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Fever and erythema: exclude all and then… think of Still's disease!

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ABSTRACT

Adult-onset Still's disease is a rare disease. Diagnosis of Still's disease is often difficult to achieve. Herein, we describe our diagnostic approach in a case report regarding an adult patient who presented with fever, erythema, lymphadenopathy and arthralgia.

Introduction

Adult-onset Still's disease (AOSD) is a rare chronic inflammatory systemic disease of unknown etiology. For the internist, the diagnostic pathway is often very challenging requiring a correct differential diagnosis with other similar diseases such as infections, neoplastic diseases and rheumatic diseases. We present a case of AOSD, which required a strict multidisciplinary approach, including several biochemical and radiological tests being performed.

Case Report

A 49-year-old Italian male was referred to our Medical Department with a symptomatic pattern characterized by malaise with high fever, hands and knees arthralgia and pharyngitis, with onset two weeks prior. In the last two days, he reported that a vanishing itching macular-papular erythema on the trunk, legs and arms had appeared, combined with lymphadenopathy of the neck. He also reported a mild sore throat. The man was a teacher, he was engaged to a woman but they had no children. He took a five-day course of antibiotic treatment (azythromicin 500 mg qd) without clinical benefit. He denied weight loss and night sweats. Personal history was negative for alcohol or herbal medicine intake, tobacco use, drug abuse and no risk factors for leptospirosis infection or Lyme's disease as well as for food poisoning were found. No recent foreign travel was reported. The patient did not have any known chronic diseases and his family history was negative too. Physical examination showed vanishing macular-papular erythema localized on the trunk mainly presenting with fever (Figure 1), hepatomegaly, splenomegaly, numerous bilateral laterocervical unpainful enlarged lymph nodes (diameter 2×2 cm), hyperemia of the pharynx and no signs of arthritis. Neurological, respiratory and cardiological examinations were negative for pathological findings. His body weight was 80 kg and his height was 180 cm. Blood pressure was 130/80 mmHg, heart rate was 100 bpm, body's temperature was equal to 39°C during fever spikes. We performed both blood and urine cultures and both routine and additional biochemical studies were planned. In particular, serum biochemical tests showed neutrophil leukocytosis, hyperferritinemia, an increase in aspartate aminotransferase, alanine aminotransferase, erythrocyte sedimentation rate (ESR), C-reactive protein (Table 1). Chest X-ray and an echocardiogram were negative. An abdomen ultrasound scan showed the liver to be of regular size, with homogeneous ultrasound structure without liver lesions, regular gallbladder without gallstones, splenomegaly (longitudinal diameter 12 cm). At first, we hypothesized an infection and we started empirical antibiotic treatment (levofloxacin 500 mg bid plus amoxicillin/clavulanic acid 2.2 g tid endovenously).

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Despite this therapy, the patient had persistent fever and serology testing for the main bacterial and viral infections, blood and urine cultures, and procalcitonin dosing were all negative (Table 1). We could not perform serological test for leishmaniasis in our Department (no serum kit available), however at light-microscopic examination no microbiological evidence of parasites was noted in any specimen we collected. Antibiotic therapy was suspended after eight days because we did not obtain any clinical or biochemical benefit. In the next few days, the patient remained in a phase of drug wash out and we performed a neck, chest and abdominal computerized tomography (CT) scan with intravenous contrast administration and a whole-body positron-emission tomography (PET)/CT. The tomography scan confirmed splenomegaly, the so called *reactive* latero-cervical lymphadenopathy and a single nodule (diameter 2×1 cm) in the thyroid gland, in the absence of abscess or tumor or thoracic/abdominal pathological lymphadenopathy. The PET/CT visualized a significant accumulation of ^{18}F-FDG uptake in the bone marrow, in the spleen and in lymph nodes of the neck. A bone marrow biopsy, a latero-cervical left lymph node biopsy and a thyroid fine needle aspiration cytology (FNAC) were performed. Bone marrow biopsy and lymph node biopsy were negative for neoplastic infiltration; bone marrow culture was negative, in accordance with the absence of any histopathological sign of bone marrow infection at light-microscopic examination. The thyroid FNAC was consistent with colloid goiter. Lymphocyte peripheral and bone marrow differential showed polyclonal pattern. Our investigations excluded infections and/or any neoplasia. Therefore, according to our biochemical tests and clinical picture, we assumed that an AOSD was probable as an exclusion diagnosis and intravenous steroid treatment (metilprednisolone 1 mg/kg/day) was initiated. This therapy was immediately effective in resolving all of the patient's symptoms, including fever, lymphadenopathy and arthralgia. The biochemical exams also improved (Table 1). The cutaneous rash was slower to respond, but finally it disappeared after one week. The patient was discharged from hospital after two weeks with a prescription for oral steroids. The patient is now well and continues with periodic clinical and laboratory follow-ups at our Rheumatology Department.

Discussion

Adult-onset Still's disease is an acute, systemic inflammatory disorder of unknown etiology. It is clinically characterized by high spiking fever, arthralgia, typical evanescent skin rash, lymphadenopathy, and hepatosplenomegaly.[1-4] Clinical features and laboratory results are nonspecific, and they overlap with those of autoimmune disease, infections, and hematologic malignancies. Therefore, the spectrum of differential diagnosis is wide and may cause difficulty in making the correct diagnosis. There are no specific tests and re-

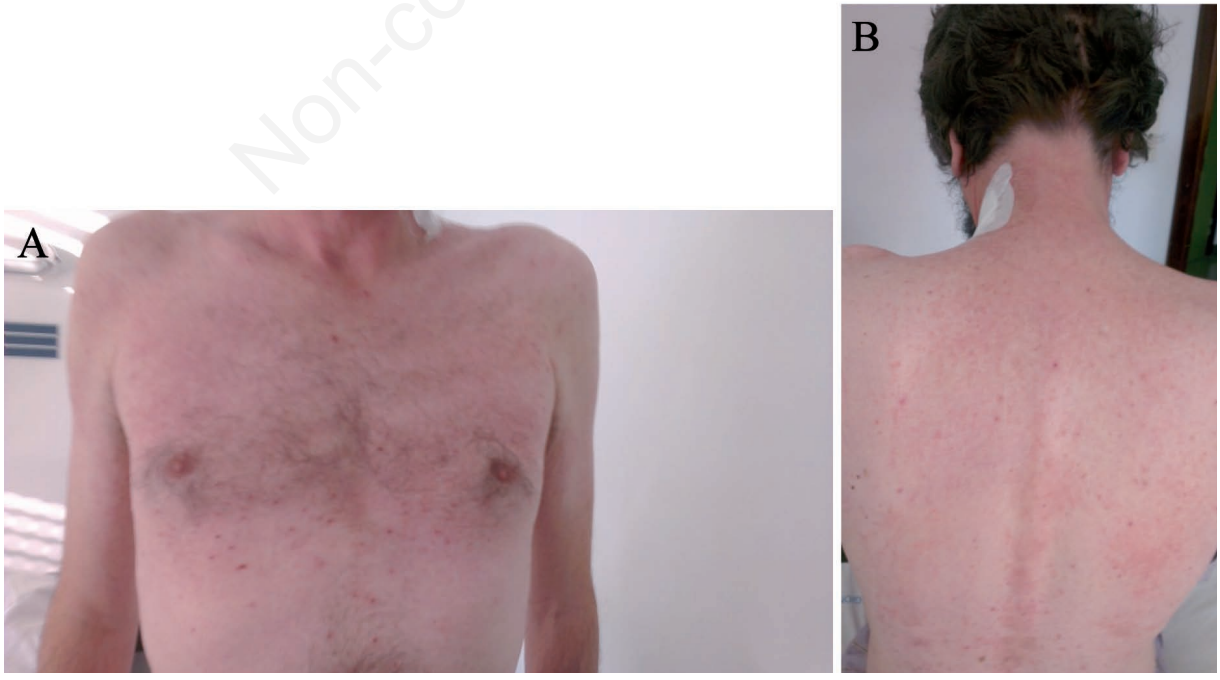

Figure 1. Physical examination showing vanishing macular-papular erythema localized on the trunk: A) front; B) back.

liance is usually placed on symptom complex. The present case highlights the role of the internist in planning a correct differential diagnosis for Still's disease. The evaluation of a patient with recurrent fever, cutaneous manifestations and lymphadenopathy should include a complete blood count, blood culture, serology for a wide spectrum of infectious diseases, autoantibodies tests and radiological tests for ruling out malignancies. Pathological confirmation of affected organs is occasionally needed for accurate diagnosis. In our opinion, it is always important to exclude viral infection such as mononucleosis and malignancies such as lymphoma or solid tumor, due to the fact that fever and erythema could potentially be infectious and/or paraneoplastic manifestations. In our case, we performed biopsy of the enlarged neck lymph nodes and bone

Table 1. Hemato-chemical parameters [start metil prednisolone (1 mg/kg/die) intravenously].

	Value	Normal value
WBC (10^3/mcL)	23,000	12,370
Hb (g/dL)	12.7	12.6
MCV (fL)	88.6	
PLT (10^3/mcL)	218	357
ESR mm/h	120	120
AST (U/L)	350	42
ALT (U/L)	550	122
Total bilirubin (mg/dL)	0.8	0.2
Direct bilirubin (mg/dL)	0.3	
GGT (U/L)	189	185
ALP (U/L)	136	97
Glycemia (mg/dL)	100	
AFP (ng/mL)	1.0	
INR	1.5	1.2
Albumin (g/dL)	2.5	3.0
Ab HAV IgM	Negative	
Ab HCV	Negative	
HBsAg	Negative	
HBcAb	Negative	
HBsAb	Negative	
Ab HIV	Negative	
Ab EBV IgM	Negative	
Ab EBV IgG	Positive	
Ab CMV IgM	Negative	
Ab CMV IgG	Positive	
Widal Wright reaction	Negative	
Ab *Lepstospira* IgM	Negative	
Ab *Bartonella* IgM	Negative	
Ab *Rickettsia* IgM	Negative	
Ab *Enterovirus*	Negative	
Ab *Borrellia* IgM	Negative	
Polyomavirus PCR	Negative	
VDRL	Negative	

	Value	Normal value
Ab TBE	Negative	
Ab *Parvovirus* IgM	Negative	
Ab *Toxoplasma* IgM	Negative	
ANA	320	
aDNA IU/mL	Negative	
ENA	Negative	
ASMA	Negative	
aLKM	Negative	
AMA	Negative	
ANCA	Negative	
C3 mg/dL	192	
C4 mg/dL	31	
RF	Negative	
Cryoglobulin	Negative	
TAS	Negative	
Fibrinogen mg/dL	788	
Ferritin ng/mL	9000	200
Transferrin mg/dL	212	
Iron mcg/dL	26	33
% Saturation transferrin	8.6	
HFE	Negative	
CEA ng/mL	1.9	
CA19.9 U/mL	3.8	
Total PSA ng/mL	1.20	
CRP (mg/dL)	28	7
PCT (ng/mL)	0.05	0.03
fT3 pg/mL	1.5	
fT4 pg/mL	13.9	
TSH mU/L	0.68	
Creatinin (mg/dL)	0.6	0.6
ACE U/L	Negative	
Quantiferon	Negative	

WBC, white blood cells count; Hb, hemoglobin; MCV, mean corpuscular volume; PLT, platelets; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; AFP, α-fetoprotein; INR, international normalized ratio; Ab HAV IgM, immunoglobulin M antibody to hepatitis A virus; HVC, hepatitis C virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; PCR, polymerase chain reaction; VDRL, venereal disease research laboratory test; TBE, tick-borne encephalitis virus; ANA, antinuclear antibody; ENA, extractable nuclear antigen antibodies; ASMA, anti-smooth muscle antibody; aLKM, anti-liver/kidney microsomal antibodies; AMA, antimitochondrial antibody; ANCA, anticytoplasmic autoantibodies; RF, rheumatoid factor; CEA, carcinoembryonic antigen; CA19.9, carbohydrate antigen 19-9; PSA, prostate specific antigen; CRP, C-reactive protein; PCT, procalcitonin; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; ACE, angiotensin-converting enzyme.

Table 2. Yamaguchi criteria.

Major criteria
1. Fever of 39°C or higher lasting 1 week or longer
2. Arthralgia lasting 2 weeks or longer
3. Typical rash (non-pruritic macular or maculopapular salmon colored rash, usually over trunk or extremities while febrile)
4. Leukocytosis (10,000/mmc or greater) including 80% or more of granulocytes
Minor criteria
1. Sore throat
2. Lymphadenopathy and/or splenomegaly
3. Liver disfunction
4. Negative rheumatoid factor and negative antinuclear antibody test
Diagnosis is made when there are 5 or more criteria which include at least 2 major criteria
Exclusions
1. Infections
2. Malignancies
3. Rheumatic disease

marrow biopsy to rule out lymphomatous diseases. We also ruled out thyroid neoplasia, suggested by PET/CT findings. The clinical value of whole-body PET/CT in rheumatic disease is now well affirmed.[5-7] Our work up did not include liver and skin biopsy for several reasons. According to literature, in most cases liver histology underlined only non-specific findings such as focal hepatitis with necrosis and mild chronic necroinflammatory changes;[8] moreover in our case rash was typically vanishing, appearing with fever and then rapidly disappearing, with an intermittent course, making it difficult to perform proper biopsies. We referred to Yamaguchi criteria for Still's disease (Table 2)[1] diagnosis observing pathognomonic biochemical changes too (Table 3).[2] Our patient presented with all major and minor criteria. High dose steroids are still the mainstay of treatment in AOSD. Conventional second-line treatments for patients with steroid-resistant refractory AOSD include immunosuppressants such as cyclosporin A, leflunomide, azathioprine, and cyclophosphamide. Recently, following new insights in autoinflammatory disorders and cytokine pathways, biological agents showed favorable effects in AOSD.[9-11] Studies have suggested that the use of immunosuppressive agents should be reserved for cases in which steroid therapy fails or when life-threatening complications arise.[12] Severe complications of AOSD include pulmonary arterial hypertension, diffuse alveolar hemorrhage, macrophage activation syndrome, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura and amyloidosis. Our patient did not present nor develop any of these complications, so we decided to use only high dose steroids and to perform close clinical and biochemical follow up. During this follow up ferritin levels constantly decreased to normal, as well as C-reactive protein and transaminases, allowing us to gradually and safely taper steroids dosage. Patient is actually still subject to regular follow-ups at our Rheumatology Department.

Table 3. Probable laboratory findings in adult-onset Still's disease.

Biochemical test[2]	Percentage of patients
ESR increase	99
White blood cells ≥10,000/mm ≥15,000/mmc Neutrophil ≥80%	 92 81 88
Albumin ≤3.5 g/dL	81
Hypertransaminasemia	73
Hyperferritinemia	70
Anemia (≤10 g/dL)	68
Platelets ≥400,000/mmc	62
ANA negative	92
RF negative	93

ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; RF, rheumatoid factor.

Conclusions

Adult-onset Still's disease is a rare chronic inflammatory and systemic disease with unknown etiology and variable clinical and serological manifestations. The diagnosis remains of that of exclusion, requiring rigorous assessment of infectious and neoplastic diseases. The Internist should keep in mind the wide spectrum of differential diagnosis when approaching

patients with clinical manifestations and laboratory findings suspicious for AOSD.

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