestations, treatments and outcomes in a retrospective study of 28 patients

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ABSTRACT

Objective: Adult-onset Still's disease (AOSD) is a rare inflammatory disease that may be life-threatening if complicated by cardiac problems. We performed a retrospective multicenter study to describe the manifestations, treatments and outcomes of cardiac involvement in AOSD.

Methods: We reviewed the medical databases of eight centers. All AOSD patients identified as fulfilling Yamagushi's or Fautrel's criteria were included in the study. Cardiac involvement, clinical manifestations, laboratory features, the course of the disease and treatments were evaluated.

Results: We included 96 AOSD patients in this study: 28 (29 %) had documented cardiac involvement (AOSD+C group) and 68 (71 %) had no cardiac involvement (control group). Cardiac complications were observed at diagnosis in 89% of cases. It were pericarditis ($n=17$), tamponade ($n=5$), myocarditis ($n=5$) and non-infectious endocarditis ($n=1$). Levels of leukocytes, neutrophils and C-reactive protein were significantly higher ($p=0.02$, $p=0.02$ and $p=0.002$, respectively in the AOSD+C group than in the control group. Admission to intensive care, and the use of biotherapy were more frequent during follow-up in the AOSD+C group than the control group ($p=0.0001$ and $p=0.03$ respectively). Cardiac involvement was associated with refractory form in multivariate analyzed ($p=0.01$). Corticosteroids were effective with or without methotrexate in 71% of patients but not in severe involvement as myocarditis or tamponade.

Conclusion: Cardiac complications are frequent, inaugural, can be life-threatening and predictive of a refractory course in patients with AOSD. Systematic cardiac screening should be proposed at diagnosis and biotherapy early use should be considered especially in myocarditis.

KEY WORDS: Adult-onset Still's disease, Cardiac involvement, Pericarditis, Tamponade, Myocarditis, Biotherapy.

Abbreviations:

AOSD: Adult-onset Still's disease
RHL: Reactive hemophagocytic lymphohistiocytosis
DMARDs: Disease-modifying antirheumatic drugs
MTX: Methotrexate
bDMARDs: Biological disease-modifying antirheumatic drugs
AOSD+C: Adult-onset Still's disease with cardiac involvement
TTU: Transthoracic ultrasonography
ECG: Electrocardiogram
PAH: pulmonary arterial hypertension
PMNs: Polymorphonuclear cells
CRP: C-reactive protein
SF: Serum ferritin
MRI: Magnetic resonance imaging
NSAIDs: Non-steroidal anti-inflammatory drugs
WBC: White blood cell
TNF α : Tumor necrosis factor-alpha
sICAM-1: soluble intercellular adhesion molecule-1
ANA: Antinuclear antibodies
RF: Rheumatoid factor

Introduction

Adult-onset Still's disease (AOSD) is a rare multisystemic disease of unknown etiology, categorized as a polygenic autoinflammatory disorder (1). The typical manifestations of AOSD include prolonged fever, arthralgia, polyarthritis, evanescent rash, leukocytosis and hyperferritinemia (2). Two sets of classification criteria based on these manifestations have been proposed for AOSD: Yamaguchi's criteria (3), and Fautrel's criteria (4).

Other, less frequent manifestations of AOSD have also been described during the evaluation and follow-up of patients (1). These manifestations include reactive hemophagocytic lymphohistiocytosis (RHL), pulmonary or neurological complications, acute hepatic or renal failure and cardiac involvement (5). Cardiac complications can affect all layers of the heart and may have a very poor prognosis, with myocarditis (6), tamponade (7) or endocarditis (8). AOSD treatment has long been essentially empirical, based on corticosteroids and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) (2). Patients with AOSD refractory to treatment with steroids and methotrexate may be improved by biological DMARDs (bDMARDs), such as IL-1 and IL-6 antagonists, which are usually well tolerated (9,10).

To date, cardiac complications have been rarely studied, with only isolated observations or small series of cases published. Herein, we provide a retrospective multicenter study describing the clinical features, treatments, and outcomes of cardiac involvement in AOSD.

Patients and Methods

Study design and selection of patients

This retrospective study was performed in eight French referral hospitals. The medical files of all patients with AOSD suspicion between January 2000 and January 2018 were collected from the hospital databases. The project was approved by the institutional review board.

The inclusion criteria were: (i) AOSD diagnosis on the basis of the Yamaguchi (3) and/or Fautrel (4) criteria and (ii) exclusion of all differential diagnoses, including infection, cancer or another type of inflammatory rheumatism. The exclusion criteria were: (i) early onset of the disease, before the age of 16 years and (ii) insufficient available medical data.

The patients included in the study were classified into two groups: the AOSD+C group, which contained all patients presenting AOSD with cardiac involvement, and a control group of patients with AOSD but without cardiac involvement.

Cardiac involvement was defined as the presence of specific cardiac complications, at diagnosis or during the course of the disease, without evidence of alternative complication such as infection. These complications included:

- pericarditis : defined by at least two criteria among : typical chest pain (sharp, improved by sitting up and leaning forward), pericardial effusion on transthoracic ultrasonography (TTU), pericardial friction rub, and typical electrocardiogram (ECG) changes (widespread ST segment elevation) (11),
- pericarditis complicated by tamponade : defined as pericarditis with ventricular dysfunction due to compressive effusion,
- myocarditis : defined by at least two criteria among : high troponin level, MRI specific lesion, and left ventricular dysfunction, without tamponade or coronaropathy (12),
- pulmonary arterial hypertension (PAH) : defined as mean pulmonary artery pressure upper than 25 mmHg by right heart catheterization in suspect patient at TTU.
- non-infectious endocarditis : defined as typical endocarditis on TTU evaluation without infectious disease proved and improvement after corticosteroids treatment.

Data collection

The following data were collected on a standardized form: demographic data (sex and age at diagnosis); the criteria for the Yamaguchi and Fautrel classifications (3,4); biological results at

AOSD diagnosis (levels of leukocytes, polymorphonuclear cells (PMNs), C-reactive protein (CRP), albumin, serum ferritin (SF), and glycosylated ferritin; the dates of symptom onset, AOSD diagnosis and the first cardiac episode after diagnosis; the occurrence and type of cardiac involvement; the clinical, biological and morphological manifestations of cardiac involvement (dyspnea, chest pain, signs of heart failure, troponin, ECG, TTU and cardiac magnetic resonance imaging (MRI); admission to an intensive care unit; the presence of RHL or pleural effusion ; treatments administered for AOSD or cardiac conditions; corticosteroid resistance or progression to a refractory state; the number and duration of cardiac or non-cardiac relapses; the date of the last consultation and vital status (patient alive or dead).

Patients were classified into three subgroups based on disease course: (i) monocyclic systemic, defined as a single episode resolving completely within months; (ii) polycyclic systemic, defined as intermittent systemic episodes associated with one or more disease flare-ups; (iii) chronic articular pattern, defined as persistent activity of the predominant rheumatologic involvement.

Corticosteroid resistance was defined as a failure to achieved remission of clinical manifestations and normalization of biological parameters in spite of high dose of corticosteroids, at least 1 mg prednisone equivalent/kg/day. AOSD is considered to be refractory if corticosteroid withdrawal, with or without MTX, is not reached.

Statistical analysis

The results are presented as absolute numbers and percentages, or as medians and interquartile range (1st quartile Q1, 3rd quartile Q3). Continuous variables were compared in non-parametric Mann-Whitney tests. Qualitative values were compared in Fisher's exact tests.

Multivariate analyses were performed by logistic regression, and odds ratios were calculated with a 95% confidence interval (CI). The choice of adjustments was done a priori, helped by the literature, from the variables that were most probably confounders (age, CRP) and the

studying variables (cardiac involvement, joint involvement, pharyngitis...). Due to small sample size, the number of variables adjustments have been kept small.

The data were analysed with GraphPad Prism 6® software (GraphPad Software, San Diego, California, USA) and Statistica version 7 (StatSoft, Inc.).

Results

Study population

The distribution of the patients is illustrated in **Figure 1**. We identified 173 patients with suspicion of AOSD, 96 of whom fulfilled the inclusion criteria. The other 77 patients were excluded: 41 for differential diagnoses, 21 for a lack of available data, 11 for not meeting diagnostic criteria, and 4 for redundancy. Twenty eight of the 96 patients included in the study (29%) were considered to have AOSD with cardiac involvement and were included in the “AOSD+C group”. The remaining 68 (71%) patients were considered to have AOSD without cardiac involvement and were included in the “control group”.

Features and treatment of cardiac involvement

Cardiac involvement was pericarditis (61%, $n=17$), tamponades (18%, $n=5$), myocarditis (18%, $n=5$) and one non-infectious endocarditis (4%) (**Table 1**). It occurred before or during the diagnostic stage in 25 cases (89%), before any specific treatment. However, one patient suffered from acute myocarditis 7 years after AOSD diagnosis, following five years of remission without any treatment. Two other patients presented acute pericarditis during the first year after diagnosis, one patient has no treatment at this time and one was refractory to corticosteroids. Cardiac involvement was the inaugural symptom in five cases (18%), one case of acute pericarditis, two of recurrent pericarditis and two of acute inflammatory myocarditis. The suggestive symptoms were chest pain in 22 patients (79%), dyspnea in 11 patients (39%), signs of right ventricular failure in 5 patients (18%) and ECG abnormalities in 13 patients (46%) (T

wave modification in 10 patients, atrial fibrillation in 3 patients and right bundle branch block in one patient). Troponin levels were high in 5/20 patients (25%). Pathological TTUs were observed in 25/27 patients (93%) (pericardial effusion in 25 patients, tamponade in 5 patients, ventricular hypokinesia in 2 patients and a 15 mm oscillating mitral valvular vegetation in 1 patient). Only seven patients underwent cardiac MRI, the results of which were abnormal for five patients (71%) (pericardial effusion in 2 patients and myocardial gadolinium enhancement in 3 patients).

Cardiac episodes were treated (**Table 2**) with corticosteroids alone in 20 patients (71%) or associated with MTX for cortisone-sparing in four patients (14%). Anakinra treatment was administered to seven patients with corticosteroid-resistant disease and one patient in first-line treatment. Three patients have received non-steroidal anti-inflammatory drugs (NSAIDs) associated with colchicine for a pericarditis.

The five patients with tamponade were treated with corticosteroids and surgical pericardial drainage, with the creation of a pericardial window in one patient. Only one of these patients had corticosteroid-resistant disease and was rapidly switched onto anakinra (**Table 2**).

One of the five patients with myocarditis was treated with corticosteroids alone, one was treated with corticosteroids associated to MTX, and one was treated with anakinra as a first-line treatment. Two patients displayed corticosteroid resistance and were successfully treated with anakinra. Endocarditis was treated with corticosteroids alone (**Table 2**).

For pericarditis, 8 patients were successfully treated by corticosteroids alone and 2 with a combination with MTX. Four patients were treated by Anakinra due to corticosteroid-resistant disease. The last three patients were those treated by NSAIDs and colchicine.

Demographic and clinical features of the AOSD population

The population of 96 AOSD patients included 47 (49%) men (**Table 3**). Median age at diagnosis was 42 years [25-55]. The median follow-up period was 34 months [11-85].

The clinical and laboratory results obtained are summarized in **Table 3**. The clinical manifestations were similar in the two groups, except for pharyngitis and pleural effusion, which were more prevalent in the AOSD+C group ($p= 0.05$ and $p=0.001$, respectively).

All patients had high median levels of leukocytes (WBC), neutrophils (PMNs) and CRP. The levels of these inflammatory biomarkers were significantly higher in the AOSD+C group than in the control group ($p= 0.02$, $p=0.02$ and $p=0.001$, respectively). SF concentration was markedly high (4176 μM [1736-12711]), with no clinically relevant difference between the two groups, as glycosylated SF (11% [9-17] vs 16% [12-22]; $p= 0.25$). Abnormal liver function test results were recorded for 59% of patients, with no significant difference between the two groups. Antinuclear antibodies were positive in 2 patients from AOSD+C group without clinical symptom or other immunological marker for a systemic lupus erythematosus.

Treatment and disease course

The main treatments prescribed for AOSD in this cohort were corticosteroids for 87 patients (91%), MTX for 45 patients (47%), anakinra for 23 patients (24%), tocilizumab for 12 patients (13%), anti-Tumor necrosis factor alpha (TNF α) for 6 patients (6%) and NSAIDs for 36 patients (38%) during diagnostic assessment (**Table 4**). bDMARDs (anakinra and tocilizumab) were more frequently used in the AOSD+C group than in the control group. Anti-TNF α treatment was ineffective in both groups.

Cardiac complications affected outcomes (**Table 5**). Patients in the AOSD+C group were more likely to be admitted to an intensive care unit: 14 patients from the AOSD+C group were admitted to intensive care, versus only two in the control group (50% vs 4%; $p = 0.0001$). The frequency of refractoriness from corticosteroid and DMARD treatment showed a tendency to be higher in the AOSD+C group than in the control group (32% vs 19%; $p = 0.19$). Patients with cardiac involvement were, therefore, more frequently treated with bDMARDs (anakinra or tocilizumab) than those in the control group (46% vs 22%; $p = 0.03$). The number of RHL

complication during the study period was two in AODS+C group and 6 in control group (7% vs 9%). However, this complication caused the death of one patient in the control group. A second death was recorded following sigmoid perforation on corticosteroid therapy in one of the patients from the control group.

Multivariate analysis

We performed a first multivariate analysis to determine predictive factors of cardiac involvement at diagnosis. In this analysis, the presence of pharyngitis (OR = 5.84, 95% CI = 1.063-32.105, $p = 0.04$) and high CRP (OR = 1.006, 95% CI=1.001-1.012, $p = 0.012$) was significantly associated with cardiac involvement during the course of the disease. Pleural effusion and age were not associated with cardiac involvement in this analyzed (respectively $p=0.069$ and $p = 0.71$).

Refractory AOSD were the most complicated forms to managed. We noted that some of these forms had cardiac involvement. We performed a second multivariate analysis to identify predictive markers of refractory AOSD, including a priori defined parameters (CRP, age at diagnosis, cardiac involvement and chronic articular pattern). We identified two significant factors: chronic articular pattern (OR = 3.492, 95% CI = 1.119-10.896, $p = 0.03$) and the occurrence of cardiac involvement during AOSD follow up (OR = 4.064 , 95% CI = 1.353-12.207, $p = 0.012$) (**Table 6**). This relation is even more significant in case of myocarditis or tamponade ($p = 0.008$, data not shown).

Discussion

AOSD patients may experience various complications, which may affect their clinical condition, management and prognosis (13). Cardiac complications are considered life-threatening and their prevalence has increased steadily over the last decade (13). This study highlights the clinical characteristics of cardiac involvement in AOSD. We found that the

overall prevalence of cardiac involvement in our population of AOSD patients was 29%. The most frequent form of cardiac involvement was pericarditis, with or without tamponade. Its prevalence reported in previous studies ranges from 3% to 37% (2). The estimated prevalence of pericarditis in our cohort was 23%, pericarditis ($n=17$) and tamponade ($n=5$), which is consistent with the prevalence of 20% reported recently (14,15). Tamponade and myocarditis are rarer cardiac complications of AOSD. We observed 5 myocarditis (5%) and 5 cases of tamponade (5%) in this study. The prevalence of myocarditis was estimated at 7% (4/57) by Gerfaud-Valentin *et al.* (6) whereas no prevalence has been yet reported for tamponade.

Our cohort also included an exceptional case of non-infectious endocarditis at the time of AOSD diagnosis. Non-infectious endocarditis is rare and is generally of neoplastic origin (marastic endocarditis) or related to systemic lupus erythematosus (16). The underlying pathophysiological mechanisms are unknown, but corticosteroids appear to be effective (17) as for our patient.

We found no cases of pulmonary arterial hypertension complicating AOSD in our series. This complication is considered exceedingly rare, with only about 22 published observations (18). The prevalence of this complication was reported to be 4.8% in a population of AOSD patients followed up for 33 years (2/41). It generally occurs in patients with persistent severe disease (18).

Systematic screening for cardiac involvement can highlight forms with few symptoms. Several studies of the systemic form of juvenile idiopathic arthritis have suggested that cardiac involvement is underestimated. In an autopsy series published in 1963 (19), 7% of the children studied had been given a clinical diagnosis of pericarditis, but this condition was detected in 45% at autopsy. In addition, Bernstein *et al.* reported that systematic TTU-based diagnosis revealed the presence of pericardial effusion in 36% of the 55 children studied (20). Routine

screening including ECG, troponin and TTTU should therefore be considered at the time of AOSD diagnosis.

Five of the patients in our cohort (13%) presented particular clinical features, with an inaugural and predominantly cardiac expression of the disease. Such forms have rarely been described (21). Their prevalence may be underestimated due to a small number of extracardiac events, late diagnosis or a lack of specialist management. The systematic determination of serum ferritin concentration and of the proportion of ferritin glycosylated would therefore be informative in cases of inflammatory, unexplained recurrent or persistent pericarditis/myocarditis.

A favorable outcome was observed in 71% of patients in the AOSD+C group treated with corticosteroids alone or with MTX for corticosteroids sparing (17/24 patients treated). High-dose corticosteroids (1 mg/kg) are rapidly effective in this condition and are therefore the treatment of choice in first-line, particularly in cases of isolated pericarditis. MTX is the conventional immunosuppressive agent (DMARD) currently recommended as a second-line treatment for its steroid-sparing effects (22). However, its efficacy has not been assessed in cases of cardiac involvement and remains a matter of debate. Until this point is resolved, the use of MTX should probably be limited to corticosteroid-dependent cases, for corticosteroids-sparing purposes.

In our series, the use of NSAIDs associated with colchicine was sufficient to ensure a favorable outcome in 3 cases of pericarditis. However, the use of NSAIDs in AOSD is discussed only for symptomatic treatment and during the diagnostic phase (22,23). Indeed, several retrospective studies have provided evidence of a lack of efficacy associated with side effects (15). The use of NSAIDs should be reserved to isolated acute pericarditis with no proven AOSD diagnosis, as recommended by the cardiological societies (24).

For patients with tamponade, a combination of surgical drainage and corticosteroid treatment was effective in 4 of 5 cases (80%) with no recurrence. In 2009, Parvez *et al.* reported efficacy of this therapeutic association in nine cases of tamponade (25). After these findings five other observations were published, four responded well to treatment. The single failure was favored by kidney damage, with nephrotic syndrome treated with intravenous immunoglobulin and cyclophosphamide (7,26–28).

For myocarditis, corticosteroids alone or with MTX were effective in only two of the four patients concerned (50%) but switching onto anakinra was successful as well as anakinra was used in first line (3/3, 100%). Five additional cases of resistant myocarditis effectively treated with anakinra have been reported (29–33).

Given the sensitivity of AOSD to corticosteroids and the absence of clinical trials evaluating bDMARDs in cardiac involvement, such treatment is restricted for the moment to cases of refractory AOSD (22). Nevertheless, corticosteroids with or without MTX was unsuccessful in 7/24 (29%) cases of cardiac involvement in our series. Some authors have proposed the early introduction of bDMARDs in the event of a serious complication (5,34). Anakinra is a recombinant IL-1 receptor antagonist. It was strikingly effective in monotherapy for one of our patients with severe myocarditis, and in a number of case reports. It appears to be a treatment of choice in this condition (29-33). It could potentially be used as a first-line treatment, or to replace corticosteroids early in treatment if these drugs do not rapidly control the cardiac condition. These findings require confirmation in prospective studies.

The choice of bDMARDs for AOSD with cardiac involvement remains empirical and is based on only a few case reports. Anakinra is the most widely used molecule (29-34). However, tocilizumab was found to be effective in one case (35). The classification of AOSD into systemic and rheumatic clinical presentations may be explained by differences in cytokine profiles. IL-18, IL-1 β and IL-6 seems to be produced mostly in systemic disease, which should

respond best to IL-1 and IL-6 antagonists. While IL-6, IL-8, TNF- α and IL-17 are more produced in chronic articular pattern, which should respond best to IL-6 antagonists and TNF α inhibitors (36-38). In our study, we found that anti-TNF α treatment was ineffective. Published data for the use of TNF α inhibitors in cardiac impairment are very limited and not in favor of their use (39,40).

None of the patients evaluated remotely by TTU in our study had any functional sequelae and no deaths related to cardiac complications were recorded. Our results are consistent with those of a previous review reporting a good short-term prognosis in 23 of 24 cases of myocarditis, in which only one death occurred after cardiogenic shock (6).

Both pharyngitis and cardiac involvements are more common in AOSD with systemic form with a high inflammatory blood level. Pharyngitis is an important early diagnostic symptom when the intensity of inflammation is high. Therefore, its association with cardiac damage was not surprising since patients with cardiac injuries are more inflammatory. However, this association does not mean that a correlation can be established.

We found that the levels of biological markers of inflammation were significantly higher in patients with cardiac involvement. These inflammatory markers are indicators of demonstrated activity of the disease (38). Cardiac involvement therefore appears to be a marker of progression and should be suspected if marked inflammation occurs during AOSD. Multivariate analysis confirmed that cardiac involvement was an independent risk factor for refractory disease. Our results are consistent with published findings identifying pericarditis as a possible marker of severe refractory AOSD requiring treatment with biologic agents (14).

In our study, we didn't find any specific biomarker of cardiac involvement. A comprehensive review of biomarkers in AOSD has been published by Mitrovic and Fautrel (38). Some biomarkers should assess severity and risk of developing RHL, such as high level of interleukin-18, interleukin-6 and glycosylated ferritin fraction if < 20%. Furthermore, interleukin-18 seems

to have a prognostic interest with a higher level of corticosteroids dependence. To date, our knowledge in specific inflammatory biomarkers in AOSD and their clinical outcome is limited. No specific biomarkers have been described in cardiac involvement. As measurement of this biomarkers are not available in routine, we need more experimental studies.

Some authors consider that RHL, the most serious complication of AOSD, as a possible continuum of systemic forms of the disease (41). However, in our study, patients with AOSD with cardiac involvement had higher levels of inflammation and were more likely to be admitted to intensive care than the controls but did not have a higher risk of RHL. The pathophysiological mechanisms underlying cardiac involvement are unclear. A role of the pro-inflammatory cytokines produced in large amounts together with an increased expression of adhesion molecules, such as the soluble intercellular adhesion molecule-1 (sICAM-1) has been suggested (42). These molecules enhance the leukocytes adhesion to the vascular endothelium and their translocation of the target organs like heart. Chen *et al.* showed that increases in IL-18 and sICAM-1 levels were associated with disease activity (43). The pathogenic role of sICAM-1 has also been demonstrated in atherosclerosis and the risk of myocardial infarction (44). A comparative pro-inflammatory cytokinic analysis of the forms associated with cardiac involvement and RHL would improve our understanding of the disease and the screening and treatment of patients at risk of complications.

The limitations of this study are its retrospective nature and small sample size. However, this cohort may be considered relatively large given the low incidence of the disease and is the largest cohort of patients with cardiac involvement described to date. Prospective studies will be required to confirm our results and to determine more precisely the place of bDMARDs in treatment strategies for AOSD.

Conclusion

Cardiac involvement is frequent and often inaugural in AOSD. Corticosteroids are mostly effective and prognosis remains good, but one third of patients are nevertheless refracted to first-line treatment or admitted to intensive care. Anti-IL1 biotherapy early use should be considered in sever form, especially in myocarditis. Cardiac involvement may be markers of disease activity and severity. It may also be predictive of a refractory form of AOSD potentially requiring treatment with a bDMARDs. Screening for cardiac involvement should be performed systematically for all patients newly diagnosed with AOSD. Further studies are required to assess the long-term outcomes of cardiac involvement and the place of bDMARDs in treatment strategies in AOSD.

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Figure 1: Patient flow chart

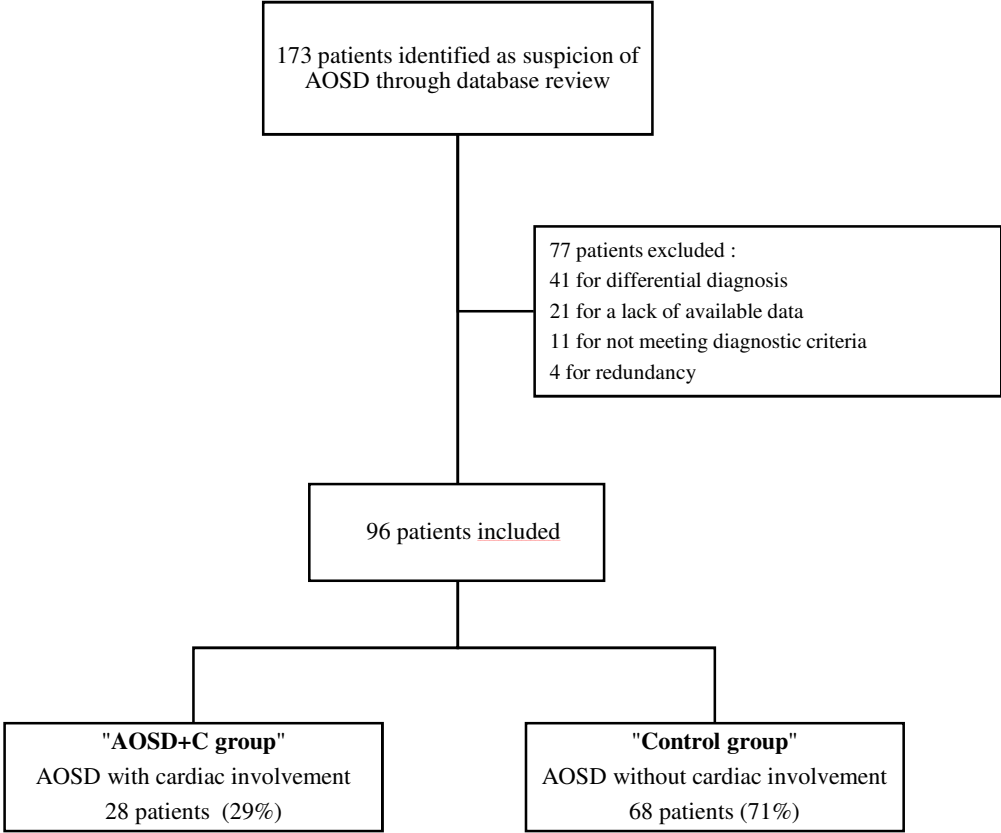


Table 1: Characteristics of cardiac events in the AOSD+C group

	AOSD+C group (n = 28)
<i>Type of cardiac involvement: n (%)</i>	
Pericarditis	17 (60%)
Tamponade	5 (18%)
Myocarditis	5 (18%)
Non-infectious endocarditis	1 (4%)
<i>Time of appearance of cardiac involvement: n (%)</i>	
Before or at diagnosis of AOSD	25 (89%)
During first year	27 (96%)
After first year	1 (4%)
Cardiac involvement predominant and inaugural	5 (18%)
<i>Clinical manifestations: n (%)</i>	
Chest pain	22 (79%)
Dyspnea	11 (39%)
Right ventricular failure	5 (18%)
<i>Examinations: n (%)</i>	
Pathological ECG	13 (46%)
High troponin levels	5/20 (25%)
Pathological TTU	25/27 (93%)
Pathological MRI	5/7 (71%)

AOSD: adult-onset Still's disease; **AOSD+C group:** AOSD with cardiac involvement

ECG: electrocardiogram, **TTU :** transthoracic ultrasonography, **MRI:** magnetic resonance imaging
Values are expressed as number (%).

Table 2: Efficacy of treatment for the cardiac episode

	AOSD+C	Pericarditis	Tamponade	Myocarditis	Endocarditis
CTC ou CTC+MTX: n (%)	17/24 (71)	10/14 (71)	4/5 (80)	2/4 (50)	1/1 (100)
Anakinra: n (%)	8/8 (100)	4/4 (100)	1/1 (100)	3/3 (100)	0/0 (-)
NSAIDs: n (%)	3/11 (27)	3/7 (43)	0/2 (0)	0/2 (0)	0/0 (-)
Tocilizumab: n (%)	0/0 (-)	0/0 (-)	0/0 (-)	0/0 (-)	0/0 (-)
Anti-TNFα: n (%)	0/0 (-)	0/0 (-)	0/0 (-)	0/0 (-)	0/0 (-)

AOSD: adult-onset Still's disease; **AOSD+C group:** AOSD with cardiac involvement; **CTC:** corticosteroid treatment, **MTX:** methotrexate, **NSAIDs:** nonsteroidal anti-inflammatory drugs, **Anti-TNF α :** tumor necrosis factor-alpha inhibitors. Values are expressed as number (%).

Table 3: Characteristics and clinical manifestations of AOSD in patients with and without cardiac involvement

	All AOSD (n = 96)	Control group (n = 68)	AOSD+C group (n = 28)	p-value
Male: n (%)	47 (49%)	32 (47%)	15 (54%)	0.12
Age at diagnosis (years): median [Q1-Q3]	42 [25-55]	42 [27-55]	44 [22-57]	0.80
Follow-up (months): median [Q1-Q3]	34 [11-85]	45 [10-98]	25 [11-52]	0.79
Clinical patterns				
Monocyclic: n (%)	46 (48%)	36 (53%)	10 (36%)	0.09
Polycyclic: n (%)	26 (27%)	13 (19%)	13 (46%)	0.01*
Chronic articular: n (%)	24 (25%)	19 (28%)	5 (18%)	0.44
Clinical manifestations				
Fever >39°C: n (%)	95 (99%)	66 (97%)	28 (100%)	1.0
Arthralgia/arthritis: n (%)	87 (91%)	61 (90%)	23 (82%)	0.32
Pharyngitis: n (%)	77 (80%)	51 (75%)	26 (93%)	0.05*
Maculopapular rash: n (%)	61 (64%)	46 (68%)	15 (54%)	0.24
Lymphadenopathy/hepatomegaly/ splenomegaly: n (%)	49 (51%)	37 (54%)	12 (43%)	0.37
Pleural effusion: n (%)	39 (41%)	20 (29%)	19 (68%)	0.001*
Fugitive erythema: n (%)	32 (33%)	21 (31%)	11 (39%)	0.48
Laboratory features				
WBC (G/L): median [Q1-Q3]	18.4 [14-23]	16.7 [13.7-21.3]	21.8 [17.0-26.0]	0.02*
PMNs (G/L): median [Q1-Q3]	15.2 [11.7-20.7]	14.6 [11.7-17.3]	18.9 [13.9-24.0]	0.02*
CRP (mg/L): median [Q1-Q3]	260 [180-347]	244 [168-300]	319 [262-390]	0.001*
Albumin (g/L): median [Q1-Q3]	29 [23-33]	31 [25-34]	27 [21-30]	0.01*
SF (μmol/L): median [Q1-Q3]	4176 [1736-12711]	3870 [1900-11530]	4305 [1261-13062]	0.58
Glucosylated ferritin (%): median [Q1-Q3]	15 [9-21]	16 [11-22]	11 [9-17]	0.25
Abnormalities in liver function tests: n (%)	57 (59%)	42 (62%)	15 (54%)	0.50
Negative for ANA/RF: n (%)	87 (91%)	60 (88%)	27 (96%)	0.28
Classification criteria				
Yamaguchi criteria	94 (98%)	66 (97%)	28 (100%)	1.0
Fautrel criteria	88 (92%)	61 (90%)	27 (96%)	0.43

AOSD: adult-onset Still's disease; **Control group:** AOSD without cardiac involvement; **AOSD+C group:** AOSD with cardiac involvement;

WBC: White blood cell; **PMNs:** Polymorphonuclear; **CRP:** C-reactive protein; **SF:** Serum ferritin concentration; **ANA:** Antinuclear antibodies;

RF: Rheumatoid factor

Values are expressed as median [Q1-Q3] or number (%).

*Statistically significant differences between control and AOSD+C group.

Table 4: Treatment of AOSD patients during follow-up

	AOSD Cohort (n = 96)	Control group (n = 68)	AOSD+C group (n = 28)
Corticosteroid treatment: n (%)	87 (91%)	63 (93%)	24 (86%)
Methotrexate: n (%)	45 (47%)	30 (44%)	15 (54%)
NSAIDs: n (%)	36 (38%)	24 (35%)	12 (43%)
Anakinra: n (%)	23 (24%)	14 (21%)	9 (32%)
Tocilizumab: n (%)	12 (13%)	5 (7%)	7 (25%)
Anti-TNFα: n (%)	6 (6%)	4 (6%)	2 (7%)

AOSD: adult-onset Still's disease; **Control group:** AOSD without cardiac involvement; **AOSD+C group:** AOSD with cardiac involvement ; **NSAIDs:** nonsteroidal anti-inflammatory drugs, **Anti-TNF α :** tumor necrosis factor-alpha inhibitors, Values are expressed as number (%).

Table 5: Complications and outcomes of AOSD

	AOSD cohort (n = 96)	Control group (n = 68)	AOSD+C group (n = 28)	p-value
Admission to ICU: n (%)	16 (17%)	2 (4%)	14 (50%)	0.0001*
Refractory AOSD: n (%)	22 (23%)	13 (19%)	9 (32%)	0.19
bDMARDs during follow-up: n (%)	28 (29%)	15 (22%)	13 (46%)	0.03*
RHL: n (%)	8 (8%)	6 (9%)	2 (7%)	1.0
Death: n (%)	2 (2%)	2 (3%)	0 (0%)	1.0

AOSD: adult-onset Still's disease; **Control group:** AOSD without cardiac involvement; **AOSD+C group:** AOSD with cardiac involvement;

ICU: intensive care unit; **bDMARDs:** Biological disease-modifying antirheumatic drugs; **RHL:** reactive hemophagocytic-

lymphohistiocytosis;

Values are expressed as number (%).

*Statistically significant differences between control and AOSD+C group.

Table 6: Predictive markers of refractory AOSD in multivariate analysis.

	Odds Ratio	IC(95%)	p-value
Age at diagnosis (years)	1.007	0.979-1.036	0.59
CRP (mg/L)	1.001	0.996-1.005	0.84
Cardiac involvement	4.064	1.353-12.2074	0.01*
Chronic articular pattern	3.49	1.119-10.896	0.03*

AOSD: adult-onset Still's disease ; **CRP:** C-reactive protein

*Statistically significant differences.