Adult Still's disease: A review of the literature with reference to two clinical cases

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Abstract

Adult Still's disease is a systemic illness of unknown aetiology. The clinical features are high fever, arthralgia and an evanescent rash. Since there are no clinical, laboratorial or histological pathognomonic markers, the diagnosis of Adult Still's disease is made by exclusion.

The authors describe two clinical cases, diagnosed using Reginato and Medsenger criteria, in two young people, one a man of 18 years and the other a woman of 28 years, both admitted for prolonged fever. A review of the literature is made, highlighting an uncommon disease with a worldwide reported number of cases in the order of several hundred.

Key words: Adult Still's disease, fever or unknown origin, evanescent rash.

Introduction

Described for the first time in 1971 by Bywaters,[1] Adult Still's Disease (ASD) is increasingly becoming a cause of fever of unknown origin.[2,3,4]

In adults, ADS corresponds to juvenile chronic arthritis.[5] In a case series studied by Cush,[6] 19% of the patients with ADS had suffered a similar episode in their childhood.

For a number of authors, this entity is characterized by the classical symptoms of high, prolonged fever of around 39ºC-40ºC, polyarthralgias and exanthema. It is frequently accompanied by odynophagia with sudden onset, and symptoms of hepatosplenomegaly and polyerositis.[4,5,6,8,9]

According to some case reports,[1,4,6,11,12] it is a disease affecting young adults,[9,10] predominantly females. In 78% of cases,[11] onset occurs at between 16-35 years.[1,9,7,13] Nevertheless, it has been described in older patients,[2,11,14,15] even patients older than 70 years.[7,16]

The first symptom is usually fever,[1] reported in around 96% of cases,[5] which is higher than 40ºC in almost all patients.[7,13,16] Usually the fever is intermittent, with one or two daily peaks, predominantly in the evening,[5,7,9,10,19] and followed by shivering; it is always prolonged (lasting more than two weeks), accompanied by weight loss, with or without other changes in overall health.[19] It is usually associated with sinus tachycardia,[9,19] even in periods of apyrexia.[7]

Joint manifestations include arthralgias (in the majority of cases)[7,9,17] or arthritis (half of cases). Acute or sub-acute migratory inflammatory polyarthritis is characteristic,[7,18] which soon becomes symmetrical,[6,7,9,19] both in the small and large joints;[7,19] In the cases studied by Cush[6], the most commonly affected joints are, in order of frequency, the knees and wrists, followed by the interphalangeal joints, ankles, and elbows. According to some authors, involvement of the intercarpal joints[1,11,20] and carpometacarpal joints[11,18] is also characteristic. For some authors, radiological changes with diagnostic value include carpitis involving the long bones, possibly leading to carpal and carpometacarpal ankylosis.[4,5,6,8,15,21,22] This polyarthritis can disappear when the ADS is "cured", but can also become chronic and even lead to osteoarticular destruction. If synovitis is present, the synovial fluid presents an inflammatory reaction with a prevalence of proteins[11] and polynuclear cells.[19]

Myalgias are frequently associated with arthralgias. They usually involve the neck, trunk, back, and muscles of the limbs, and are aggravated in the periods of hyperthermia;[2,5,7,10,13,19] sometimes, their intensity mimics a condition of myositis, but with normal or slightly elevated level of enzymes.[7] Nevertheless,

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cases of ADS associated with polymyositis have also been described.[23]

Another typical manifestation is a morbilliform[13] or maculopapular[1,9,13,20] skin rash with small pink[9,19] or salmon[5,10,21,24] spots, of approximately 3mm diameter and irregular contours; it rarely takes the form of purpura[7]. It tends to vanish, and is [9,19] slightly itchy;[5,9,10,18] it mostly affects the trunk of the body and the limbs roots[18] and less frequently, the palms and soles.[10] The face is rarely affected. The rash is more intense at the end of the day, accompanied by fever peaks,[5,9,19,20] and disappearing with apyrexia.[7,13] However, some authors, have reported its occurrence even in the absence of fever.[3] In more than half the cases, it occurs early in the development of the disease, and may reappear in the acute phases.[10] Although it is considered by some authors as an important diagnostic criteria, it is not detected in around 15% of cases;[16] on the other hand, its presence strongly suggests the diagnosis.[18]

Skin biopsy is unspecific,[19] revealing signs of perivascular inflammation with edema and lymphocyte and histiocyte infiltration.[7]

Odynophagia occurs is around 60% of cases,[2,7,9,10] and may be the first manifestation of the disease that is not indicative of infection;[4,11] it usually takes the form of a non-exudative pharyngitis.[13]

The incidence of hepatomegaly and splenomegaly is between 30% and 59%.[7,9,10,11,13,19] Adenopathies are also common, and the cervical region is the region most commonly involved.[25] Ganglion hypertrophy can mimic lymphoma[7] and an association of immunoblastic lymphoma with ADS has recently been described.[26]

Pleural and pericardial effusion are not uncommon,[7,20] both in the form of exudates and transudate, and, although the myocardium and endocardium may be involved,[7,27] acute pericarditis is most frequent,[1,7,10,19,22] with a good response to corticosteroids. Although rare, myocarditis, which was documented for the first time by Bank et al. in 1985,[27] is considered a possible manifestation of ADS.

Although abdominal pain, nausea and vomiting[7,18] may occur, peritoneal inflammation is rare.[13,19]

The nervous system may be affected,[10,11] with signs of mental confusion, peripheral facial palsy,[7,13,28] epilepsis,[7,28] meningoencephalitis[7,13,19,25] and also focal lesions.[29] Involvement of the central and peripheral nervous system is rare.[28]

Kidney lesions occur rarely, but hematuria,[19,25] transient proteinuria,[6,25] glomerulonephritis and interstitial nephritis[7,19] have been described.

Pulmonary involvement takes the form of transient pulmonary infiltrates[7,11,13,22] or pleuritis, and respiratory failure has been reported in rare cases.[22,30] Chest X-ray may reveal thickening or pleural effusion, or even atectasis.[22]

Eye manifestations include conjunctivitis and visible exudates in the images of the ocular fundus.[19]

All this systemic involvement can be observed in ASD, and complications may occur more rarely, such as amyloidosis[4,6,7,11,25,31,23] and DIC[7,10,11,14,19,25]. Other diseases associated with ASD have also been reported, such as sarcoidosis,[3] Sjogren's Syndrome,[24,25] Takayasu's arthritis,[7] and even fulminant acute hepatitis;[5,18,19] viral diseases have also been reported, such as measles, parainfluenzae, echovirus, VHB,[4] EBV, CMV and parvovirus B19; these agents are attributed with having a possible trigger role of the disease in individuals who are genetically predisposed.[12,28] Wouters describes three cases of ASD in which the possible trigger viruses were the agent causing measles in two cases and echovirus 7 in another case.[33]

The diagnosis of ASD is by exclusion, without any specific laboratorial or imaging data for the disease.[10] The diagnostic criteria vary from author, although association of several semiological data is common; therefore, according to Reginato, a main criterion must exist: fever, leukocytosis, exanthema or arthritis, and one or more less significant criteria: polyserositis, odynophagia and involvement of the RES.[7,9,10] For Cush, Medsger and Christy, ASD is characterized by high fever (>39ºC), accompanied by arthralgias, arthritis, vanishing rash, polyserositis, hepatosplenomegaly and leukocytosis; the rheumatoid factor and antinuclear antibodies (ANA) are negative.[6]

Therefore, although the association of hectic fever, signs of joint inflammation, morbilliform eruption and hyperleukocytosis (>15000) in negative cultures strongly suggest a diagnosis of ASD;[19] the absence of these symptoms makes the diagnosis more difficult. Clinical improvement is also important for the diagnosis after therapeutic attempts with corticosteroids.[13]

The differential diagnosis with other diseases should be performed, particularly infectious, neoplastic, granulomatous and connective tissue diseases.[13,17,18] It is worth noting that in the early phases, the disease may take atypical forms.[10]

The laboratory data characteristic of this diagnosis include the most consistent changes: leukocytosis above 15000[7,9,10,13,19] or even above 18000, neutrophilia in 60% of the cases,[11] normochromic and normocytic anemia, usually moderate,[5,9,10,19] and thrombocytosis.[10,11,19] The leukocytosis sometimes can persist for a long time, even with treatment.[19] Even so, some cases have been reported of ASD with normal or decreased levels of leukocytes.[10,34]

ESR is increased[5,9] and in two thirds of cases it surpasses 100 mm in the 1st hour;[13,19] CRP is also high;[19] in serum protein electrophoresis, an increase in alpha-2 and hypergammaglobulinaemia is observed,[4,7,10,11,18,19,25] with a particular increase in IgG[9]. Complement activity is usually normal or increased.[4,11,25]

Hypoalbuminaemia (lower than 3.0 gr/dL) is frequent[7,10,11,13,19] and a moderate increase in transaminase and alkaline phosphatase levels[9,10,11,13,19,25] is observed, though not beyond twice the normal level.

The rheumatoid factor and ANA are negative or low,[5,9,10,11,19] although the anti-dsDNA antibody is always negative in ASD.[9]

As in the general population, a slight increase in ASTO maybe observed, which can contribute to a delayed diagnosis.[19]

There is an increase in plasma ferritin,[8,11,17,21,25,35,36] which is not seen in other rheumatic diseases,[21,25,36] with abnormally high values (>4000 ng/mL), suggesting that this value could be used as a possible marker, whether for diagnosis[2,7,8,9,11,19,25] or for therapeutic control.[2,7,8,9,11,19,25] The reason for the increase in protein in this disease is not known, but it is thought that hepatic cytolysis, frequently in ASD, may accentuate the increase in serum ferritin.[37] An increase in haptoglobin is also seen.[13] HLA typing did not show any consistent association.[4,11]

Regarding the histological appearance, the bone marrow revealed a non-specific inflammatory infiltrate[5,10,20] and in the organs of the RES, there is almost always an inflammatory hyperplasia;[2,9,19,26] a hyperreactive plasmacytosis can also be found.[20] A case of diffuse cutaneous mucinosis, not reported earlier, was recently described.[18]

In published studies, and when hepatic biopsy is performed, this revealed infiltrates of the portal tracts, consisting mainly of mononuclear cells, and sometimes associated with minimum hepatitis, with necrosis or lesions of steatosis, and portal fibrosis of small intensity.[5] Troita et al. (1993) also describe histological characteristics that mimic a lymphoma.[26]

The initial choice of treatment for ASD consists of salicylates at doses of 100 mg/Kg/dia,[2,7,13,19] AINE[6] being one of the alternatives, such as naproxene[2] and indomethacin for example, the latter administered at dose of 50 mg 4 id.[13] Corticoids, used as second line therapy, should be reserved for cases where there is polyserositis, myocarditis or involvement of the central nervous system, or when the abovementioned drugs cannot control the systemic activity or the joint symptoms of the disease.[2,9,19] Prednisolone, given at a dose of 1 mg/Kg/day, should be given for a long period[19] carefully and gradually adjusting the dose needed to control the symptoms.[9] In more severe cases, there may be a need to associate other drugs, namely, immunosuppressants,[31] such as cyclophosphamide, or methotrexate, in low doses, which can also be administered alone or as an alternative,[9,10] but their efficacy is still not duly established. Other medications used, without much success, are gold salts,[9,10] and d-penicillamine,[9,10,19] salazopyrine[9] and synthetic antimalarials (e.g.: hydroxychloroquine),[9,10,19] the latter are rarely used due to the high rate of recurrence.[11]

The therapeutic complications deserve mention, as these can put the patient's life at risk. Cataracts, kidney stones, osteoporosis, osteoporosis, bone necrosis, and opportunistic infections (such as tuberculosis) have been described as possible complications associated with the treatment.[6]

Despite initially being recognized as a disease with good prognosis, this is generally reserved, and there are cases of rapid remission and others with chronic evolution and exacerbations,[9] even after treatment;[7] there is significant morbidity associated with this disease.[4,17] Exacerbations are common, even several years after the onset of the disease; recurrences vary in frequency and severity, but the symptoms are generally milder than at the start of the disease.[4]

ASD has two clinical forms: systemic and joint, generally with distinct evolution in each case: the predominantly systemic forms generally respond to high doses of salicylates or corticotherapy, and have a benign evolution; the cases affecting mainly the joints can evolve rapidly, progressing to severe injuries[10] that can destroy or deform the bones.[5,7,10,19]

Even with steroids, the recurrence of systemic symptoms is common, occurring, in nearly half of cases, when the dose is suspended or reduced.[5]

Although some authors report that ASD is only rarely the direct cause of death,[11] the literature reports that a worse prognosis may be associated with the complications that can arise, such as myocarditis and pericarditis with cardiac tamponade,[6] respiratory failure, CID[20], etc. The absence of characteristic rash at the time of presentation is associated with earlier remission.[20]

Regarding the effects during pregnancy, the literature reports that it does not affect the ASD, and neither does the ASD affect the pregnancy or fetal growth.[38]

Clinical cases

Case 1

JJPM, 18 years, male, White, a student, born and residing in Figueira da Foz, and admitted to the infectious diseases services for study of fever with 15 days of evolution, accompanied by sweating, particularly around the knees. He had had some complementary exams through his attending physician: hemogram revealing leucocytosis, R. Widal, R. Wright, R. Paul-Bunnel negative; abdominal ultrasound normal. He was medicated with erythromycin and antipyretic, without improvement.

Epidemiological history without relevance. Personal and family history without relevance.

Initial investigation revealed a patient with reasonable general state slightly pale skin and mucosa, temp-39ºC; he had a painful cervical enlarged lymph node and a painless hepatomegaly of 1 cm. Analytical results: Hb 11.6 gr/dL; Ht 34.5%, erythrocytes 4,200,000 MCV 86.9 fL; leukocytes 30500(N 74.5%); platelets 454000; biochemical parameters normal, except for albumin (29 gr/L) with total proteins of 81 gr/L.

Study of the fever was initiated, with the following complementary exams:

ECG and Chest X-ray normal; blood cultures[10] negative; tuberculin at 3U – negative; ESR 105mm in the 1st hour, CRP 15 mg/dL; immunity for toxoplasmosis, rubella, CMV and EBV, HIV serologies, syphilis, brucellosis (including IFA), typhoid fever - negative; urine II without alterations; GFR, ASTO, LE cells, Waaler-Rose, normal; complement – normal; bronchofibrescope normal with microbiology of the bronchial aspirate negative in culture for BK, commonplace germs and fungi; proteinogram with alfa-2 peak; medullogram revealing the presence of three normal cell strains with megaloblastic alterations and myeloculture negative (including BK).

The patient continued to have fever, therefore ibuprofen was commenced, at a dose of 400 mg 3id on day 6, without improvement; he continued with hyperthermia and marked asthenia, without any other complaints. Ophthalmoscopy was normal.

The analytical control on day 8 showed a hemogram with the following values: Hb 10.8 mg/dL; Htc- 32.1%; leukocytes 23400 (N 82.6%); platelets 521000; ESR 106 mm in the 1st hour.

At this stage, oral iron and doxycycline were prescribed, the latter at a dose of 200 mg/day, without effect, and the patient continued to have fever and myalgias, particularly in the lower limbs. Other complementary exams were performed: BK tests in the urine (3 samples) – negative; serologies for Leptospira, Borrelia, Coxiella, Coxsackie virus (2 samples) – negative; serologies for tuberculosis and leishmania – negative; antinuclear and antimitochondrial Antibodies, anti-smooth muscle antibodies - negative; X-ray of the sinuses of the face - normal; SACE – normal; factor VIII – normal; T3, T4, TSH – normal; CT of the chest and abdomen "beyond a slight increase in liver volume, no alterations worth recorded were noting, such as the presence of enlarged lymph nodes of the mediastinum or abdomen, or the presence of effusion".

On day 38, besides the fever, symptoms of polyarthralgias without arthritis began, and on day 42, the patient reported pain in the small joints and the appearance of a morbilliform rash, mainly on the trunk, which disappeared on the following day. At this stage, the hypothesis of ASD was considered, and therapy started with indomethacin (day 44) at a dose of 100 mg 12/12h; the fever disappeared on the 4th day after starting this drug.

Analytically, he presented an ESR of 124 mm in the 1st hour; leuk 24500(N 83.9%); Htc 28; MCV 78 fL; platelets 612000.

Due to an episode of melaena, EDA was performed, revealing an erosive duodenitis (or bulbitis) and hemorrhagic suffusions of the submucosa in the body of the stomach.

X-ray of the skeleton was performed, which did not show any alterations, and bone scintigraphy of the joint, revealing non-specific alterations.

The study of lymphocyte populations revealed a normal immunological phenotype.

The patient was discharged on day 51, medicated with indomethacin-100 mg 2 id, ranitidine, sucralfate and oral iron.

After 3 weeks, the patient was admitted again due to fever and worsening of the arthralgias, with persistence of the leukocytosis and identical values of Hb and platelet values; deflazacort was prescribed, at a dose of 80 mg/day, with a significant improvement in the complaints and disappearance of the fever.

The evolution was good, and at the end of one month of treatment, the patient was in good general health, having gained weight, definitively apyretic, and reported only slight arthralgias, particularly in the mornings, in the wrists and metacarpal joints. Objectively, physical examination was normal.

The analytical control showed a hemogram with Hb 12 mg/dL, leuk 20 400, platelets 487 000 and ESR 32mm in the 1st hour; determination of serum ferritin level, on day 24 of the treatment, was 118 ng/mL.

Taken together, the symptoms: febrile syndrome with myalgias, arthralgias, evanescent rash on the trunk, involvement of the lymph nodes with continued leukocytosis, anemia, thrombocytosis, increased ESR, and hypoalbuminaemia, led to a diagnosis of Adult Still's Disease.

Case 2

MLVF. 24 years, female, White, a housewife, born and residing in Torres Novas. She was admitted to the Medicine Service on 28th July 1995 with protracted febrile syndrome.

She reports that she became ill one month before admission, with uncharacteristic odynophagia, which was followed by the onset of fever; this was daily, particularly in the evenings, and high, reaching more than 40ºC and accompanied by chills and sweating. Concomitantly, she reports intense, generalized myalgias and symmetrical arthralgias of the scapulohumeral, coxofemoral, tibiotarsal, metacarpophalangeal and metatarsophalangeal joints. She also reported adynamia, anorexia and weight loss of 3 Kg in a period of four weeks. She consulted her family doctor, and was medicated with doxycycline. Due to worsening of the symptoms, she came to the emergency service of the C.H.C where she was admitted.

She denied having eaten fresh cheese or unpasteurised dairy products, blood transfusions, trips outside the Country, recent contact with animals, similar cases within the family unit or area of residence; she had no symptoms other than those reported. There was nothing of relevance in the personal and family history.

Wrist joint – signs of carpitis.

FIG. 1

On objective examination, she had high fever(41ºC), septic facies, rhythmic tachycardia (110 ppm), signs of inflammation of the wrist, metacarpophalangeal and tibiotarsal joints; there was a pinkish maculopapular rash, limited to the insides and fronts of the thighs, which appeared during periods of fever and disappeared in periods of apyrexia.

The first laboratory investigation revealed a normocytic and normochromic anemia with hemoglobin of 11,4 gr/dL, leukocytosis (21.500/mm3) with neutrophilia (89.1%) and thrombocytosis of 556.000/mm^3, ESR 115mm in the 1st hour and CRP 17.7mg/dL. The chest X-ray was normal. Oral erythromycin was commenced, at a dose of 500 mgr 6/6 hours. The fever persisted with the same characteristics: occurring daily, mainly in the evenings (*Fig. 1*), accompanied by the rash described above. The myalgias persisted, with signs of inflammation of the joints and major functional impotence, and permanent tachycardia. On day 5 of hospitalization, the patient had chest pain on the left side, with pleuritic characteristics, accompanied by non-productive cough and dyspnea. Clinical and radiological exams revealed bilateral pleural effusion and widening of the heart silhouette. To clarify the clinical situation, successive complementary diagnostic exams were performed: glycaemia, urea, creatinine hepatic, muscle enzymes and urine type II tests – without alterations.

Electro- and immunoelectrophoresis of the serum proteins (G/L): albumin 21.7, a_1 -5, a_2 -9,5, b-7,3, g

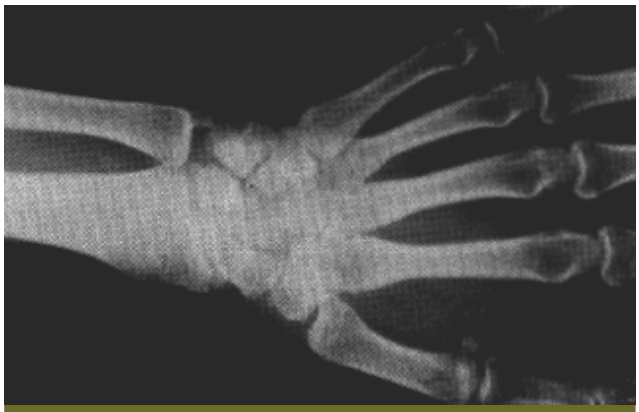
-12.3; IgA-2,4, IgM -2.3 and IgG-14.6.

Hemocultures and urocultures – negative; Mantoux test with 2U negative; serologies for toxoplasmosis, CMV, EBV, HSV1 and 2, rubella, HIV, VHB, VHC, Brucella, Salmonella, Coxiella, Borrelia, Legionella, Chlamydia, Mycoplasma, syphilis, Leptospirosis and tuberculosis – all negative. ASO – normal; rheumatoid and Waaler Rose factor – negative; ANA, particularly the antiDsDNA, ANCA, and circulating immune complexes – negative.

Serum complement fractions slightly low: C3 0.81, C4 0.075 and CH100 <20; abdominal ultrasound and CT – no enlarged organs or lymph nodes.

Chest X-ray, chest CT and echocardiogram revealed the existence of moderate pericardial effusion and bilateral pleural effusion. Cytobacteriological exam of the pleural liquid was suggestive of non-bacterial and non-neoplastic exudate. Bronchoalveolar washing did not show the presence of neoplastic cells, and transbronchial biopsy was normal; lung biopsy revealed "non-specific pleuritis"; in the bronchial aspirate, the cultures were negative for commonplace germs and KB.

When the hypothesis of ASD was made, the serum ferritin level was determined as 3970 ng/mL (normal value between 10-115 ng/mL). Therapy was commenced with indomethacin at a dose of 200 mg/day, without improvement. Due to the existence of symptoms of pleuropericardial serositis, the patient was put on corticoids (deflazacort) at a dose of 80 mg/day, in divided doses, with a significant improvement in the symptoms, particularly the fever, polyserositis, arthromyalgia and rash, as well as normalization of the laboratory alterations i.e. the leukocytes, hemoglobin, ESR and ferritin. The patient was discharged and referred for external consultation. The corticoids are gradually and cautiously being reduced, without recurrence of the disease; due to persistence of the chronic arthralgias, with edema and functional impotence of the metacarpal phalangeal and carpal joints, radiography was carried out, showing carpal ankylosis (*Fig.* 2), an alteration that is described in the literature as a common complication of ASD.



Wrist joint – signs of carpitis.

FIG. 2

Discussion

The first clinical case, besides present the major characteristics reported by Reginato, presented negative or normal results in all the microbiological, serological and imaging studies.

The differential diagnosis should be established with four groups of diseases: infectious, neoplastic, diseases of the connective tissue, and granulomatous diseases:

1) The fever, arthralgias and rash can be attributed to a viral disease, but the leukocytosis with high neutrophilia and ESR are not suggestive, besides which all the serologies carried out were negative.

Infectious endocarditis was ruled out, because despite the fever, rash and joint manifestations, there were no murmurs, the hemocultures were negative, and the echocardiogram was normal.

Tuberculosis, another cause of protracted febrile syndrome, was ruled out, because there were no chest lesions in the radiology, the Mantoux and serology tests were negative, and the tests for KB in the urine and bronchoalveolar washing were also negative.

It was also important to rule out a borreliosis; however, despite the absence of a history of tick bites, and the fact that the skin complaint was in the form of erythema migrans and the joints were only affected much later, this is usually mono- or oligoarticular; concomitantly, the serology was also negative.

Other systemic or localized infections were ruled out due to the negativity of the serologies, microbiological exams and normal results of the chest and abdominal CT.

2) Due to the clinical symptoms of fever, arthralgias, hepatomegaly, cervical adenopathy, anemia and leukocytosis, a hypothesis of hematological disease was initially proposed; however, the peripheral blood smear did not reveal malignant cells, and the

medullogram only showed alterations suggestive of anemia of chronic diseases. TC of the abdomen and chest did not show other enlarged lymph nodes, and cervical adenopathy disappeared after some time with anti-inflammatory therapy, therefore this hypothesis was ruled out, as were solid neoplasias, due to the negativity of the imaging and endoscopic exams and the tumor markers.

3) The existence of prolonged fever, joint and skin manifestations, hepatomegaly, anemia, leukocytosis and high ESR ruled out diseases of the connective tissue, namely, systemic lupus erythematous. Hypersensitivity vasculitis, polyarthritis nodosa, or Takayasu arthritis; however, age, male gender, the absence of cutaneous vasculitis, and the existence of renal or neurological complaints, corroborated by the absence of immunological markers or a decrease in serum complement, ruled out this hypothesis. Rheumatic fever, although it can occur with fever, rash and arthritis, presents cardiac involvement and evidence of preceding streptococcal infection, which was not the case in this patient.

4) The last group to consider is that of granulomatous diseases, namely, sarcoidosis which was excluded, as the chest X-ray and SACE were normal; factors against a diagnosis of Crohn's disease are the clinical symptoms and the normality of the radiological and endoscopic exams.

In view of the symptoms presented in the second clinical case, various diagnostic hypotheses were proposed, which were not confirmed by the complementary exams. Infectious diseases were ruled out due to the negativity of the microbiological and serological exams: neoplastic and granulomatous diseases were ruled out by the normality of the imaging and histological exams of the lung and pleura; among the rheumatic and immunological diseases, SLE, vasculites, classic rheumatoid arthritis and rheumatic fever were ruled out due to the non-existence of diagnostic criteria. The diagnosis was based on the following criteria: hepatic fever lasting more than two weeks and resistant to antibiotics, evanescent maculopapular eruption, arthritis, leukocytosis >12000/mm3 in at least two hemograms, and elevated serositis and ferritin, the later considered by some authors as a biological marker of the disease. Clinical, laboratory and analytical improvement after corticotherapy was another diagnostic data, as well as the existence of clinical and imaging signs of carpitis. ■

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