

An unusual adverse drug reaction?

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ABSTRACT

Introduction: Adult Still Disease (ASD) is a rare (incidence 1-1,6/1.000.000 in Europe) seronegative polyarthropathy diagnosed with clinical criteria, excluding other etiologies.

Minocycline, a semisynthetic derivative of tetracycline, has been associated with many adverse effects.

We present the case of a 18-years-old man with a high suspicion of an adverse drug reaction (ADR), that was finally diagnosed of ASD.

Material and methods: In order to exclude other diseases, laboratory test, radiology and allergological studies were performed. The results of the allergological studies excluded the possibility of an ADR. The rest of the results determined the diagnosis of ASD.

Conclusion: It's necessary to emphasize the importance of an accurate differential diagnosis in cases like this, because many diseases may mimic an ADR, and may be underdiagnosed (or misdiagnosed).

Key words: Adult Still Disease. Minocycline. Rheumatologic disease. Minocycline hypersensitivity syndrome. Adverse drug reaction.

RESUMEN

Introducción: La Enfermedad de Still del Adulto (ESA) es una poliartropatía seronegativa con muy baja incidencia (1-1,6 casos/1.000.000 en Europa). Es de diagnóstico clínico, excluyendo otras patologías.

La minociclina es derivado semisintético de la tetraciclina y se ha asociado a efectos adversos muy variados.

Presentamos en caso de un varón de 18 años con un diagnóstico de sospecha de reacción adversa a medicamentos (RAM), que fue diagnosticado finalmente de ESA.

Material y métodos: Con el fin de excluir otras enfermedades se efectuaron estudios de laboratorio, radiológicos y alergológicos. Por el estudio alergológico se descartó la causa medicamentosa del cuadro clínico. El resto de los resultados determinaron el diagnóstico definitivo de ESA.

Conclusión: Es clave un correcto diagnóstico diferencial en casos como este, porque muchas enfermedades pueden simular cuadros de RAM, y pueden pasar inicialmente desapercibidas.

Palabras clave: Enfermedad de Still en adulto. Enfermedad reumática. Minociclina. Reacción adversa a medicamentos. Síndrome de hipersensibilidad en minociclina.

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INTRODUCTION

Adult Still Disease (ASD) is a rare (incidence 1-1,6/1.000.000 in Europe) seronegative polyarthropathy associated with sudden onset high fever and chills, with evanescent rash on the trunk and extrem-

ities. Bony erosions are uncommon, although fusion of the carpal bones may occur.

ASD is diagnosed with clinical criteria, excluding other etiologies.

Minocycline, a semisynthetic derivative of tetracycline, has been associated with serum sickness², hypersensitivity pneumonitis³, Sweet's syndrome⁴, poliarteritis nodosa⁵, drug induced lupus⁶ and hypersensitivity syndrome⁷.

CASE REPORT

A 18 years-old man complained of maculopapular exanthema during the last 24 hours, was admitted to the emergency room (ER). He was taking oral minocycline (100 mg/12 h) the last 12 days because of an infected fat cyst in the left ear.

Suspecting an adverse drug reaction (ADR), minocycline was withdrawn and treatment with oral prednisone (30 mg/d) and dexchlorpheniramine (6 mg/d) was started.

48 hours later he returned to ER presenting urticaria and symmetrical arthralgias (knees, elbows, wrists, metacarpophalangeal 2°-3°), fever 38 °C and odynophagia.

Physical examination showed maculopapular exanthema without signs of vasculitis, articular pain with active and passive movements without signs of arthritis and 2 posterocervical lymphadenopathies of inflammatory type. Cardiac and pulmonary auscultation and abdominal palpation showed no abnormalities.

Patient was admitted to the hospital and a diagnostic procedure was performed.

Treatment with prednisone (80 mg/d) in diminishing doses, indomethacin (75 mg/d), dexchlorpheniramine (12 mg/d), omeprazol (20 mg/d), sodium dalteparine (2500 UI/d) and IV fluids (glucosaline 2500 ml/d) was started. 24 hours later the patient felt better.

5 days after starting treatment and when prednisone was slowly tapered until 40 mg/d, exanthema returned and pleuritic chest pain with pleural rubbing and dyspnea appeared. Electrocardiogram showed infero-lateral ST elevation and a positive troponin T test was obtained. A diagnosis of pleuropericarditis was performed.

All symptoms and signs dissappeared when prednisone was increased until 120 mg/d.

The patient remained stable during 8 days and was discharged from hospital with oral prednisone (60 mg/d) and the diagnosis of Adult Still Disease (ASD).

At present, the patient remains stable with a single dose of prednisone (5 mg/d).

DISCUSSION OF THE CLINICAL AND ANALYTICAL STUDY

According to table I, when the patient was diagnosed, he complied 5 criteria (2 major criteria).

Arthralgias (at least 2 weeks) and fever (at least 1 week) were not present during the time required because the patient was treated before (prednisone).

In the differential diagnosis should be excluded, in our case, drug induced lupus, minocycline hypersensitivity syndrome, other autoimmune diseases, neoplasias, infections and hereditary periodic fever syndromes (familial Mediterranean fever, hyper IgD syndrome and TNF-receptor-associated periodic syndrome).

The characteristics of the clinical picture and the negative or normal results of batteries of specific antibodies, immunoglobulins, serum tumoral specific markers (CEA, AFP, CA 125, CA 19.9), beta-2 microglobulin, blood and urine cultures, serologies, radiological studies and tolerance to the oral challenge test to minocycline, excluded these possibilities.

In our patient, during the acute phase, hypoalbuminemia, high erythrocyte sedimentation rate (ESR), hyperfibrinogenemia, hypertransaminasemia, glomerulonephritis (proteinuria), thyroiditis (high anti-thyroid peroxidase antibodies-TPO), and neutrophilic leucocytosis were observed, all of them may be present in ASD (table II).

When the patient became asymptomatic, all of the laboratory disorders returned to normal values, except for IgG, beta and gammaglobulins that remained slightly low.

Table I

Criteria for classification of ASD

Major criteria

1. Fever 39 °C or more, during one week or more
2. Arthralgias, during 2 or more weeks
3. Evanescent exanthema
4. Leucocytosis (10.000/mm³ or more) with 80 % or more of granulocytes

Minor criteria

1. Odynophagia
2. Lymphadenopathy and/or splenomegaly
3. Hypertransaminasemia
4. ANA and rheumatoid factor negatives

Exclusions

1. Infections (specially sepsis and EBV)
2. Neoplasms (specially malignant lymphomas)
3. Rheumatoid diseases (specially vasculitis and panarteritis)

Table II
Laboratory data in the acute phase

Hemogram		
Leucocytes	15170/mm ³	(82 % granulocytes)
ESR (mm/h)	31	
Coagulation		
Fibrinogen	594 mg/dl	(200-400)
Blood chemical values		
C-reactive protein	5'8 mg/dl	(0-1)
Total protein	5'6 g/dl	(6'6-8'7)
Cholesterol	106 mg/dl	(150-200)
LDH	54 mg/dl	(240-480)
Alanine aminotransferase	93 mg/dl	(5-40)
24 hours urine		
Proteins	395 mg/day	(0-150)
Proteinogram		
Albumin	2'95 g/dl	(3'68-4'77)
Beta-globulin	0'43 g/dl	(0'58-0'97)
Gamma-globulin	0'74 g/dl	(0'78-1'44)
Immunology		
Anti-TPO	508 UI/ml	(0-40)
IgG	708 mg/dl	(800-1700)

The rest of the values of hemogram, coagulation, blood chemical (ferritin included), Rheumatoid Factor, ANA, ANCA, anti-Sm, anti-RNP, anti-SS-A, anti-SS-B, anti-Scl-70, anti-Jo 1, Circulating Immune Complexes, C3, C4, IgD, serologies (lues, rubella, CMV, EBV, HIV, HBV, HCV and Borrelia), blood and urine cultures were negative or within normal limits.

Chest X-ray, chest and abdominal CT and echocardiography were performed with normal results.

Allergological study with minocycline including skin tests and patch test (5 % in pet.) were performed with negative result.

Oral challenge test was done as follows: 1st day 50 mg, 2nd day 100 mg, 3rd-4th-5th days 200 mg.

During the oral challenge test the patient was taking his single oral dose of 5 mg of prednisone, need-

ed to maintain his clinical stability, and not enough high to abolish a drug adverse reaction (in a supposed case of minocycline hypersensitivity syndrome), taking into account that minocycline was administered for several days at high doses.

Along the last year the patient has had 3 recurrences (arthralgias, exanthema, fever and high serum C-reactive protein). The first time as a result of a 15 days suspension of oral corticosteroids, and the other two due to upper respiratory tract infection. Probably the infected fat cyst in his ear was the cause of the first appearance of the ASD.

It's necessary to emphasize the importance of an accurate differential diagnosis. Many diseases may mimic an ADR, because the patients in the context of the disease (in this patient was the first manifestation of ASD) usually are taking medications to achieve the control of the symptoms. Therefore, it's easy to believe that this medications are the cause of the clinical picture and the main etiology, if the doctor doesn't think about other possibilities, may remain underdiagnosed (or misdiagnosed).

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