Still's Disease – Unlikely Diagnosis on the Old Age

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Abstract

Adult Still's Disease is a rare systemic inflammatory disease. It is characteristically identified in the young adult, with few cases described in older patients. The aetiology and pathogenesis remain unknown. The absence of uniformly accepted diagnostic criteria may contribute to underdiagnosis.

We present a case of 74 year old patient with fever, polyarthralgia, odynophagia, salmon evanescent rash, elevated inflammatory parameters and serum ferritin. Excluded other diagnostics (infections, neoplasia and other immune diseases), the diagnosis of Adult Still's Disease was assumed. The clinical and analytical improvements with immunosuppressive therapy, and long follow-up without symptomatology, give strength to the diagnosis.

We present this case by the rarity of this pathology in this age and to emphasize the need to consider this entity whenever we are studying an fever of unknown origin with this clinical triad (daily spiking high fevers, evanescent rash, arthritis) and biologic triad (hyperferritinaemia, hyperleucocytosis with neutrophilia and abnormal liver function test).

Keywords: Adult-Onset Still's disease, fever of unknown origin, arthralgia, ferritin.

Introduction

Adult Still Disease (ASD) is a systemic inflammatory disease characterized by the clinical triad - daily febrile peaks, arthritis, and salmon colour evanescent rash; and by the biological triad - leukocytosis greater than 10 000 leukocytes with a predominance of neutrophils, hyperferritinemia (with decreased glycosylated ferritin) and changes in liver function tests[1]. Less common manifestations include odynophagia, serositis, myalgias, lymphadenopathy and hepatosplenomegaly.

Its etiology and pathogenesis remain unknown, but some factors have been described: genetic predisposition (association with HLA-B17, HLA-B18, HLA-B35 and HLA-DR2), innate immune system activation (elevated levels of IL1, IL6, IL18, TNFα and interferon γ) and environmental factors[2].

A variety of infectious triggers have been suggested, including viral agents (Rubella, Measles, Echovirus 7, Epstein-barr, Cytomegalovirus, Parvovirus B19, Adenovirus, Herpesvirus 6, Influenza, Parainfluenza, Hepatitis B virus and Hepatitis C virus) and intracellular bacteria (*Chlamydia Pneumoniae, Mycoplasma Pneumoniae, Borrelia burgdorferri, Brucella abortus, Yersinia enteroclitica*)[3-5].It has an equal distribution between genders, with a bimodal age peak: 16 to 25 years and 35 to 45 years. There are few reported cases in patients over 70 years old [6-7].

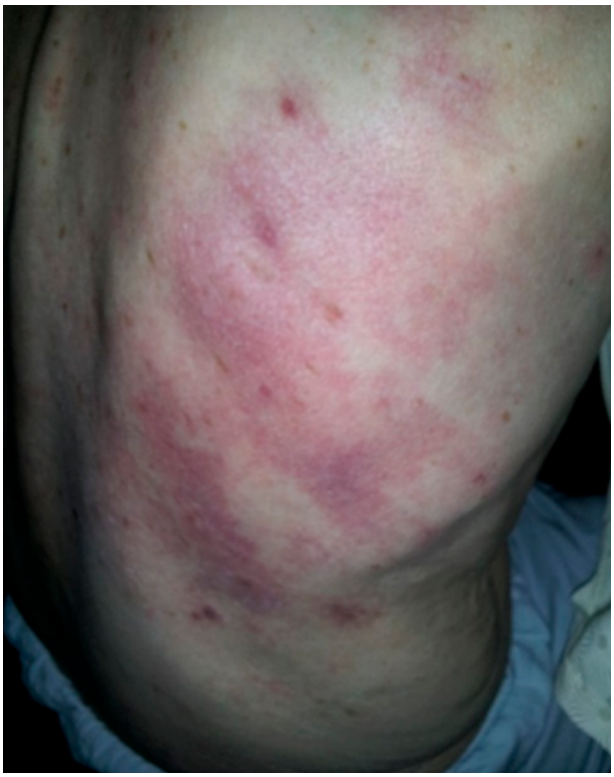
Clinical case

We report a case of 74 years old male, caucasoid. His medical problems included hypertension, benign prostatic hypertrophy, varicose ulcers of the lower limbs, and joint pain. He was treated with antihypertensive and occasionally anti-inflammatory drugs.

He was admitted for daily febrile peaks (39ºC), predominantly evening, with 3 weeks duration, odynophagia, myalgias, asthenia and weight loss (approximately 5 kilograms). He also had additive symmetric inflammatory polyarthralgia, with chronic and persistent evolution, involving dorsolumbar, large and small joints (shoulders, wrists, interphalangeal joints).

Patient examination revealed a decrease pulmonary sounds at left pulmonary base, with increase vocal vibrations in the same location; left axillary adenopathy with 1.5 centimeters of greater diameter (elastic consistency, not adhering to deep planes, painless). He presented an evanescent salmon colour macular rash affecting the trunk and limbs, slightly pruritic, with Koebner phenomenon (predominant involvement of the areas of greatest friction) that was intensified during the fever peaks and during the night (figure 1). He had no signs of arthritis or articular deformities on the skeletal muscle examination. There were no changes on the oropharynx observation.

Fig. 1. Salmon colour evanescent macular rash more evident in the posterior trunk (zone of greater friction)



The complementary study showed leukocytosis (34.1 x 10^3 / µL) with a predominance of polymorphonuclear cells (> 90%), elevated C-reactive protein (188 mg / L) and sedimentation rate (76 mm / 1h),

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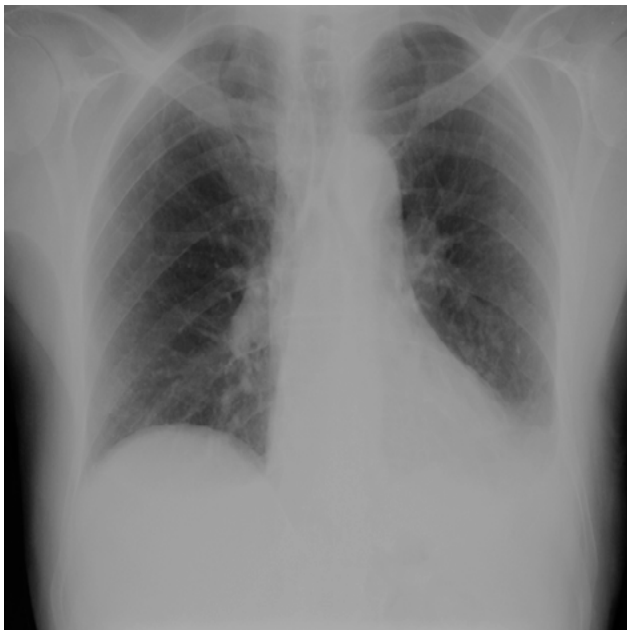
Como citar este artículo: Campos Nogueira A, Manuel Fernandes T, Costa A Still's Disease – Unlikely Diagnosis on the Old Age. *Galicia Clin 2019; 80 (3): 53-55*

Recibido: 19/10/2018; Aceptado: 13/11/2018 // http://doi.org/10.22546/53/1806

Fig. 2. Chest radiograph showing left pleural effusion



higher serum ferritin (> 4000 µg / L - five times higher than normal), increase in transaminases (146 U / L, 144 U / L), lactate dehydrogenase (437 U / L) and alkaline phosphatase (219 U / L); chest X-ray presented a small left pleural effusion (Figure 2).

Considering patient's age, a diagnostic investigation was initiated prioritizing the search for infectious and neoplastic diseases.

Infectious disease were excluded: negative blood cultures (aerobic bacteria, anaerobic bacteria and fungi), negative microbiological of pleural fluid and bronchoalveolar lavage (aerobic bacteria, anaerobic bacteria and mycobacteria), negative viral serologies and bacterial serologies (Human immunodeficiency virus 1 and 2, Hepatitis B, Hepatitis C, Syphilis, Epstein Barr virus, Cytomegalovirus, Parvovirus B19, *Borrelia burgdorferi* and *Coxiella burnetii*), Widal test, Weil-Felix, Wright and Paul-Bunnel negative, transthoracic and transoesophageal echocardiography without images suggestive of endocarditic vegetations.

Neoplastic disease was excluded: serum protein electrophoresis without peaks suggestive of monoclonality, peripheral blood immunophenotyping without suggestive alterations of lymphoproliferative disease, normal PSA, thoracoabdominal-pelvic computed tomography revealed the left pleural effusion, thyroid ultrasonography, endoscopic studies of digestive tract and bronchofibroscopy without changes, cytology of the pleural fluid and bronchoalveolar lavage negative for malignant cells, normal thyroid hormones.

Other rheumatologic diseases were excluded: increased immunoglobulin G, anti-nuclear antibodies (ANA's) 1:80, normal C3 and C4, negative ENA's, ANCA's, Anti-LKM, rheumatoid factor, anti-citrulline and HLA B27.

Despite patient advanced age, this clinical picture was very suggestive, and the hypothesis of ASD was considered (more than 5 criteria of Yamaguchi - 4 major criteria and 3 minor criteria; 4 major Fautrel criteria - figure 3).

We assumed the diagnosis of ASD and started immunosuppressive therapy with prednisolone, with rapid clinical and analytical response (normalization body temperature, improvement arthralgias and general symptoms, disappearance trunk rash and pleural effusion, normalization of leukocyte count, transaminases, ferritin and sedimentation rate) (figure 4).

Discussion

The absence of uniformly accepted diagnostic criteria contributes to the fact that it may be underdiagnosed. This pathology probably represents 5-10% of patients with fever of unknown origin [8].

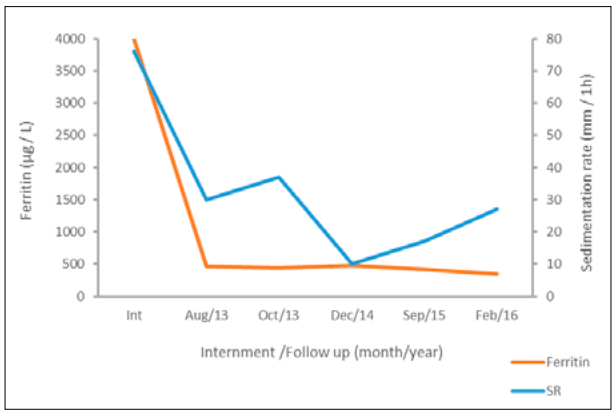
Since the main manifestations of ASD are not specific and shared by numerous pathologies, it is an exclusion diagnosis [9].

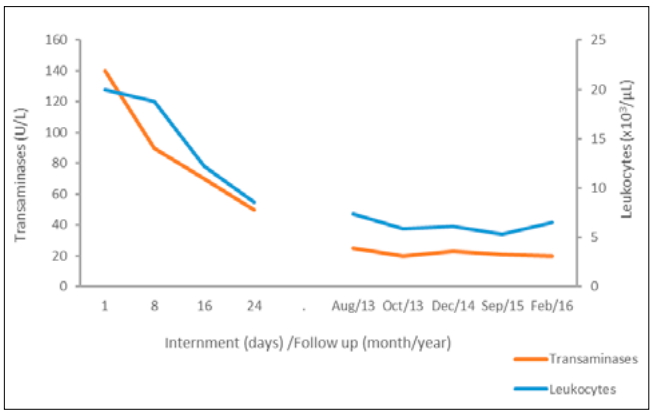
It is considered a diagnosis of the younger populations, and there are very few cases described in patients over 70 years old [10,11] Unless there is great suspicion, the diagnosis of ASD in older people is even more difficult. In older patients presenting with fever of unknown origin, the appearance of rash should make

Fig. 3. Criteria for diagnosis of ASD

	Yamaguchi Criteria (5 criteria - minimum of 2 major criteria and no exclusion criteria)	**Fautrel Criteria** (≥ 4 major criteria or 3 major criteria more 2 minor criteria)
Major Criteria	› Fever (≥ 39ºC), intermittent, lasting more than one week › Arthralgias or arthritis with > 2 weeks duration › Typical Rash › Leucocytosis (≥ 10000/mm^3), including ≥ 80% neutrophils.	› Febrile peaks ≥ 39ºC › Arthralgias › Transient erythematous Rash › Odynophagia › Polymorphonuclear ≥ 80% › Glycosylated Ferritin ≤20%
Minor Criteria	› Odynophagia › Recent lymphadenopathy › Hepatomegaly or splenomegaly › Changes in liver tests (aminotransferases and lactate dehydrogenase) › Negative Rheumatoid factor and ANA´s	› Maculopapular Rash › Leucocytosis ≥ 10000/mm^3
Exclusion Criteria	› Infections › Neoplasms › Others rheumatic diseases	

Fig. 4. Analytical evolution after immunosuppression initiation.





suspect ASD[12]. In this patient, the rash was a valuable diagnostic signal. After excluding other diseases (immunological, infectious, lymphoproliferative and neoplastic), reviewing the Yamaguchi and Fautrel diagnostic criteria (sensitivity and specificity above 92%), the diagnosis of ASD was assumed.

The prognosis of ASD depends on the clinical course of the disease: the disease can be self-limited / monophasic (with good prognosis), intermittent / polycyclic or chronic (with worse prognosis).

Due to rarity of this entity and the lack of clinical trials, there are no guidelines for the treatment of ASD. Available treatment modalities include non-steroids anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying drugs (DMDs) and biological agents. Approximately one quarter of patients respond to NSAIDs, but most patients require immunosuppression with systemic corticosteroids, DMDs, such as methotrexate, and biological agents [10,13]. In patients with resistance or dependence on corticosteroids, the choice is methotrexate.

Although there are few reported cases of methotrexate use in older patients, the treatment of these patients may be useful in disease control, avoiding relapses, and a corticosteroid sparing agent, minimizing it's adverse effects[11].

This patient appears to have a disease with a good prognosis (monophasic form), and presented clinical and analytical improvement with immunosuppressive therapy, remaining without symptoms with minimal corticosteroid doses (≤ 7,5 mg) (follow-up more than 5 years).

This case reflects a rare entity in this age, but should not be overlooked in older patients with fever of unknown origin.

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