Adult Still's sisease

Raquel Nazareth, João Pacheco Pereira, Francisco da Silva, José Pimenta da Graça

Abstract

Adult Still's Disease is a systemic inflammatory disease that manifests itself as a myriad of symptoms being the most frequent high-spiking fever, a characteristic rash and arthralgias/arthritis. Although rare it should be considered as a cause of fever of unknown origin, and it is usually an exclusion diagnosis. Its aetiology is currently unknown although it has been suggested genetic and various infectious agents. The clinical course is variable but it can be divided in three main patterns: monophasic, polycyclic and chronic. It should be kept in mind that acute and chronic serious complications can occur. Treatment consists in limiting the intensity of the symptoms through the use of aspirin and NSAIDs and controlling its evolution with corticosteroids and immunomodulating agents.

Key words: Adult-onset Still's Disease, Adult Still's disease, Still's Disease.

INTRODUCTION

Adult Still's Disease (ASD) was initially described in the pediatric population by George Still in 1896 but only in 1971, it was acknowledged by Eric Bywaters as a distinctive clinical entity, to name adults who did not meet the Classic Rheumatoid Arthritis criteria although having similar features to those children with Juvenile Rheumatoid Arthritis.[1-3]

The incidence is 0.16 cases per 100.000 subjects per year.[1,3] It has a bimodal age distribution, peaking around the range 15-25 and 36-46 years old, without a difference between gender.[1,3]

The precise pathophysiologic mechanism is unknown however it is recognized an immunological component, possibly triggered by a viral or bacterial infection, albeit the importance of genetic factors can not be excluded.[1,3-6]

This is a systemic inflammatory pathology characterized by three main symptoms: fever, arthralgia/arthritis and typical exanthem.

We report a case with an unusual clinical presentation, initially considered an atypical pneumonia with reactive arthritis. Regarding the clinical case, a literature review was carried out on the Adult Still's disease, namely its most rare clinical manifestations.

CLINICAL CASE

A 26 years old man, Surveyor student, admitted in June 2007 due to a cough with mucus sputum, fever (axillary temperature 38°C) and generalized myalgia evolving for a fortnight.

He denied anorexia, weight loss, odynophagia, arthralgias, exanthem, dyspnea, thoracic or abdominal pain, nausea, vomiting and diarrhoea.

On the fourth day of the disease his Assistant Physician prescribed amoxycillin and clavulamic acid, to which clarithromycin was added 5 days later as the symptoms did not disappear.

At the time, he had leukocytosis (Leukocytes: 17.8 x 10^9/L and neutrophilia 86%), CRP 18.8 mg/dL, thrombocytosis (platelets: 513 x 10^9/L), increase on ALT (113 UI/L) and ferritinemia of 890 ng/mL, compatible with an inflammatory condition. A thorax teleradiography has shown a bilateral bronchovascular thickening, but pulmonary infiltrates, pericardial or pleural effusion were not evident and there were no intrathoracic adenopathies.

The patient's personal history was irrelevant. Recently he had been in a rural setting, in a context

Medicine II Service, Hospital Center of West Lisbon (Egas Moniz Hospital), Lisbon

Received for publication on the 17th April 2009
Accepted for publication on the 6th April 2010

of a research project. He denied recent trips abroad, medication, allergies, smoking, drinking or use of illegal drugs endovenously, contact with the same symptoms and risk situations for HIV infection.

He was admitted with a diagnosis of undetermined Febrile Syndrome.

On admission he was febrile (axillary temperature 38.6ºC), normotensive, slightly tachycardic with a regular pulse, a good O_2 saturation in the air, no changes on the skin and mucosa, bilateral pulmonary vesicular murmur slightly coarse, without cardiac sounds and with a normal abdominal and muscle-skeletal exam. No other changes were seen, namely exanthems, subcutaneous nodes, alopecia, oral ulcers, oropharynx lesions and adrenomegaly.

The supplementary study has revealed Hb: 13.5 g/dL; leukocytes: 17.8 x 10^9/L (N: 86%); platelets: 644 x 10^9/L; creatinine: 0.9 mg/dL; ALT: 111 UI/L; LDH: 507 UI/L; CK: 37 UI/L; Na+: 135 mmol/L; K+: 4.0 mmol/L; CPR: 16.0 mg/dL.

Thorax teleradiography in postero-anterior incidence was overlapping the previous one. The ECG was normal.

An experimental antibiotic therapy with endovenous levofloxacin. The sputum microbiological exam did not isolate any agent and both the hemoculture and uroculture were sterile.

On the subsequent days emerged a pain in the chest, of pleuritic type of light intensity, on the right hemithorax and arthralgias of inflammatory rhythm, more intense at knee level, interphalangeal joints of feet and hands and metatarsal, with a light pain upon palpation. At this time, blood tests have shown a slight normochromic normocytic anemia (Hb: 11.9 g/dL), small reduction of the inflammation parameters (Leuk: 14.3 x 10^9/mcL (N: 79.7 %); CPR: 14.0 mg/dL), increase on ESR and ferritin (71 mm/1st h and 352 ng/mL (20-250) respectively), small increase on ALT (70 UI/L), AST: 35 UI/L; gamma-GT: 86 UI/L; Alkaline Phosphatase: 147 UI/L. Negative serum tests for *Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae* and *Coxiella burnetti*. Negative serum tests for HIV 1 and 2, EBV, CMV, VHB, VHC and VDRL.

The patient received naproxen 500 mg q12h, with a fever disappearing and an improvement on cough and myalgia.

He was discharged on the 5th day after admission, improved, with a diagnosis of Atypical Pneumonia with reactive arthritis and mediated with levofloxacin during a further couple of days, being referred to the Internal Medicine Consultation 2 weeks later.

A week after being discharged new febrile peaks emerged with a temperature reaching 39ºC and arthralgia. He kept increased inflammation values, with ESR of 82 mm/1st h and ferritinemia of 735 ng/mL. Autoantibody serum tests, requested as outpatient, have revealed positivity for ANA (1/320), and the reminder tests were negative (RA test, anti-DNAds, anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Scl-70 e anti-Jo1).

On the 30th day of the disease, in a warmer environment, it was seen for the fist time a macular exanthem, of salmon color, non pruriginous, evanescent, located on the back and posterior face of the right arm, typical of Still's Disease *(Fig. 1 and 2)*.

The diagnosis of Adult Still's Disease was accepted and corticotherapy was started on a daily dose of 20mg of prednisone and afterwards, hydroxychloroquine 400 mg as wrist arthritis was persisting, with a total clinical and laboratorial remission.

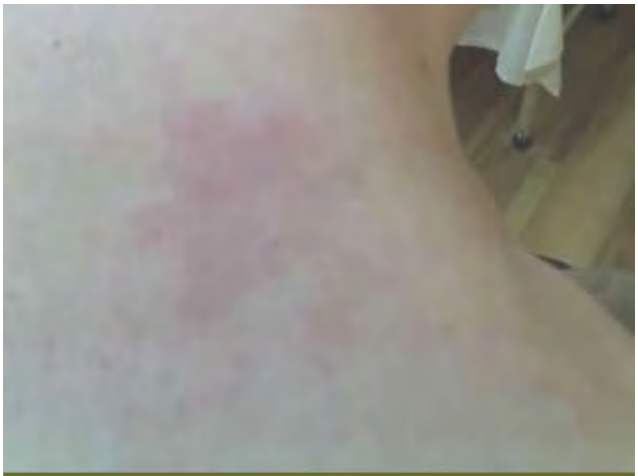
DISCUSSION AND CONCLUSIONS

ASD accounts for around 6% of cases of prolonged undetermined febrile syndrome (above 6 months). [6]
In Still's Disease fever manifests itself under the form of one to two daily peaks with temperature above 39ºC, mainly in the afternoon, that can vary around 4ºC in 4 hours, returning to normal in around 80% of patients.[1] It should be highlighted that in such periods, the patient seems alright.

The macular or maculo-papular cutaneous exanthem, a pinkish-salmon color, is evanescent occurring typically only after the febrile periods and in proximal limbs, it can affect the palm of the hands and the sole of the feet. Its appearance is triggered by mechanical or thermal stimulation, and this is called the Koebner's phenomenon.[1,3]

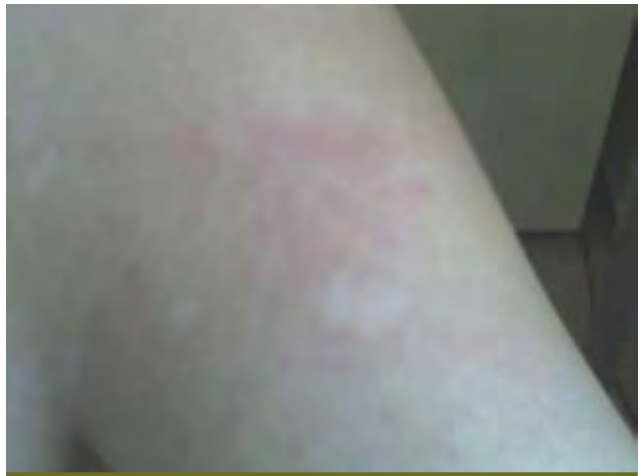
Arthralgia/arthritis has predominantly an oligoarticular involvement, mainly at knee level, tibiotarsal, elbows, wrists, metacarpophalangeal and metatarsophalangeal. Radiologically, a non erosive narrowing of the inter-articular line that subsequently can result in a bone fusion.[6]

Other forms of presentation include non-exudative pharyngitis, fatigue, weight loss, anorexia, adenomegaly, splenomegaly, myalgia, pericarditis, pleural effusion, pulmonary infiltrates and pancytopenia[1]. Among



Macular lesion on the posterior neck.

FIG. 1



Macular lesion on the posterior right arm.

FIG. 2

the rarest manifestations are the secondary Sjögren's syndrome, aseptic meningitis, cranial nerves paralysis, retina lesions, iritis, panophthalmitis, interstitial nephritis, glomerulonephritis and thrombotic thrombocytopenic purpura[6]. More severe forms can happen as fulminating liver failure, myocarditis and the acute respiratory distress syndrome (ARDS).[1]

Analytically, it is highlighted an exaggerated systemic inflammatory response, translated by a strong increase on ESR and ferritin, leukocytosis with neutrophilia, reactive thrombocytosis, normochromic normocytic anemia and hypoalbuminemia.[6] The increase on liver enzymes occurs in three quarters of all patients,[6] and can suggest a viral hepatitis which must be excluded.[7] Serum ferritin and interleukin 18 values are related with the disease activity.[6,7] Rheumatoid factor and ANA are typically negative, i.e., no sign of auto-immunity is present.[7]

ASD clinical presentation is heterogenous with a wide differential diagnosis range, including infectious diseases (acute rheumatic fever, also evolving with odinophagia,[8] tuberculosis, toxoplasmosis, infectious mononucleosis, abscesses), neoplasm (namely the lymphoma[7] in this case, due the patient's age range) and auto-immune (rheumatoid arthritis, systemic erythematous lupus, polymyositis and polyarteritis nodosa) which should be initially excluded, due to its potential severity.

According to recent literature, a non-identified infectious agent may have been the ASD etiology, being mixed with the symptoms, in an initial stage, as an atypical pneumonia. There are authors who consider that among the potentially infectious agents are included atypical bacteria as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[9,10,11] Other suggested agents are *Yersinia enterocolitica*, the rubeola virus, echovirus, Epstein-Barr, cytomegalovirus, parvovirus B19, influenza A, parainfluenza, Coxsackie, adeno, herpes, hepatitis B and C.[1,3] The hypothesis that one of these agents can trigger the referred pathology suggests a similarity with reactive arthritis.[3]

ASD diagnosis is of exclusion, supported in isolated and unspecific clinical and laboratorial criteria. Several criteria groups were considered, being those of Yamaguchi the ones presenting higher sensitivity (93%) and specificity.[1,3] 5 criteria should be present, including at least, 2 major ones. Our patient gathered 4 major and 1 minor criterion *(Table I)*.

The disease progresses in three groups in equal ratio, with a growing severity: monocyclic, polycyclic and chronic. In the last one, the patients may present a disabling chronic arthritis. The presence of polyarteritis in the early stages of the disease, the involvement of scapular or pelvic girdle, a previous episode during childhood and the need for 2 or more years of corticotherapy, are factors of a bad prognosis.[6] The absence of an exanthem or its later emergence in the natural history of the disease are factors of a good prognosis.[6] ASD fatal cases are due to an infectious pathology, amyloidosis, liver failure, ARDS and disseminated intravascular coagulation.[6]

Treatment consists of corticotherapy, as only

Table I

Yamaguchi Criteria[1,5]

MAJOR CRITERIA
Fever ≥ 39ºC lasting ≥ 1 week
Arthralgia lasting ≥ 2 weeks
Typical exanthem
Leukocytosis (≥ 10.000/mcL) with ≥ 80% neutrophils
MINOR CRITERIA
Odynophagia
Adrenomegaly and/or splenomegaly
Increased transaminases
Negative FR and ANA

7-15% of patients respond to NSAIDs.[3] Around 76 to 95% of patients respond favorably to corticosteroids. Anti-rheumatic (cyclosporine A, hydroxychloroquine, gold, penicillamine, azathioprine, cyclophosphamide and methotrexate) are often associated to corticosteroids to reduce the dose of these in case of intolerance or due to the emergence of adverse effects.[3] Recent studies point out to the advantages of using other immunomodulators agents, namely endovenous gamma-globulin, etanercept, infliximab and anakinra.

The diagnosis was not immediately apparent due to the late onset of exanthem, typical and virtually pathognomonic, featuring the disease natural course, and being a characteristic of a good prognosis.[3,6] It is to highlight the inexistence, in Portugal, of any ASD diagnostic test; this is done through the presence of suggestive clinical and laboratorial characteristics and excluding other diseases. Recent studies suggest that a ferritin value above 1500 mcg/L in a patient with fever of unknown origin is very suggestive of ASD.[5]

ASD can manifest itself as pathology essentially rheumatologic, dermatologic or with isolated fever, without other symptoms or signs[7]. The continuous physical observation of patients with prolonged febrile syndromes can reveal crucial signs leading to a diagnosis, enabling to obviate a potentially unnecessary investigation and to start an appropriate therapy at the earlier stages and with better clinical outcome. ■

References

1. Lisa Mandl, John Esdaile, Adult Still's disease, www.uptodate.com, 2006 (2007-07-07)

2. Eric B Larson, Adult Still's disease – Recognition of a clinical syndrome and recent experience – Specialty Conference, The Western Journal of Medicine 1985; 142: 665-671.

3. P Efthimiou, P K Paik, L Bielory, Diagnosis and management of adult onset Still's disease, Ann Rheum Dis 2006; 65: 564-572.

4. SCA Meijvis, H Endeman, ABM Geers, EJ ter Borg, Extremely high serum ferritin levels as diagnostic tool in adult-onset Still's disease, The Netherlands Journal of Medicine, June 2007, 65: 212-214.

5. R Sivakumar, S Pavulari, Fever of unknown origin: case outcome, BMJ 2006; 333; 691.

6. Chandran V, Aggarwal A, Misra R, Adult-onset Still's Disease – Case report, J Indian Rheumatol Assoc 2002: 10: 19-21.

7. Fautrel B, Adult onset Still's disease, orphanet encyclopedia, 2004; 1-5 (2007-07-07).

8. L Christopher-Stine, Adult Onset Still's Disease - Case 11, Case Rounds, Physician corner, The Johns Hopkins Arthritis Center, Johns Hopkins Medicine, www.hopkins-arthritis.org (2007-07-07).

9. Perez C Artola V, Adult Still's disease associated with Mycoplasma pneumoniae infection, Clin Infect Dis. 2001 Mar 15; 32(6):E105-6. Epub 2001 Mar 7 (2007-07-07).

10. Wouters JM, van d Veen J, van de Putte LB, de Rooij DJ. Adult onset Still's disease and viral infections. Ann Rheum Dis 1988; 47:764-767.

11. Takeda H, Ling M, Ochi M, Watanabe K, A patient with adult Still's disease with an increased Chlamydia pneumoniae antibody titre, J Infect Chemoter. 2002; 8 (3): 262-265.