ADULT ONSET STILL DISEASE

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Abstract

Introduction. *Adult Onset Still Disease (AOSD) is a systemic inflammatory disease, of unknown etiology, affecting young adults. It is, at least in part, a diagnosis of exclusion. Characterized by high fever with spikes, with or without complete defervescence outside of said spikes, arthritis, and evanescent rash. Also, sore throat, hepatomegaly, splenomegaly, serositis, lymphadenopathy might be present. Fatal risk is mainly attributed to Macrophage Activation Syndrome. Biologically its main trait is a marked inflammatory syndrome with unusually elevated ferritin levels.*

Case presentation. *31 year old male, known with a history of alopecia areata, treated with Diprophos, last dose one month prior to admission, with fever, odynophagia, sore throat, diffuse myalgia, debuted twelve days before.*

On blood samples, at admission and during his hospital stay, marked inflammatory signs are present (elevated ESR up to 100mm/h, C-reactive protein up to 37.4mg/dl and marked ferritin of 6240 ng/ml) accompanied by leukocytosis with neutrophilia, lymphopenia, low grade normochromic, normocytic anemia, thrombocytosis, slightly elevated liver function tests, cholestasis (GGT 502 U/L, ALKP 255 U/L) with normal bilirubin, D-dimers over 3000 with lowering values to 1344, spontaneous INR at 1.57. Normal values for rheumatoid factor, no antinuclear antibodies present, negative serology for hepatitis B, C, HIV, atypical bacterial infections (Chlamydia, Coxiella, Mycoplasma) Epstein-Barr Virus, syphilis, vasculitis markers (pANCA, cANCA) and anti-double stranded DNA, all coupled with 5 different hemocultures and 3 different urocultures all negative.

Repeated ENT evaluation was within normal, chest X-Ray, echocardiography and CT scans of neck, thorax and abdomen reported back no significant abnormalities.

INTERNAL MEDICINE

Clinical Cases

Thus, by applying Yamaguchi criteria, after a complex evaluation of the case, the diagnosis is AOSD, and during his stay at the Internal Medicine department of Colțea Clinical Hospital, despite antiinflammatory, antithermic, antibiotic and corticosteroid treatment, the patient remains symptomatic, with high fever (up to 38.8 degrees Celsius) with chills and diffuse myalgias.

At the indication of a rheumatologist, inside a specialty clinic, pulse-therapy with Methylprednisolone is initiated (500mgs a day for 5 days) with fever remission for more than 72 hours. The corticosteroid treatment is continued at home, with the patient self-monitoring for symptoms. Two months after corticoid therapy was initiated, the patient is almost without any symptoms (alopecia areata still present partially) and the inflammatory syndrome is greatly diminished.

Conclusion. *We present the case of a 31 year old male, with AOSD, defined by Yamaguchi criteria, with persistent symptomatology, mainly as high fever, without response to usual treatment, with the exception of pulse-therapy with Methylprednisolone.*

The diagnosis proved to be difficult, in part being one of exclusion, but also the clinical presentation, so unspecific, might easily lead to a different diagnosis.

Keywords: *Adult Onset Still's disease, fever, inflammatory syndrome.*

Rezumat

Introducere. *Boala Still a adultului este o boală inflamatorie sistemică, de etiologie necunoscută, care afectează adulții tineri, în mod egal ambele sexe. Este, cel puțin pe de o parte, un diagnostic de excludere. Este caracterizată în principal de accese de febră înaltă, cu sau fără afebrilitate completă între accese, artrită și erupții cutanate. De asemenea, odinofagie, hepatosplenomegalie, poliserozită, limfadenopatii. Complicația cea mai severă este sindromul de activare macrofagică. Biologic este caracterizată de sindrom inflamator accentuat, cu niveluri specific elevate ale feritinei serice.*

Prezentarea cazului. *Pacient în vârstă de 31 de ani se prezintă la spital pentru febră vesperală (până la 39,5°C), disfagie, odinofagie, mialgii difuze, debutate cu 2 săptămâni anterior prezentării. Afirmativ, a urmat numeroase scheme de antibioterapie administrate empiric și medicație simptomatică pentru remiterea febrei, dar fără beneficiu clinic. Din antecedentele recente menționăm alopecia areata pentru care s-a investigat în vederea excluderii unei componente autoimune. Rezultatele au fost negative, dar a urmat tratament cu Diprophos administrat lunar timp de 7 luni.*

Biologic, la internare și pe parcursul internării, prezintă sindrom inflamator (cu creșterea

valorilor VSH-ului - valori de până la 100 mm/h, PCR - valori de până la 37.4 mg/dl și elevarea marcată a feritinei 6240 ng/ml), însoțit de leucocitoză cu neutrofilie, limfopenie, anemie ușoară normocromă, normocitară, trombocitoză, ușoară citoliză hepatică, sindrom de colestază (GGT 502 U/L, FA 255 U/L), cu valori normale ale bilirubinei, D-dimeri >3000 la internare, cu valori în dinamică descrescătoare până la 1344, INR spontan crescut (1.57). Au fost raportate valori normale ale FR și profil ANA extins negativ, serologie negativă pentru hepatita B, C, HIV, infecții cu germeni atipici (*Coxiella*, *Chlamydia*, *Mycoplasma*) EPV, sifilis, markeri de vasculită negativi (pANCA, cANCA, Ac anti-ADNdc), alături de 5 hemoculturi și 3 uroculturi cu rezultate negative. Evaluarea ORL repetată este în limite normale, radiografia toraco-pulmonară, evaluarea ecocardiografică și tomografia computerizată cervicală și de regiune toraco-abdomino-pelvină, fără modificări semnificative. Aplicând criteriile Yamaguchi, după evaluarea complexă a cazului, suspiciunea diagnostică este de boală Still a adultului. În scop diagnostic și terapeutic se administrează corticoterapie parenterală - dexametazonă 16 mg/zi, sub care se obțin 2 zile de afebrilitate, cu reluarea apetitului și ameliorare clinică evidentă. După acest interval, însă, reapar febra și mialgiile cu limitarea mobilizării.

Considerând că pacientul beneficiază de investigații suplimentare într-o clinică de specialitate, se efectuează transfer într-un serviciu de reumatologie. După evaluarea cazului, concluzia diagnostică a fost de boala Still a adultului și s-a inițiat puls-terapie -metilprednisolon 500 mg zilnic, 5 zile. Se obține remisiunea febrei după 72 de ore și se optează pentru continuarea tratamentului corticosteroid la domiciliu cu auto-monitorizarea simptomatologiei. La două luni de la inițierea corticoterapiei, pacientul este paucisimptomatic (cu persistența alopeciei areata), iar sindromul inflamator este semnificativ redus.

Concluzie. A fost cazul unui pacient în vârstă de 31 de ani, cu boală Still a adultului, în urma aplicării criteriilor Yamaguchi, cu simptomatologie persistentă, în principal sub forma unui sindrom febril aresponsiv la tratament cu excepția puls-terapiei cu metilprednisolon.

Diagnosticul a fost dificil, dat fiind că este unul de excludere, iar simptomatologia clinică, nespecifică, putea preta ușor la confuzie cu multitudinea de diagnostice diferențiale.

Cuvinte cheie: Boala Still a adultului, febră, sindrom inflamator.

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology usually affecting young adults; spiking fever, arthritis and evanescent rash are commonly observed during the disease. Other frequently observed clinical features include sore throat, hepatomegaly, splenomegaly, lymphadenopathy and serositis. It is, at least in part, a diagnosis of exclusion.

During AOSD, laboratory tests reflect the systemic inflammatory process showing high levels of erythrocyte sedimentation rate and C-reactive protein. In addition, the ferritin levels are typically higher than those observed in other autoimmune, inflammatory, infectious, or neoplastic diseases⁽¹⁾.

Analysing AOSD disease course, 3 different clinical patterns of AOSD have been identified: i. monocyclic pattern, characterised by a systemic single episode; ii. polycyclic pattern, characterised by multiple, ≤ 1 year lasting,

INTERNAL MEDICINE

Clinical Cases

flares, alternating with remissions; iii. chronic pattern, related to a persistently active disease with associated polyarthritis⁽¹⁾.

The worst clinical outcome possible in AOSD is due to Macrophage Activation Syndrome (MAS). MAS is a life-threatening condition, and it is a subset of hemophagocytic lymphohistiocytosis (HLH). The clinical features include a persistent high-grade fever, hepatosplenomegaly, lymphadenopathy, hemorrhagic manifestations, and a sepsis-like condition. From the clinical features, it is usually difficult to differentiate between a true sepsis, disease flare-ups, or MAS⁽²⁾. First described in children by George Still in 1896, "Still's disease" has become the eponymous term for systemic juvenile idiopathic arthritis. In 1971, the term "adult Still's disease" was used to describe a series of adult patients who had features similar to the children with systemic juvenile idiopathic arthritis and did not fulfill criteria for classic rheumatoid arthritis⁽³⁾.

Adult Still's disease is very uncommon. A retrospective French study estimated the annual incidence of adult Still's disease (ASD) to be 0.16 cases per 100,000 people, with an equal distribution between the sexes⁽⁴⁾.

Case presentation

A 31-year old male with a history of alopecia areata (scalp, eyelids, facial hair, abdomen),

partially remitted, to which he received systemic corticosteroid treatment (betamethasone) in the UK for a period of 7 months, all prior to admission (last dose one month prior to presentation), is currently presenting with fever (38.6 degrees Celsius) with a debut twelve days before, diffuse myalgias, sore throat and odynophagia. Associated weight loss of approximately 10 kilograms. Three consecutive RT-PCR tests for COVID-19 remain negative. Anamnesis reveals intermittent myalgia at home, dysuria (single episode) with denial of recent travels, coughing, diarrhea, constipation, abdominal pain, peripheral edema. He is a known smoker with family history of asthma (mother) and gout (father).

Clinical examination on admission reveals cushingoid facies, truncular obesity, stretch marks on the skin of the trunk and thighs, muscular hypotrofia (especially legs bilaterally), all due to the corticosteroid treatment. Alopecia areata is present on the aforementioned regions on the body. No rash or arthritis are present. ENT examination is normal the same day, ecocardiography within normal range and abdominal ultrasonography with a prehepatic diameter of the liver standing at 16cm and a spleen diameter 14cm long, coupled with a right pleural effusion 9 mm wide. Chest X-Ray shows a single fibrous band in the inferior lobe of the right lung.

Data:	19	22	23	24	25	26	27	28	29	30	31	1	2
Hb (g/dL)	15	13,9			13,4			13,1			13		12,6
PLT #	425	424			447			502			535		494
WBC #	24,1	20,26			16,65			21,67			22,19		23,01
NE #	21	17,64			13,64			18,1			18,26		19,88
LYM #	2,05	1,46			1,89			2,51			2,78		1,88
FIB (mg/dl)		602			609			540			516		
ESR(mm/h)		93			101			62			98		
CRP		37,3			35,2		24,9				25,3		34,3
D-DIMER		>3000			2607						1344		
INR		1,43			1,57			1,15			1,28		
PROC			0,26				<0.5				<0.5		<0.5
RF					8,4								
FERRITIN								6240					
LDH		377			307						286		
BILIRUBIN		1,1			0,8			0,4			0,56		
C BIL		0,9			0,5			0,2			0,3		
CK		31			26								
CK-MB		3			3								
AST	50	73			42			67			56		
ALT	82	111			67			85			74		
ALB		3,883			3,63			3,48			3,61		
GGT		502,6			381			255,8			283		

Table 1. Blood work done during the patient's hospital stay in our clinic

INTERNAL MEDICINE

Clinical Cases

Figure 1. AOSD patients may be stratified according to different disease courses: i. the monocyclic course is defined as a single episode followed by sustained remission through the entire follow-up period; ii. the polycyclic course is characterised by recurrent systemic flares with remissions between flares; the chronic course is defined as at least one episode of persistent symptoms (source Giacomelli, R., Ruscitti, P., & Shoenfeld, Y. - 2018. A comprehensive review on adult onset Still's disease. *Journal of Autoimmunity*, 93, 24–36)

YAMAGUCHI'S CRITERIA		
Five or more criteria are required. Two or more criteria must be major		
Major Criteria	Minor Criteria	Exclusion Criteria
Fever $>39^{\circ}\text{C}$ lasting 7 days or longer	Sore throat	Infections
Arthralgias or arthritis for 14 days or longer	Hepatomegaly or splenomegaly	Malignancies
Typical rash	Lymphadenopathy	Other rheumatic disease
WBC count $>10,000/\mu\text{L}$ with $>80\%$ neutrophils	Abnormal aminotransferases	
	Negative rheumatoid factor and anti-nuclear antibody	

Table 2. Yamaguchi's criteria for Adult Onset Still's Disease

Blood works collected from admission to discharge (see full table below – table 1) show marked inflammation all throughout the hospital stay, with elevated erythrocyte sedimentation rate (up to 100mm/h), C-reactive protein (up to 37.4mg/dl), fibrinogen (up to 600mg/dl), extremely elevated ferritin levels (6240 ng/ml), leukocytosis with neutrophilia, lymphopenia, low grade normocytic, normochromic anemia, thrombocytosis, slightly elevated liver function tests, elevated alkaline phosphatase, gamma glutamyl transpherase and lactate dehydrogenase. Elevated D-dimers (>3000 on admission, with a decreasing pattern to 1344) and a spontaneous INR of 1.57 are also present. Rheumatoid factor, creatine kinase (CK, CK-MB) and cortisol levels are within normal range. Renal function within normal. Also, infectious markers for Hepatitis B, C and HIV are negative. Five different blood cultures and three different urocultures are negative. Due to technical shortcomings, serology testing for tuberculosis (Quantiferon B) was not performed. Serology testing for atypical bacterial infection (Coxiella, Chlamydia, Mycoplasma), EPV infection, syphilis and extensive autoimmune profiling (ANA, pANCA, cANCA, anti-double stranded DNA, Rheumatoid Factor) was negative.

CT scan evaluation (native only, due to the risk of allergic reaction) of the neck region doesn't display any pathological signs, with the exception of an infracentimetric adenopathy (9mm) of the cervical region. The CT scan evaluation of the thoracic and abdominal regions is coherent with the abdominal ultrasonography, displaying minimal right side pleural effusion and hepatomegaly.

In the course of his hospital stay, despite different regimens of antithermic

(Acetaminophen, Metamizole), antibiotic (Amoxicillin, Levofloxacin, Ceftriaxone, Doxycycline), NSAIDs (Ibuprofen, Naproxen) and glucocorticoid treatment (88mg total dose of Dexamethasone), the patient remains febrile, with two spikes daily (one in the morning and one in the evening) with values around 38 degrees Celsius (max 38.8 degrees Celsius) during said spikes, but without complete defervescence during the remainder of the day, with subjective distress, alongside with tiredness and recurrent myalgia.

All things considered, for a differential diagnosis, after such complex evaluation, we are interpreting:

- an acute bacterial infection, with fever, leukocytosis and elevated acute phase reactants – but without a positive blood culture and lacking response to three different regimens of antibiotic therapy
- atypical bacterial infection, with a lack of response to typical antibiotic therapy – but with negative serology.
- a systemic rheumatic disease (rheumatoid arthritis - RA, systemic lupus erythematosus - SLE, dermatomyositis, reactive arthritis etc.), with elevated acute phase reactants, fever, diffuse myalgias and a single episode of dysuria – but lacking conclusive serology (normal Rheumatoid Factor levels, anti-double stranded DNA antibodies negative), lacking inflammatory myositis and lacking cutaneous rash (a sign of SLE) and presenting with fever spikes (unlike the fever in RA)
- vasculitis, with fever and constitutional symptoms – but negative serology, thus excluded.
- malignancy of the blood, with fever,

INTERNAL MEDICINE

Clinical Cases

leukocytosis, hepatosplenomegaly – but with a peripheral blood smear presenting only with rare Dohle bodies and a cytologic examination of the bone marrow with changes corresponding to inflammation.

- Still disease to which we applied the Yamaguchi criteria (table 2) – with fever, WBC over 10.000/mL (>80% neutrophils) as major criteria and sore throat, splenomegaly, liver abnormalities, ANA and Rheumatoid factors negative and without any exclusion criteria

At the indication of a rheumatologist, the patient recovered after corticoid pulse-therapy (500mg daily of Methylprednisolone for 5 days) with fever remission and inflammatory syndrome greatly diminished. It was opted for the continuation of Prednisone orally at home (0.75mg/kg body weight), with the patient self-monitoring his temperature and symptoms.

It was at this time that during a cranial CT scan, an infracentimetric cerebelous lesion was found, possibly a microinfarction sequelae, confirmed by an MRI scan two months later, requiring close follow-up.

In the follow-up period, two months after pulse therapy, the patient went into full clinical remission, alopecia areata still present and with an inflammatory syndrome

still being present (elevated ESR, ferritin, leukocytosis – without neutrophilia) but with normal C-reactive protein, D-dimer level and liver function tests.

Discussion

We report the case of a 31-year old male without any major chronic illness in evolution who developed a fever of unknown origin, resistant at empirical antibiotic treatment. The marked inflammatory syndrome present, leukocytosis with neutrophilia, sore throat, liver function tests abnormal, negative rheumatoid factor and ANA profile, without any exclusion criteria led us to the diagnosis of Adult's Onset Still's Disease. (AOSD)

But that was not until we performed a thorough examination and check-up of all the other possible diagnoses, since AOSD is, at least in part, a diagnosis of exclusion. We also bear in mind that the patient did not have a constant fever of over 39 degrees Celsius, as the Yamaguchi criteria demand, thing which we consider due to Acetaminophen treatment, but it came in spikes and without complete defervescence during the remainder of the day.

Outside Japan, as of the day this case report is published, there is no guideline on how to manage and treat AOSD.

The current therapeutic approach is split in regards to the clinical presentation into mild,

moderate and severe disease. The former two refer to clinical presentation with fever, joint expression, rash or even organ involvement but missing any life-threatening condition, which is the attribute of the latter. (severe hepatic disease, major coagulopathy or cardiac tamponade) Thus, while the first line of treatment has NSAIDs as its mainstay, usually glucocorticoids are necessary, at least in low-dose, to control the inflammatory process, even for what is considered to be mild disease. Other than that, in moderate disease, nonbiologic or biologic disease-modifying antirheumatic drugs (DMARDs) may be needed for long-term management, prevention of joint and other organ injury, and treatment of refractory inflammatory manifestations(5) while in severe forms, high-dose or pulse glucocorticoid therapy must be established early.

We followed this approach, trying to maintain our options clear, but without significant therapeutic response until pulse glucocorticoid treatment was applied, thus leaving us with the question if this was a mild to moderate form (no life threatening organ damage) or a

severe form (withstanding any treatment until pulse Methylprednisolone).

As for the disease course pattern, more time is required for us to understand if it was a monocyclic, with a single, albeit difficult to assess form, or if the disease is evolving into a chronic pattern with a future possible arthritic involvement, given the biologic inflammatory syndrome still being present two months after pulse therapy, which is pertaining to the question if and when more severe complications will arise, with special attention being paid to MAS.

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