Electronic Journal of Medical and Dental Studies
2025, 14(1), em0109
e-ISSN: 2753-2658
https://www.ejmds.com

MODESTUM

Original Article

OPEN ACCESS

Adult onset Still disease: A retrospective study including 65 patients in Tunisia

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Citation: Frikha O, Ghribi M, Derbel A, Mekki S, Snoussi M, Ben Salah R, Frikha F, Marzouk S, Bahloul Z. Adult onset Still disease: A retrospective study including 65 patients in Tunisia. ELECTR J MED DENT STUD. 2025;14(1):em0109. https://doi.org/10.29333/ejmds/16004

ARTICLE INFO

Received: 16 Sep. 2024

Accepted: 09 Jan. 2025

ABSTRACT

Adult onset Still disease (AOSD) is a rare systemic auto inflammatory disease of unknown origin. It is characterized by its clinical and biological polymorphism. Eliminating differential diagnoses is one of the most important steps when the diagnosis of adult Still's disease is suggested, given the absence of clinical or laboratory signs to support the diagnosis; adult Still's disease is a so-called "diagnosis of exclusion". We conducted a retrospective study to describe clinical and laboratory features, treatment, course, and complications of AOSD in 65 Tunisian patients and to compare them to the literature. All patients responded to Yamaguchi criteria. There were 52% women (80%) and 13 men (20%). The mean age at diagnosis were 36.5 years old (range: 16-70 years). Fever was constant, associated with an altered general condition in 27 patients (41.5%). The other signs were polyarthritis (63.8%), skin involvement (83.1%) with a typic rash in 66.3%, throat sore (33.8%), lymphadenopathy (31.3%), splenomegaly (25%), hepatic involvement (50%) and pericarditis (18.5%). The inflammatory biological syndrome was constant. Leukocytosis greater than 10,000 Elt/mm^3 was described in 87.3% of cases with polynuclear neutrophil > 80% in 63.6%. Hyperserotonemia was observed in 56 patients (96.5%). Treatment was based on corticosteroids, as a first line treatment, and methotrexate as a second line treatment. In terms of disease course, 68.3% of cases evolved to the systemic form and 31.7% of them to the chronic articular form. AOSD is a relatively benign disease. It can be life-threatening due to its severe systemic damage and functionally damaging due to its destructive joint damage.

Keywords: adult onset Still disease, polyarthritis, methotrexate, IL-1 inhibitors, IL-6 inhibitors

INTRODUCTION

Adult onset Still disease (AOSD) is a rare autoinflammatory disease. It affects young people between the age of 16 and 35 years old. Its physiopathology remains, till now, unclear. There is a hyper activation of the innate immune system (macrophages and neutrophils) and a hypersecretion of proinflammatory cytokines contributing to its development [1].

AOSD typically presents with 4 cardinal signs: high hectic fever, evanescent rash, arthralgia or arthritis and leukocytosis with elevated polynuclear neutrophils (PNN) [2]. Other non-specific clinical and laboratory features can also be found.

The treatment remains empirical. Systemic corticosteroids (CS) is the gold standard of treatment for AOSD. In case of cortico-dependence or resistance, conventionnel synthetic disease-modifying-anti-rheumatic drugs (csDMARDs) can be indicated, methotrexate (MTX) in particular. The biological agents, such as interleukin 1 and interleukin 6 inhibitors, are efficient in severe and refractory cases [3].

The course of the disease is unpredictable. It can evolve to a systemic form or a chronic articular form. The functional prognosis depends on the articular involvement and the vital one depends on the systemic involvement and its complications. In our study, we report clinical and laboratory features, treatment, course, and complications of AOSD in 65 Tunisian patients.

PATIENTS AND METHODS

This is a retrospective study conducted in the department of internal medicine at Hedi Chaker Hospital from January 1996 to December 2018. We studied 65 cases of AOSD that responded to Yamaguchi criteria. Clinical and laboratory data were collected and analyzed by SPSS version 25.

RESULTS

Clinical Features

We identified 65 cases of AOSD with an annual incidence of 2.95 cases/year. They were 52 women (80%) and 13 men (20%) with a sex ratio of 0.25. The mean age at diagnosis was 36.5 years old (range: 16-70 years). A pic of frequency was noted between the age 20 and 39 years old. We have found only one elderly patient affected by the disease.

Table 1. Different types of articular involvement

Type	n	P (%)
Polyarthritis	37	63.8
Oligoarthritis	2	3.4
Inflammatory arthralgia without arthritis	19	32.8
Bursitis	1	1.7
Joint deformities	15	25.9

Note. n: Number of cases & P: Percentage

Table 2. Topography of the articular involvement

Topography	n	P (%)
Wrists	47	81.0
Elbows	32	55.2
Shoulders	15	25.9
Knees	49	54.5
Ankles	24	41.4
Hips	2	3.5
Metacarpophalangea	32	55.2
Proximal interphalangeal	32	55.2
Metatarsophalangeal	2	3.5

Note. n: Number of cases & P: Percentage

The median delay to diagnosis was 5.13 months (range: 17 days- 72 months).

The disease-onset manifestations were the symptomatic triad including fever, articular involvement and skin rash (38.5%), febrile polyarthritis (13.8%), isolated fever (4.6%), isolated skin rash (1.5%), altered general condition (20%) and lymphadenopathies (6.2%).

The fever was constant. It was higher than 39° in 50.8% of the cases. It was associated with altered general condition and weight loss in 41.5% of the cases.

Articular involvement was noted in 58 patients (89.2%). It was bilateral and symmetrical in 89.7%, polyarticular in 93.1% of the cases and oligoarticular in 6.9% of the cases.

Table 1 and **Table 2** shows the different types of articular involvement and the joints affected.

Myalgia was reported by 19 patients (29.7%). Skin involvement was described in 54 cases (83.1%). It was a typical rash in 66.2% of the cases, which was associated with livedo in one case and generalized pruritus in 5 cases. Other non-specific lesions were observed: urticaria in 8 patients (12.3%), vascular purpura in 2 patients (3.1%) and isolated generalized pruritus in 1 case (1.5%).

A splenomegaly was found in 16 patients (25%). Lymphadenopathies were noted in 20 cases. The most frequent locations were cervical in 20% of the cases, axillar and inguinal in16.9% of the cases. Hepatomegaly was found in 14 cases. Two patients had jaundice.

A sore throat was reported by 22 patients (33.8%). Twelve patients had pericarditis. It was associated with pleuritis in 2 cases and with myocarditis in 2 cases also. A tamponade was noted in one patient.

Pleuritis was found in 7 cases. A woman had an acute pulmonary edema and died before completing the tests.

Abdominal pain was reported by 8 patients. A man suffered from aseptic peritonitis requiring surgery 3 times.

Three patients had nephrotic syndrome. Another 3 patients suffered from peripheral neurological involvement: multi-neuritis in 2 cases and poly-reticuloceratids in one case.

Table 3. Patients clinical manifestations at time of diagnosis

Characteristics	n	P (%)
Female	52	80.0
Male	12	20.0
Median age at diagnosis (years)	36.5	
Median delay of diagnosis	5-13 m & R (17 d-72 m)	
Fever	65	100
Weight loss	27	41.5
Arthritis	39	67.2
Myalgia	19	29.7
Typical rush	43	66.2
Lymphadenopathy	20	31.3
Splenomegaly	16	25.0
Hepatomegaly	14	21.5
Sore throat	22	33.8
Pericarditis	12	18.5
Myocarditis	2	3.1
Pleuritis	7	10.8
Abdominal pain	8	12.3
Nephrotic syndrome	3	4.6
Neurological involvement	3	4.6

Note. n: Number of cases; P: Percentage; R: Range; m: Month; & d: Day

Table 4. Patient laboratory characteristics at time of diagnosis

Characteristics	n	P (%)
White blood cells >10,000/mm^3	55	87.3
White blood cells >15,000/mm^3	42	66.7
PNN ≥ 80%	35	63.6
Anemia	53	84.1
Thrombocytosis	15	23.8
Thrombopenia < 100,000/ mm^3	2	
Mean CRP (mg/l)	147.9 (R: 20-529)	
Elevated ESR	60	93.8
ESR > 100	40	62.5
Ferritin levels ≥ 1,000 ng/ml	47	81.0
Ferritin levels ≥ 2,000 ng/ml	21	36.2
Cholestasis	17	26.2
Cytolysis	23	35.4
Fulminant hepatitis	2	3.1
Activation syndrome	3	4.6

Note. n: Number of cases; P: Percentage; & R: Range

Detailed information about the different manifestations are displayed in **Table 3**.

Laboratory Features

Leukocytosis (white blood cells count > 10,000/mm^3) was present at diagnosis in 55 patients (87.3%) and was composed of more than 80% PNN in 35 cases (63.6%). Anemia was found in 53 patients (84.1%) and thrombocytosis (platelets > 440,000/mm^3) in 15 cases (23.8%). The CRP levels were increased in 61 patients (95.3%) and the erythrocyte sedimentation rate (ESR) in 60 patients (93.8%). The ferritin level, measured in 58 cases, was also increased in 96.5%. The glycosylated ferritin was measured in 1 patient. It was under 20%. Half of the patients had an altered liver function. Seventeen had cholestasis and twenty-three had cytolysis. Cholestasis was associated with cytolysis in 9 cases (13.8%). Two patients suffered from fulminant hepatitis. Myolysis was noted in 13 cases (20%).

Anti-nuclear antibodies and rheumatoid factor were absent in all patients. Bone marrow aspiration was carried out in 43 cases. It has shown macrophage activation syndrome (MAS) in 3 cases. **Table 4** illustrates the different biological anomalies found in our patients.

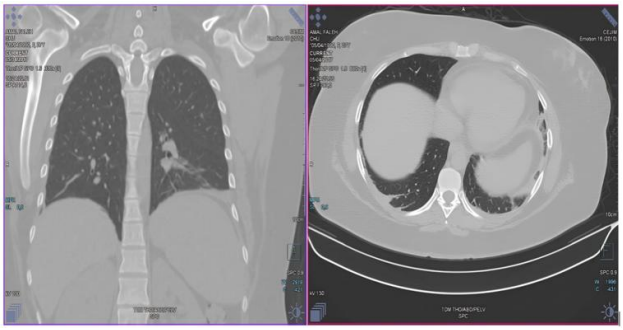

Figure 1. Coronal and axonal CT sections: Band ventilatory disorders such as atelectasis and bilateral basal condensations (Reprinted with permission of patient)

Five patients had skin biopsy. It was non-specific in 4 and has shown leukocytoclastic vasculitis in 1 case. The pathology examination of 9 lymphadenopathies has shown non-specific reactive lymphadenitis in 8 cases and lymph node amyloidosis in 1 case. A liver biopsy was performed in 9 patients, it concluded to microvacuolar steatosis in 2 cases, reactive hepatitis in one case, non-specific inflammatory state in one case, moderate portal septal and centrilobular inflammation and fibrosis with hepatocyte necrosis in one case and nodular hyperplasia of the liver, occurring 3 years after the diagnosis of AOSD in one patient. It was normal in the other cases.

Three patients had a kidney biopsy. It has shown kidney amyloidosis.

Pleural puncture, performed in 2 patients, brought back an exudative fluid without germs.

Thirty-two thoraco-abdomin-pelvic CT scans were performed. Three have shown deep lymphadenopathies (mesenteric in 2 cases and mediastinal in 1 case). One woman suffered from bilateral basal pulmonary condensations (**Figure 1**).

Treatment

Twenty-six patients (40%) received nonsteroidal anti-inflammatory drugs (NSAIDs) as first line treatment in 9 cases (13.9%), and as a second line treatment in the chronic articular form in 17 cases (26.2%). The drugs used were Indomethacin in 15 cases, diclofenac in 8 cases and aspirin in 3 cases.

CS were prescribed for all patients, as a first line treatment in 56 cases (86.2%) and as a second line in 9 cases (13.9%). The initial dose was 0.5/mg/day in 4 cases (6.2%) and 1 mg/kg/day in 61 cases (93.8%). The duration of this initial dose varied between 3 and 8 weeks.

Seven patients required pulses of methylprednisolone (1g/day for 3 days) due to the severe symptoms. Low pulses of methylprednisolone (100 mg/day for 3 days) were used in 5 patients due to an articular flare.

Twenty-eight cases (43.1%) received MTX as a csDMARDs. It was indicated as second line treatment because of CS-dependance in 6 cases (9.2%), CS-resistance in 3 cases (4.6%) and frequent relapses in 19 cases (29.2%). The initial dose was 10 mg/week. Then it was increased to 15mg/week in 6 cases (13.3%) and to 20 mg/week in one case. The mean delay between CS and MTX prescription was 2.2 months (range: 2-76 months).

Table 5. The different treatments used in our study

Treatment	n	P (%)
NSAIDs	26	40.0
CS (0.5-1.0 mg/kg/day)	65	100
Pulses of methylprednisolone (1 g/day for 3 days)	7	10.8
Pulses of methylprednisolone (100 mg/day for 3 days)	5	7.7
MTX	28	43.1
Synthetic anti-malarials	10	16.4
Joint steroids infiltrations	6	9.2

Note. n: Number of cases & P: Percentage

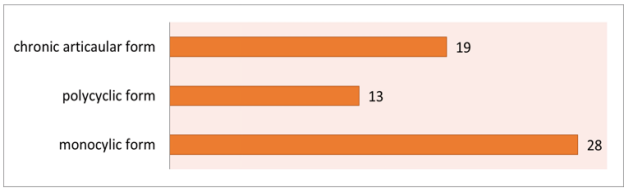

Figure 2. Evolutionary patterns found in our serie (Source: Authors' own elaboration)

Synthetic anti-malarias were used in 10 cases (16.4%) as first line csDMARDs in 5 old cases, in association with MTX (2 cases) and in case of desire for pregnancy (3 patients).

Three women had a refractory articular form. We proposed a biologic agent (tocilizumab), but it was refused by the insurance company.

Joint steroids infiltrations were indicated in 6 patients. The joints treated were the knees (3 cases) and proximal interphalangeals (3 cases).

The different lines of treatment are resumed in **Table 5**.

Disease Course

Five patients were lost to follow-up. The remaining cases evolved to a systemic form, in 41 patients (68.3%) in whom 28 had monocyclic form, and chronic articular form in 19 cases (31.7%) (**Figure 2**).

In the monocyclic form, 2 patients required MTX due to CS-resistance. The other patients recovered on CS only. The CS were stopped in 15 cases (53.6%) after a mean of 37 months (range: 10 months-14 years).

In the polycyclic form, the average number of flares was 3 (range: 2-6). These patients (13 cases) were treated by CS. Nine cases received MTX due to the relapses. Remission was reached in 11 cases and MTX was stopped in 3 cases after an average of 23.3 months.

In the chronic articular form, the average number of flares was 3 (range:1-8). Fifteen patients suffered from joint deformities and ankylosis. It touched the hands (10 cases), elbows (6 cases) and the knees (1 case). Joint destruction was noted in 14 cases. It concerned mainly carps inter carpal space narrowing (9 cases), radiocarpal space narrowing (3 cases) and erosions (3 cases).

These patients were treated with CS (19 cases), MTX (14 cases), NSAIDs (15 cases), low doses of methylprednisolone (7cases) and joint steroids infiltrations (6 cases). The disease was stabilized in 15 cases. Three patients continued having articular flares. A biological treatment was proposed.

Four patients were deceased by septic choc (3 cases) and sudden death (1 case).

Table 6. Epidemiological features comparison

Epidemiological features	References				Our study
	[11]	[8]	[10]	[9]	
Country	France	USA	China	Japan	Tunisia
Number of cases	57	106	517	513	65
Sex ratio M/W	0.90	0.45	0.39	0.56	0.25
Median age	36.00	43.08	37.70	53.10	36.49

We tried to compare the chronic articular form and the systemic form then the monocyclic form and the polycyclic form using the clinical and laboratory characteristics. We did not find any associations predicting the disease course to a particular form.

DISCUSSION

AOSD is a multigenetic and auto inflammatory disease. Its pathophysiology is complex, including innate and specific immunity. Several factors can trigger, in genetically predisposed patients, an inappropriate inflammatory response, cytokine storm, which is responsible for the development of the disease [4]. Noesis, activity, phenotype prediction and prognosis of the AOSD.

Before retaining the diagnosis of AOSD, we need to eliminate all the infectious, neoplastic, auto immune and other auto inflammatory diseases. Several classification criteria were proposed. But the Yamaguchi and Fautrel criteria were the only ones used [4]. They offer a sensitivity of 96.3% and a specificity of 98.2% [5]. A combination of Yamaguchi criteria and a glycosylated ferritin level ≤ 20% can reach a sensitivity of 98.2% and a specificity of 98.6% [4].

AOSD is a rare disease. Its estimated prevalence rate is 0.16-0.4/100,000 people in France [6] and 3.7/100,000 people in Japan [7]. In our study, the annual incidence rate was 2.95 cases/year.

AOSD affects young people. The median age at diagnosis varies from 37.7 to 53.1 years depending on the studies [8-10]. In the latest French retrospective study, it was 36 years. Eighteen percent of these study were aged more than 55 years [11]. In our study, the median age at diagnosis was 36.49 ans.

A female predominance has been reported in several studies with a frequency that varies between 53 and 72% [7, 8, 10, 11]. In our study, AOSD affected 80% of the women with a sex ratio of 0.25. **Table 6** compares the epidemiological features.

The current findings are consistent with those reported in the main literature [1, 7, 9-11]. Hyperserotonemia is a diagnostic marker for AOSD. It is reported in 82-95.8% of the cases [1, 7, 10, 11]. A level exceeding 1,000 µg/l is sensitive but unspecific (41-46%) referral element for the diagnosis [12]. A collapse of the glycosylated ferritin level below 20% (normal level > 50%) supports the diagnosis of AOSD. It is neither constant nor totally specific. It can be seen in others diseases (such as severe systemic infections and MAS).

Classically, 3 different disease courses were described in the literature: monocyclic, polycyclic and chronic form [6]. The monocyclic form frequency varies between 19-44% [6, 8, 11, 13]. In our study, it was about 46.7% which higher than the French study (30%) [11]. The polycyclic form frequency was between 10-44% [6, 8, 11, 13]. In our study, it was about 21.6% which was lower than the French one (44%) [11]. The chronic form frequency varies between 26-67% [6, 8, 11, 13]. In our study, 31.7% of the cases evolved to a chronic form. They were close to the French study (26%) [6].

However, this classification has a limited interest for the management of patients from a prognostic and therapeutic point of view [14]. A new dichotomy has been proposed based on the cytokine profile and predominant clinical manifestations [15, 16]. It classifies AOSD into 2 phenotypes [12, 14]:

1. A systemic form, combining the monocyclic and polycyclic form: It is characterized by the predominance of systemic signs, elevated levels of inflammation markers and ferritin, and possible multi-systemic involvement related to major macrophagic activation.
2. A chronic articular form: It seems to be more frequent in women. It is characterized by the predominance of chronic polyarthritis, with a possible joint destruction that resembles rheumatoid arthritis, and a less important inflammatory state. Some patients may have systemic flares at the disease onset and then progress to a chronic articular form.

Occasionally, AOSD can present life-threatening or functional complications. These include [17] MAS, severe hepatitis, disseminated intravascular coagulation (1-5% [9, 17]), thrombotic microangiopathy, cardiac and pulmonary involvement, organ failure and AA amyloidosis (0.88%) [18]. These complications, apart from amyloidosis, most often occur at disease onset [19]. MAS is the most common complication [11]. It occurs in 10-15% of the cases. It seems to be more frequent in the persistent or refractory systemic forms. It has a high mortality rate which is estimated to be about 10-20%. In our study, 3 patients (4.6%) suffered from MAS. They well responded to CS.

AOSD is a relatively benign disease. Its mortality rate varies between 3.11 and 12% of cases [4, 6, 9]. Deaths are related to infections, acute respiratory distress syndrome, organ failure in MAS, thrombotic microangiopathies, or central nervous system involvement [6]. In our study, the mortality rate was 6.15%. In AOSD, the prognosis is twofold [20]: functional, related to potentially destructive joint involvement with joint deformities and iatrogenic complications (mainly CS), and life-threatening, related to the severity of systemic involvement.

It was proposed a systemic score to evaluate the prognosis at disease onset [21]. It was confirmed that a cut-off of 7 points of the systemic score identifies the patients at high risk of death related to AOSD [22]. They also suggested that comorbidities at disease onset are predictive of a more severe prognosis. It was summarized the results of different studies harvesting prognosis factors [12]: polyarthritis and initial joint erosions are associated with chronic articular form, fever exceeding 39.5 °C at disease onset is associated with systemic monocyclic form, lymphadenopathy, splenomegaly and thrombopenia are correlated with MAS and thrombopenia with higher mortality rate of MAS complicating AOSD, leukocytosis exceeding 30 000/mm^3, elevated ESR, C-reactive protein (CRP) and ferritin levels are associated with higher risk of relapses, higher ferritin levels and lower glycosylated ferritin levels seem to be correlated with MAS, using glycosylated ferritin levels at diagnosis may shorten the diagnosis delay and favor a monocyclic evolution, and, splenomegaly, young age at disease onset, collapsed glycosylated ferritin levels, and a major increase in ESR are associated with CS-dependency.

The treatment of AOSD remains till now empirical due to the lack of double-blind randomized prospective studies. Available evidence on treatment is obtained from small retrospective series [1, 12]. Recently, biological agents have been proven to be effective in controlling AOSD [6, 12, 23, 24].

The NSAIDs are no longer a first line treatment. They controlled the symptoms of AOSD in 16-18% of the patients with side effects in 20% of the cases [6, 11, 25]. In front of the unfavorable risk/benefit ratio, NSAIDs should be considered as a supportive treatment during the diagnostic process and whenever CS and csDMARDs are insufficient [4, 6, 25]. The CS are the first line treatment [1, 4, 6, 12]. They induce remission in 60-65% of the cases [1, 6]. The initial dose is 0.5-1mg/kg/day. Pulses of methylprednisolone are indicated in case of severe visceral involvement and a MAS [1, 4, 6]. It was reported that patients treated by high doses of CS (≥ 40 mg or 0.8 mg/kg/day) reach remission faster and suffer from less relapses than those treated by low doses [26]. The response to CS is rapidly reported within a few days. Its tapering should begin after 4-6 weeks of treatment after the symptoms and inflammatory laboratory parameters normalization [1, 4, 6]. CS-dependency occurs in 45% of the cases [1, 6]. It was reported that splenomegaly, low glycosylated fraction of ferritin, increased ESR and early disease onset are predictive of CS-dependency, suggesting an early addition of a steroid-sparing agent [25]. In our study, CS induced remission in 44.6% (29/65).

MTX is the most frequently used DMARD for its steroid sparing effect. It is indicated in case of CS-dependence or resistance [1]. It was shown that MTX at doses of 7.5-17.5 mg/week reduces the daily intake of CS of 69% of the cases in 26 CS-dependent or resistant patients [27]. It also induces a complete remission in 69.2% of the cases and CS withdrawal in 42.3% of the cases. It seems to be efficient in both articular and systemic forms. In our study, MTX was administered as a second line treatment in case of CS-dependency (12.5%), CS-resistance (6.3%) and frequent relapses (37.5%). It reached remission in 75% of the cases (21/28). Previously, others csDMARDs, such as cyclosporine, hydroxychloroquine, gold, D-penicillamine, azathioprine, leflunomide, cyclophosphamide and tacrolimus, were used in the refractory forms with a variable efficiency [28].

Limited studies are reported about hydroxychloroquine and cyclosporine efficiency [12]. In the Chinese study [10], hydroxychloroquine was prescribed to 174 patients (33.7%). It was associated with CS in 18 cases and has induced a remission in 85.7%. In the other cases, it was associated with other csDMARDs. In our study, it achieved remission in 70%. It was associated with other csDMARDs in 2 cases. Biological agents are indicated in the refractory forms resisting CS and csDMARDs [1, 6, 12, 13].

In our study, biological agents were proposed to 3 patients. But it was refused due to insurance problems. The high costs of the biological agents may explain their limited use in some countries like Tunisia, China and Turkey [10]. The present study presents some limitations. First, it is a retrospective study. Second, it was carried out in a single university hospital in southern Tunisia. It might have caused a higher percentage of severe cases. It does not show the patients characteristics in the other Tunisian institutions. Moreover, more developed software and more close data would explore better the prognosis factors.

CONCLUSION

We conducted a retrospective study that illustrates the clinical and laboratory features, treatment, course, and complications of AOSD in a North African country. Our results are consistent with the literature. The most common treatments are CS and MTX. Biological agents should be provided for refractory forms. AOSD is a relatively benign disease. The main deaths are related to treatment side effects.

Author contributions: OF: formal analysis, writing – original draft; **MG & SMa:** supervision, validation; **ZB:** resources; **AD, SM, MS, RBS & FF:** investigation. All authors have agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Ethical statement: The author stated that the approval of the ethics commettee was not required for retrospective studies since no new treatment or therapeutic strategy has been introduced. Written informed consent was obtained from all patients. All patients have consented to publication of this study, imaging, and all data.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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