International Journal of Medical Science and Health Research

Vol. 4, No. 03; 2020

ISSN: 2581-3366

Adult Still's Disease in Spain: Description of New Cases, and Systematic Review

Alende-Castro V[1], Perez-Garcia C[1], Sande D[1], Brea Aparicio R[1], Baz Lomba A[1], Fernandez Villar J[1], Valle B[1], Fernández Morales M[1], Perez Fernandez S[1], Velo-García A[2], Rodriguez Garcia JC[2]

AUTHOR AFFILIATIONS:

[1] Department of Internal Medicine, Salnes Hospital, Villagarcia, Galicia, Spain

[2] Department of Internal Medicine, University Teaching Hospital, Pontevedra, Spain

Abstract

Background: Adult Still's disease is an inflammatory and very uncommon disorder. While there is a significant body of literatura in children, little is known about this disease in adult population.

Objectives: to summarize the scientific evidence adult Still's disease in Spain and describe new cases.

Methods: Patients with diagnosis of Still's disease in our regional hospital were included. Systematic review: We conducted a search of the Pubmed/Medline database. The search identified 75 articles, of which 15 were selected for extraction and data analysis. 60 studies were excluded because they failed to match the main criteria.

Results: We present 12 new cases of adult Still's disease with a mean age of 39,3 years. The most frequent form of presentation was fever, arthritis or arthralgia and typical rash. None of the patients died. In this systematic review we identified suitable for inclusion 97 additional cases with a mean age of 38,8 years. A potential exposure risk was found in 3 patients. Five patients presented complications and none of the patients died.

Conclusions: This is the first study to report on an adult Still's disease case series in Galicia. It shows that in this region, the disease affects young population -even in the absence of risk factors- and is linked to a low mortality. The most frequent form of presentation was fever, typical rash and arthritis or arthralgia with complications in some cases. Usually, it is necessary a clinical suspicion to do the diagnosis.

Vol. 4, No. 03; 2020

ISSN: 2581-3366

Keywords: Still; arthritis; rash; fever; ferritin

List of abbreviations

CMV: cytomegalovirus

EBV: Epstein-Barr virus

MIF: migration inhibitory factor gene

NSAIDs: nonsteroidal anti-inflammatory drugs

1. Introduction

Adult Still's disease is an inflammatory, rare and multisystemic disorder characterized by high fever, arthritis and/or arthralgia, and an evanescent rash. It is also called systemic juvenile idiopathic arthritis[12]. Among the laboratory findings are included neutrophilic leukocytosis, hyperferritinemia and abnormal liver function tests[34]. The etiology of adult Still's disease is still unknown; both genetic factors and a variety of infectious triggers have been suggested[56]. Since its description, Still's disease has been widely studied in children. In adults, the disease characteristically affects younger people[7]. The annual incidence of adult Still's disease is 0.16 cases per 100,000 people, with an equal distribution between the sexes[7].

The relevance of Adult Still's disease in Spain is not well known. Thus, to our knowledge there have been no previously reported cases serie of Adult Still's disease in Galicia.

Diagnosis of adult Still's disease remains difficult. Mortality is low despite frequent complications as reactive hemophagocytic syndrome may occur in patients[89]. The diagnosis of adult Still's disease is a diagnosis of exclusion and classification criteria have been proposed for diagnosis[1011].

Several case reports have been published so far in adults, and our aim was to summarize the current literature in order to better delineate the patients' profile with respect to possible triggers, clinical characteristics, laboratory workups and management.

We herein conducted a review of Still's disease cases reported in adults and tried to summarize the clinical and laboratory characteristics of these patients. Accordingly, the main objectives of this study were: on one hand, to describe an adult Still's disease case series in Galicia for the first time; and on the other, to conduct a systematic review to clarify and analyse all available data on the disease in Spain.

Vol. 4, No. 03; 2020

ISSN: 2581-3366

2 Materials and methods

2.1 Case-series report:

We reported twelve cases of adult Still's disease presented in our hospital from Galicia (Pontevedra, north-west Spain) which serves approximately 280.000 inhabitants. All cases were of over 18 years old people. Clinical, epidemiological, radiological and biochemical variables were collected by reviewing patients' electronic medical records to check for diagnosis of adult Still's disease. Other diseases were excluded.

2.2 Ethics statement

The study was conducted in accordance with the principles of the Declaration of Helsinki and in full conformity with prevailing regulations. Vulnerable populations did not participate in this study and neither will economic compensation be given to patients for their participation. The investigators will be free to publish the results of this study, regardless of the results obtained. No economic retribution will be received for this study.

2.3 Systematic review

We conducted a systematic review in order to identify observational studies published describing adult Still's disease case series in Spain. To this end, we searched the Pubmed/Medline database using the following terms: adult Still's disease OR Systemic idiopathic arthritis AND Spain. These search methods yielded a total of 75 studies; after a critical perusal of titles and abstracts, 60 were excluded for failing to fulfil the main eligibility criteria (series reports with a complete clinical description), because of methodological problems, incomplete clinical information or series duplication. We included all articles matching these criteria and reporting on adults over 18 years old. We excluded articles referring to pediatric cases (patients under 18 years old of age). Finally, 15 studies were included in the systematic review.

3 Results

3.1 Cases presentation:

Table 1 summarizes the main clinical characteristics and outcomes of these 12 patients. We recollected twelve patients diagnosed with adult Still's disease in our hospital. Hospital admission in the Internal Medicine department was required in all cases. 7 were female with a mean age of 39,3 (range 21-60). None of the patients had reported a potential risk exposure before the appearance of clinical symptoms. The most frequent form of presentation was fever (100%) and arthralgia (83,3%). Cutaneous manifestations were detected in 11 patients (91,6%). All patients presented a favourable evolution with treatment. The most frequent regimen included corticosteroids and NSAIDs. Methotrexate was associated in one patient and Tocilizumab in another patient. A diagnosis of exclusion was made in all cases, including screening for infectious and systemic diseases. None of

Vol. 4, No. 03; 2020

ISSN: 2581-3366

the patients died. None of the patients presented complications. All case patients continued undergoing long-term treatment with corticosteroids. Attending to the course of the disease, 58,3% was monocyclic, 33,3% polycyclic and 8,4% with a chronic course.

3.2 Systematic review:

The database searches identified 75 articles, and after the removal of the duplicated or incomplete studies, 15 studies were chosen on the basis of the title and the abstract.

Results: a total of 97 patients (female gender: 60,8%; mean age 38) were included. With regard to clinical manifestations, fever and cutaneous manifestations were the most frequent (72.2%), followed by arthritis or arthralgia (48.8%), lymphadenopathy (35%), esplenomegaly (28.8%), hepatomegaly (16.5%) and upper respiratory tract symptoms (29.8%). Four patients presented pericarditis and one patient fever of unknown origin. Factor risk was identified in only 3.09% (n=3) of patients. There is a low complication rate (6.2%): two patient presented hemophagocytic syndrome, one patient liver failure, one patient vascular renal AA amyloidosis, one patient thrombotic thrombocytopenic purpura and one patient acute respiratory distress syndrome. None of the patients died. The treatment included NSAIDs, corticosteroids and immunosuppressive treatment in most of the cases. A breakdown of the main data available from the studies is shown in Table 2.

4 Discussion:

In the present study we describe for the first time in Galicia, epidemiological and clinical data on adult Still's disease.

Adult Still's disease is an inflammatory and very uncommon disorder[2]. In the absence of reported case series from Galicia (north-west Spain), this study sought to describe a Still's disease case series in this region for the first time, and conduct a systematic review to analyse all available data on the disease in Spain. Furthermore, the present study is one of the few existing efforts in Spain to evaluate clinical characteristics and prognosis of adult Still's disease.

The first description by George Still in 1896 included only pediatric patients. Adult case of Still's disease was described by Bywters in 1971[12]. They found similarities with the previously described disease in children[4]. They described fourteen patients with a typical rash, fever and polyarthritis. Therefore, they found that the rheumatoid factor and antinuclear antibodies were absent from the serum. Prognosis is usually good. In their case series, all fourteen patients were female.

Adult Still's disease is a rare entity with an estimated annual incidence of or being 0.16 cases per 100,000 people[2]. Among the 97 patients, there was a female predominance (60,8%) with a mean age of 38.8 which shows that this disease typically affects young

Vol. 4, No. 03; 2020

ISSN: 2581-3366

adult men and women and it had been described in all regions of the world, in any case patients older than 70 have been reported[136].

From a clinical point-of-view, the adult Still's disease cases included in this review were presented with fever, evanescent rash, arthritis or arthralgia. This fact occurs in about 75 to 95 percent of patients[3]. Furthermore, multiorgan involvement can occur[78]. These findings include lymphadenopathy, splenomegaly, hepatomegaly and upper respiratory tract involvement, which was the most frequent feature in our study. With reference to biochemical tests, blood leukocytosis, liver dysfunction tests and high serum levels of ferritin can be found in these patients[910]. Among laboratory alterations the level of seric ferritin is very important and whose value is usually above 10.000. When we can fraction this seric marker with the glycosidal part, we can obtain diagnostic and prognostic value, given that values superior to 20% are very suggestive of Still´s disease and in general associated with a good prognosis. Neverthless, low prognosis fractions are related to more serious diseases or syndromes associated with Still´s disease such as the macrophagical activation syndrome or the hemophagogytic syndrome. Another potencial laboratory marker is the elevation value in the soluble receptor for interleukin-2.

In addition, as reported by other authors, potentially fatal complications can occur, such as macrophage activation syndrome[11]. Among the 97 reviewed cases, we observed a lower proportion of complications: none were found in our patients and only 6.2% with regards to the systematic review. These findings are in line with those reported by studies undertaken elsewhere[9]. With regard to risk factors, these were found in only 3 patients (3.09%). The cases were related to drugs or infections. Among the triggers, we should consider many viruses, such as Epstein-Barr virus (EBV), cytomegalovirus (CMV) and other agents such *Yersinia* enterocolitica and *Mycoplasma pneumoniae.* Numerous studies have been published evidencing the genetic role in the pathophysiological basis of the disease as functional promoter polymorphisms in the migration inhibitory factor (MIF) gene[3].

There are not specific tests for diagnosis of adult Still's disease. For the diagnosis we need the presence of characteristic clinical and laboratory features without another condition that may cause similar symptoms and findings (including infection, rheumatology diseases, malignancy or auto-inflammatory disorders). Based on this, the diagnosis is based on clinical criteria. The most commonly accepted are the Yamaguchi criteria[14]. Clinical and analytical findings of the reviewed literature are similar for adult and pediatric patients[7]. Adult Still's disease is a diagnosis of exclusion. Proposed clinical differential diagnoses included: infections, systemic autoimmune and inflammatory rheumatic diseases, malignancy, and adverse reactions to medications[31516].

Regarding the clinical course, several patterns have been described: monophasic or monocyclic pattern, intermittent or polycyclic patterns and chronic patterns. In our study,

Vol. 4, No. 03; 2020

ISSN: 2581-3366

the most frequent pattern observed was monocyclic**.** Attending to our patients, two subjects has monocyclic pattern. The reported frequency of clinical pattern in the included studies is heterogeneous and inconclusive.

If we focus on the treatment, the therapeutic approach recommended by a majority of authors was also followed in our patients: systemic corticosteroids associated with nonsteroidal anti-inflammatory drugs (NDAIS) was the most commonly used combination. Nevertheless, nonbiologic or biologic disease-modifying antirheumatic drugs are frequently necessary for the control of the disease according to our systematic review and previous studies[17181920]. A further important issue emerging out of this review is that few studies have investigated the clinical characteristics and outcomes of adult Still's disease in the adult subjects.

In summary, in our region (Galicia), the adult form of adult Still's disease was predominantly diagnosed in young people. Likewise, adult Still's disease is a rare but potentially severe disease. We herein present a review of adult Still's disease cases reported in the literature to date, aiming to raise awareness of this entity by better defining these patients' profile with regards to possible triggers, clinical presentation, laboratory workup alterations, management and outcome. A high index of suspicion is needed to diagnose this pathology and to deliver proper therapy.

The main limitation of our series report is the retrospective design which could compromise the accuracy of some clinical data included with information on exposures.

5 **Conclusions**:

To the best of our knowledge, this is the first adult Still's disease case-series study to have been conducted in Galicia (north-west Spain). In short, we presented three new cases of adult Still's disease along with a systematic review of the literature.

Adult patients with Still's disease are a heterogeneous population that requires specialty approach to provide optimal care. The results of this systematic review allowed us to conclude that the presence of adult Still's disease in this area is relevant and affects the young population even in the absence of risk factors. As previous studies have reported, it is linked to a low mortality rate and contact with risk factors is not usually reported. Our data indicate that number of cases of adult Still's disease associated with risk factors and fatal complications are presented in some subjects. The monocyclic pattern is the most frequent. In our area fever, cutaneous manifestations and arthritis or arthralgia are the most frequently seen.

Better knowledge of prevalence of disease in different areas and a higher level of clinical suspicion are therefore needed, in order to improve diagnosis of this disease in Spain.

Vol. 4, No. 03; 2020

ISSN: 2581-3366

Acknowledgments: None

Conflict of interest: all authors declare no conflict of interest.

References

1. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/es/30publications/10policies/b3/17c.pdf. Accessed October 30, 2015.

2. Magadur-Joly G, Billaud E, Barrier JH, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. *Ann Rheum Dis*. 1995;54(7):587-590. http://www.ncbi.nlm.nih.gov/pubmed/7668903. Accessed July 9, 2018.

3. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al. Adult-Onset Still Disease. *Medicine (Baltimore)*. 2014;93(2):91-99. doi:10.1097/MD.0000000000000021

4. Still GF. On a form of chronic joint disease in children. *Arch Dis Child*. 1941;16(87):156-165. http://www.ncbi.nlm.nih.gov/pubmed/21032202. Accessed February 18, 2019.

5. Uson J, Peña JM, del Arco A, Barbado FJ, Vazquez JJ. Still's disease in a 72-year-old man. *J Rheumatol*. 1993;20(9):1608-1609. http://www.ncbi.nlm.nih.gov/pubmed/8164226. Accessed July 5, 2018.

6. Steffe LA, Cooke CL. Still's disease in a 70-year-old woman. *JAMA*. 1983;249(15):2062-2063. http://www.ncbi.nlm.nih.gov/pubmed/6834596. Accessed July 9, 2018.

7. Cabane J, Michon A, Ziza JM, et al. Comparison of long term evolution of adult onset and juvenile onset Still's disease, both followed up for more than 10 years. *Ann Rheum Dis*. 1990;49(5):283-285. http://www.ncbi.nlm.nih.gov/pubmed/2344206. Accessed July 9, 2018.

8. Cheema GS, Quismorio FP. Pulmonary involvement in adult-onset Still's disease. *Curr Opin Pulm Med*. 1999;5(5):305-309. http://www.ncbi.nlm.nih.gov/pubmed/10461535. Accessed July 9, 2018.

9. Cush JJ, Medsger TA, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. *Arthritis Rheum*. 1987;30(2):186-194. http://www.ncbi.nlm.nih.gov/pubmed/3827959. Accessed July 9, 2018.

10. Akritidis N, Giannakakis I, Giouglis T. Ferritin levels and response to treatment in patients with Adult Still's disease. *J Rheumatol*. 1996;23(1):201-202.

http://www.ncbi.nlm.nih.gov/pubmed/8838544. Accessed July 9, 2018.

11. Coffernils M, Soupart A, Pradier O, Feremans W, Nève P, Decaux G. Hyperferritinemia in adult onset Still's disease and the hemophagocytic syndrome. *J Rheumatol*. 1992;19(9):1425-1427. http://www.ncbi.nlm.nih.gov/pubmed/1433011. Accessed July 9, 2018.

12. Bywaters EG. Still's disease in the adult. *Ann Rheum Dis*. 1971;30(2):121-133. http://www.ncbi.nlm.nih.gov/pubmed/5315135. Accessed July 9, 2018.

13. Uson J, Peña JM, del Arco A, Barbado FJ, Vazquez JJ. Still's disease in a 72-year-old man. *J Rheumatol*. 1993;20(9):1608-1609. http://www.ncbi.nlm.nih.gov/pubmed/8164226. Accessed July 9, 2018.

14. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol*. 1992;19(3):424-430. http://www.ncbi.nlm.nih.gov/pubmed/1578458. Accessed July 9, 2018.

15. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs*. 2008;68(3):319-337. http://www.ncbi.nlm.nih.gov/pubmed/18257609. Accessed July 9, 2018.

16. Fautrel B. Adult-onset Still disease. *Best Pract Res Clin Rheumatol*. 2008;22(5):773-792. doi:10.1016/j.berh.2008.08.006

17. Bharucha KN, Brunner HI, Calvo Penadés I, et al. Growth During Tocilizumab Therapy for Polyarticular-course Juvenile Idiopathic Arthritis: 2-year Data from a Phase III Clinical Trial. *J Rheumatol*. July 2018:jrheum.170326. doi:10.3899/jrheum.170326

18. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. *Arthritis Rheum*. 2010;62(8):2530-2535. doi:10.1002/art.27532

19. Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)*. 1991;70(2):118-136. http://www.ncbi.nlm.nih.gov/pubmed/2005777. Accessed July 9, 2018.

20. Nordström D, Knight A, Luukkainen R, et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. *J Rheumatol*. 2012;39(10):2008-2011. doi:10.3899/jrheum.111549

21. Narváez Garcia FJ, Pascual M, López de Recalde M, et al. Adult-onset Still's disease with

atypical cutaneous manifestations. *Medicine (Baltimore)*. 2017;96(11):e6318. doi:10.1097/MD.0000000000006318

22. Jara Calabuig I, Sánchez Soriano RM, Marco Domingo TF, Pérez Ortiz C, Chamorro Fernández AJ, Chamorro Fernández CI. Recurrent Pericarditis as the Presenting Form of Adult Still's Disease. *Rev Española Cardiol (English Ed*. 2017;70(3):208-209. doi:10.1016/j.rec.2016.06.016

23. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol*. 29(2):331-336. http://www.ncbi.nlm.nih.gov/pubmed/21385548. Accessed July 5, 2018.

24. Muñoz-Ortego J, Lara J, Navarro Ferrando JT. Mujer de 21 años con fiebre, artralgias y leucocitosis. *Med Clin (Barc)*. 2011;136(1):31-37. doi:10.1016/j.medcli.2010.07.003

25. Terán Á, Casafont F, Fábrega E, Martínez-Taboada VM, Rodríguez-Valverde V, Pons-Romero F. Enfermedad de Still del adulto con desarrollo de insuficiencia hepática que precisa trasplante hepático. *Gastroenterol Hepatol*. 2009;32(10):681-686. doi:10.1016/j.gastrohep.2009.06.009

26. Bosch-Barrera J, Montero A, López-Picazo JM, et al. Adult onset Still's disease after first cycle of pemetrexed and gemcitabine for non-small cell lung cancer. *Lung Cancer*. 2009;64(1):124-126. doi:10.1016/j.lungcan.2008.09.013

27. Riera Alonso E, Olivé Marqués A, Sallés Lizarzaburu M, Holgado Pérez S, García Casares E, Tena Marsà X. [Adult onset Still's disease: review of 26 cases]. *Med Clin (Barc)*. 2007;129(7):258-261. http://www.ncbi.nlm.nih.gov/pubmed/17683708. Accessed July 5, 2018.

28. Fernández-Guarino M, González C, Bardal Ruiz A, Calvo Pulido M, Harto Castaño A, Jaén Olasolo P. [Adult Still's disease with atypical skin manifestations]. *Actas Dermosifiliogr*. 2006;97(9):591-593. http://www.ncbi.nlm.nih.gov/pubmed/17173765. Accessed July 5, 2018.

29. Montoro J, Freixenet N, Lozano A, Bertomeu F. An unusual adverse drug reaction? *Allergol Immunopathol (Madr)*. 33(4):235-237. http://www.ncbi.nlm.nih.gov/pubmed/16045865. Accessed July 5, 2018.

30. Perez C, Artola V. Adult Still's Disease Associated with Mycoplasma pneumoniae Infection. *Clin Infect Dis*. 2001;32(6):e105-e106. doi:10.1086/319342

31. Garciá-Porrúa C, González-Gay MA, Crespo F, González-Juanatey C. Adult onset Still's

disease in Catalonia, Spain. *J Rheumatol*. 2000;27(1):280-281. http://www.ncbi.nlm.nih.gov/pubmed/10648058. Accessed July 5, 2018.

32. Rivera F, Gil CM, Gil MT, Batlle-Gualda E, Trigueros M, Olivares J. Vascular renal AA amyloidosis in adult Still's disease. *Nephrol Dial Transplant*. 1997;12(8):1714-1716. http://www.ncbi.nlm.nih.gov/pubmed/9269657. Accessed July 5, 2018.

33. Portolés J, de Tomás E, Espinosa A, Gallego E, Nieva GS, Blanco J. Thrombotic thrombocytopenic purpura and acute renal failure in adult Still's disease. *Nephrol Dial Transplant*. 1997;12(7):1471-1473. http://www.ncbi.nlm.nih.gov/pubmed/9249789. Accessed July 5, 2018.

34. Morrondo CD, Zarza LP, Gil JG, Pinto Tasende JA, Diez PD, López JMB. Benefit of Tocilizumab Therapy for Adult-Onset Still Disease Complicated With Acute Respiratory Distress Syndrome. *JCR J Clin Rheumatol*. 2016;22(5):291-293. doi:10.1097/RHU.0000000000000374

Table 1. Clinical and epidemiological characteristics of the 12 patients.

ANA: antinuclear antibodies AST: aspartate amino-transferase. ALT: alanine amino-transferase. GGT: gamma glutamyl-transferase. AP: alkaline phosphatase. RF: rheumatoid factor. NSAIDS: nonsteroidal anti-inflammatory drugs

Vol. 4, No. 03; 2020

ISSN: 2581-3366

	Total n (%)
Age	39,3 (range 21-60)
Female	7 (58.3)
Risk factor	0 (0)
Fever	12 (100)
Arthralgia or arthritis	10 (83.3)
Rash	11 (91.6)
Lymphadenopathy	2 (1,7)
Esplenomegaly	1 (0,8)
Hepatomegaly	1 (0,8)
Hyperferritinemia	12 (100)
Negative ANA/FR	12 (100)
Leukocytes > 10000/µL	11 (91.7)
Leukocytes < 5000/µL	0 (0)
Cytolysis (AST/ALT > 45 IU/L)	7 (58.3)
Cholestasis (GGT > 55 IU/L or AP > 150 IU/L)	9 (75.0)
Complications	0 (0)
Death	0 (0)
Evolution	
Monocyclic	6 (50.3)
Polycyclic	5 (41.7)
Chronic course	1 (8.4)
Treatment	
NSAIDS	4 (3.3)
Corticosteroids	10 (83,3)
Other immunosuppressive treatment	2 (1.7)

Table 2. Main data obteined from the studies included in the systematic review

STUDY Location	Date	N	Clinical presentation	Mean Age	Sex	Epidemiology	Risk factor	Laboratory findings	Evolution	Complications	Treatment
Francisco Javier Narváez Garcia et al[21]. Barcelona	January 1985 - December 2015	3	Nonclassical skin rash	45 (range 29-54)	Female 2 Male 1	66,7% caucasian 33,3% hispanic	No	WBC (mean) 14.9 10^9/L Ferritin level (mean) 3.042 mg/L Liver dysfunction tests Negative RF/ANA	Chronic articular polycyclic systemic course (2 patients) Polycyclic systemic course (1 patient)	Hemophagocytic syndrome 1 patient	NSAIDs, antihistamines, corticosteroids, MTX and TCZ
Irina Jara Calabuig et al.[22] Alicante	April 2008	1	Pericarditis and fever	38	Male	ND	No	WBC 15.0 10^9/L Hyperferritinemia Liver dysfunction tests	Recurrent pericarditis	No	
E. Riera et al.[23] Barcelona	1984 - 2008	41	Mainly polyarthritis and fever	38.19 years (range 17–68)	Female 25 Male 16	ND	No	Liver dysfunction tests Hyperferritinemia	Monocyclic 44% Polycyclic 26% Chronic articular 30%	No	NSAIDs , high-dose corticosteroids, methotrexate. biological treatment with anti TNF-α anti-IL-1
Juan Mun˜ oz-Ortego et al.[24] Barcelona	ND	1	Fever and the upper respiratory tract symptoms	21	Female	caucasian	No	Ferritin 43.600 ng/ml Liver dysfunction tests WBC 7.6 10^9/L	ND	ND	
Alvaro Teran et al.[25] Santander	January 2007	1	Fever and the upper respiratory tract symptoms	23	Male	caucasian	No	Ferritin 4.351 mg/dl Liver dysfunction tests	ND	liver failure requiring liver transplantation	Corticosteroids, anti-IL-1
Joaquim Bosch-Barrera et al.[26] Pamplona	ND	1	Nonpruritic generalized maculopapular evanescent rash and fever after treatment with pemetrexed treatment for lung cancer (day+6)	62	Male	ND	Treatment with permetrexed	Ferritin level 8.250 ng/mL	ND	ND	Corticosteroids
Riera Alonso et al.[27] Barcelona	1984-2004	26	fever (100%) arthritis (81%) rash (92%) sore throat (92%) lymphadenopathy (42%)	40 (17-68)	Male 8 Female 18	Caucasian 23 Hispanic 3	No	Liver dysfunction tests Leukocytosis Hyperferritinemia	Monocyclic course 54% Polycyclic 46%	ND	NSAIDs, corticosteroids, MTX
Fernández-Guarino et al.[28] Madrid	ND	1	Rash, arthralgias and fever	29	Female	ND	No	WBC 15.3 10^9/L	Monocyclic	No	NSAIDs
Montoro et al.[29] Villareal	ND	1	Maculopapular Exantema, fever, lymphadenopathy and odynophagia	18	Male	ND	Treatment with minocycline	WBC 15.1 10^9/L	ND	ND	NSAIDs, corticosteroids

Perez et al.[30] Pamplona	ND	1	Cough, sore throat, fever, headache, arthralgias, myalgia, and non-pruritic ras during *Mycoplasma pneumoniae* infection	17	Male	ND	*Mycoplasma pneumoniae* infection	Liver dysfunction tests WBC 22.33 109/L	Monocyclic	No	Erythromycin, NSAIDs, corticosteroids
Uson et al.[5] Madrid	September 1990	1	Fever of unknown origin	72	Male	ND	No	WBC 21.32 109/L Ferritin level 9.282 ng/mL	Monocyclic	No	NSAIDs, corticosteroids
Garcia Porrúa *et al.*[31] Catalonia	April 1984 – December 1998	16	ND	40.38 (SD 17.74)	Female 12 Male 4	ND	No	ND	Asymptomatic without treatment 7 Monocyclic 6 Polyciclic 1	No	NSAIDs, corticosteroids, MTX
Rivera et al.[32] Alicante	ND	1	Fever, transient maculopapular rash, lymphadenopathy, splenomegaly, and symmetrical polyarthritis	42	Male	ND	No	Normal	ND	Vascular renal AA amyloidosis	ND
Portoles et al.[33] Albacete	ND	1	Fever, evanescent rash, arthralgias, myalgias	31	Male	ND	No	WBC 16.6 109/L Liver dysfunction tests Ferritin 7.458 ng/mL	Monocyclic	Thrombotic thrombocytopenic purpura	Plasmapheresis, fresh frozen plasma infusions, corticosteroids and hemodialysis
Morrondo et al.[34] León	August 2004	1	Fever, sore throat, cutaneous rash, arthritis, bilateral pleural effusion, splenomegaly, pericardial effusion, and lymphadenopathy	22	Male	ND	No	Liver dysfunction, Leukocytosis Hyperferritinemia	Polyciclic	Acute Respiratory Distress Syndrome	Corticosteroids, anti TNF-α, TCZ

NSAIDs = nonsteroidal anti-inflammatory drugs

MTX = methotrexate

TCZ: tocilizumab

WBC: white blood cells