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Case of Adult-Onset Still's Disease in 65-year-old man

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Abstract

Adult-onset Still's disease (AOSD) is an uncommon condition that presents itself as difficult to diagnose, due to non-specific symptoms and the necessity to exclude any underlying causes. We present a case of a 65-year-old man with slight fever, loss of weight, pain and stiffness of joints. After successful diagnosis, corticosteroids were administered, which resulted in rapid improvement in the condition of the patient.

Key words: Adult-onset Still's disease; fever; autoimmune disease; joint

Introduction

Systemic Juvenile Idiopathic Arthritis (SJIA) or Still's disease was first described by George F. Still in 1896 [1] – at that time it was known for several years as sporadic occurrence of the symptoms similar to those seen in the cases of rheumatoid arthritis. In 1971 E. G. L. Bywaters published a study on the counterpart of this disease in adults [2], which was referred to as the adult-onset Still's disease (AOSD).
AOSD can manifest itself in various symptoms. The most important being joints pain due to arthritis, daily high spiking fever peaking in the evening (sometimes twice a day) and characteristic, evanescent skin rash. Other symptoms may include sore throat, elevated inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and ferritin, liver dysfunction, splenomegaly, neutrophilia and lymphadenopathy [3]. The diagnosis can be troublesome because of the necessary exclusion of infectious, systemic and tumoral aetiology (Table 1) [4].

Table 1. Differential diagnosis of AOSD.

Group	***Examples***
Infections	HIV, herpesvirus, hepatitis, mycoplasma pneumoniae
Malignancies	Lymphomas, myeloproliferative disorders
Autoimmune diseases	Systemic lupus erythematosus, rheumatoid arthritis, infective endocarditis
Drug reactions	Stevens-Johnson syndrome, erythema multiforme
Others	Sarcoidosis, reactive arthritis

The incidence of AOSD is very difficult to assess due to its rare occurrence. In northern Norway the disease affects about 0.4 per 100 000 adults annually (which resembles SJIA epidemiology), with more cases among males, mean age of affected individuals was 33.8 years old [5]. The Japanese population showed a different distribution – the incidence of about 3.9 per 100 000 people with mean age onset of 46 years old and the predominance among women – 72% of the affected individuals are female [6]. The results of the retrospective study in west France showed far lower incidence of about 0.16 per 100 000 people without sex bias and mean age of the patients of 36 years old [7].
The pathogenesis of the disease is unclear, although similarly to most autoimmune diseases it is thought to be multifactorial. One of the factors could be the allergy - the aggravation of symptoms was previously correlated with specific allergen [7]. The central point of auto-aggressive response is overactivation of innate immune cells and the intense production of

specific cytokines such as interleukin-1 (IL-1), IL-6 or IL-18 [8]. Due to etiology AOSD is usually treated with immunosuppression. There are clinical trials in progress with the use of biological treatment, more specifically anti-interleukin therapy [8].
AOSD can be the cause of not only dangerous and possibly disabling complications due to arthritis such as joint destruction, pericarditis or myocarditis but it can be the reason of occurrence of life-threatening complications such as macrophage activation syndrome, disseminated intravascular coagulopathy (DIC), diffuse alveolar hemorrhage or pulmonary arterial hypertension as well [4].

Case Report

A 65-year-old man was admitted to the Department of Internal Medicine with fever, lasting for approximately 3 weeks. Patient complained of joint pain, mainly ankle, also knee and shoulder joints, bilaterally, with morning stiffness, sore throat, cough, loss of weight. He negated chronic diseases and past treatment. Due to these symptoms, he was treated with antibiotics (amoxicillin/clavulanic acid, later changed to levofloxacin). Initial laboratory tests showed elevated CRP, with low PCT (procalcitonin), anemia, leukocytosis (28,1 G/l at highest), thrombocytosis, slightly increased AST (aspartate transaminase), ALT (alanine transaminase), GGTP (gamma-glutamyltransferase). In microbiological trials (blood and urine culture) bacterial infection was excluded. Imaging examinations (chest X-ray, abdominal USG, echo, abdominal and chest CT) showed small amount of liquid in pleural and pericardial cavity. Others results were insignificant. In the purpose of diagnostics of anemia, iron and ferritin level tests were conducted. Lack of improvement in the patient's condition during antibiotic therapy brought focus towards autoimmune diseases. Additionally, during hospitalization, medical personnel noticed red maculopapular exanthema, which appearance correlated with peak of temperature. Another tests were commissioned: anti-rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), and antinuclear antibodies (ANA) were negative, with the ferritin levels exceeding 1500 ng/ml. On the 20th day of hospitalization, 200 mg of hydrocortisone was administered, resulting in improvement of overall patient's condition, with decrease of inflammatory markers and temperature. Due to previous antibiotic therapy, a patient developed esophageal candidiasis, which was treated with fluconazole. Patient was discharged with a prescription for orally administered 20 mg prednisone daily, for 4 weeks, then reduce to 15 mg daily, with the recommendation of medical check-up in a month.

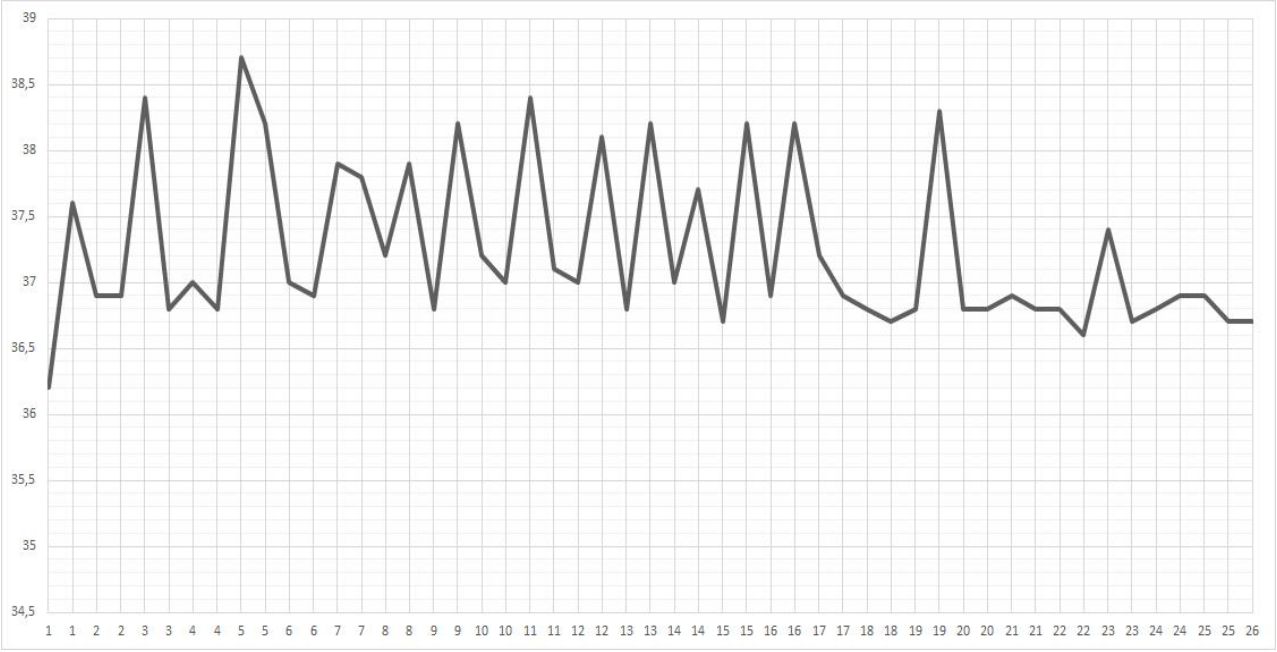

Figure 1. Temperature chart during hospitalization, on the horizontal axis following days are repeated due to temperature measurements taken in the morning and evening.

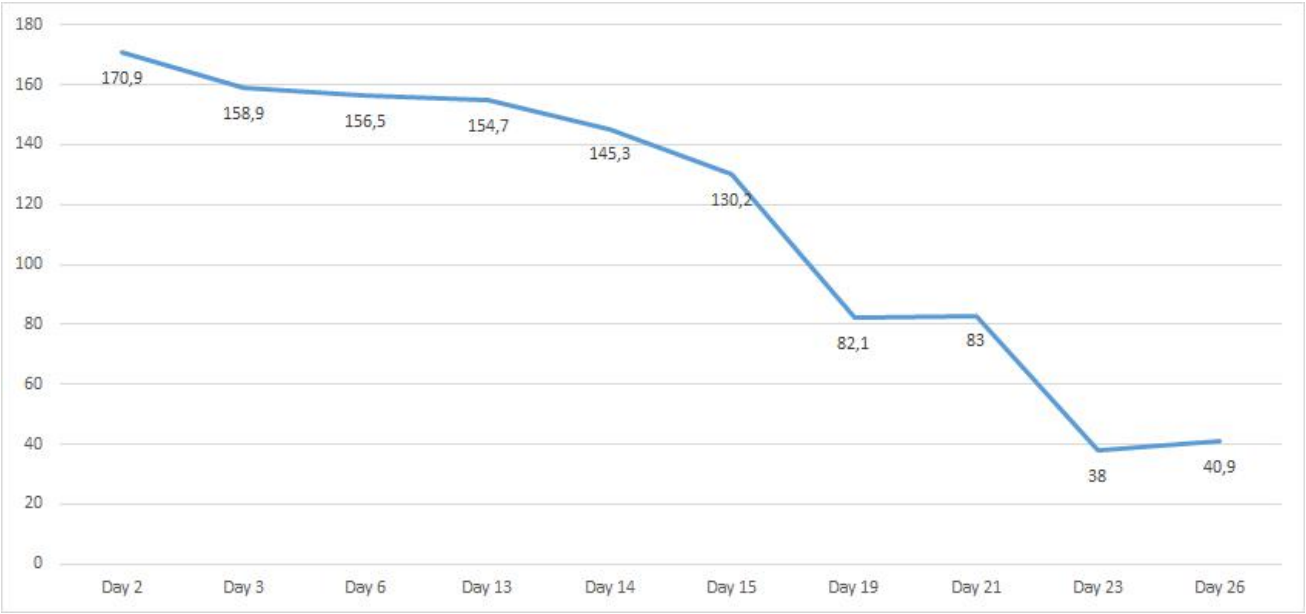

Figure 2. Chart showing CRP levels during hospitalization

Discussion

Diagnosis of AOSD is one of the major problems as the main symptoms are not specific. There is a triad of dominant manifestations, based on which specialists can suspect AOSD. The first one is fever, very often above 39 degrees, with two peaks in the morning and/or in the evening [9]. Our patient partly met this criterium as his temperature repeatedly rose in the evening and rarely in the morning without exceeding 39 degrees, most likely because he was receiving antipyretic drugs. The next symptom is arthralgia which affects mostly knee joints, ankles and wrists [10]. The patient complained about the pain in the first two joints that were mentioned as well as in the both shoulders. The last symptom of the triad

is salmon-pink maculopapular erythema that appears during the fever [11]. The rash was observed in our patient on the chest and thighs.
According to some studies there are many minor symptoms which do not occur so frequently. Puchot et al. claimed that almost 92% of 62 patients with AOSD that took part in the trial had sore throat and 76% of 62 lost their weight [12]. These two symptoms were also reported in our patient. Other manifestations may be: odynophagia, myalgias, liver abnormalities, splenomegaly, lymphadenopathy, pericarditis [13, 14].
Exact aetiology of AOSD remains unknown. Some studies showed correlation between infectious factors and this disease. A huge number of bacteria, such as mycoplasma pneumoniae, chlamydia pneumoniae, yersinia enterocolitica, brucella abortus, borrelia burgdorferi [5] and viruses for example rubella, measles, echovirus 7, coxsackievirus B4, cytomegaly, Epstein-Barr virus were found to activate immune system [15]. These infectious factors as well as the rest which stay unknown induce autoinflammatory response only in people who are genetically predisposed [13]. AOSD is associated with some gene groups such as human leukocyte antigen (HLA) [16], with polymorphisms in genes of IL-18 [17], macrophage inhibitory factor (MIF) [18] and serum amyloid A1 [19]. These genes and its mutations in combination with other triggers cause macrophages activation, that secrete cytokines (IL-6, IL-8, TNF-α). That leads to cytokine storm and intensive inflammatory response with high serum ferritin [20], procalcitonin, CRP and ESR levels, leukocytosis, neutrophilia, anemia and thrombocytosis [21,22,23,24]. Because of liver abnormalities that can occur in AOSD the level of liver enzymes can be increased [14]. Our patient met all the criteria (Table 2).

Table 2. Our patient's changes in laboratory tests

Marker	**Our patient's results**	**Norm**
CRP	170,9 mg/l (first day of hospitalization)	<5 mg/l
Leukocytes	28,1 G/l	4,0-10,0 G/l
Neutrophils	16,6 G/l	1,8-7,5 G/l
Red blood cells	3,95 T/l	4,5-6,0 T/l
Hemoglobin	7,5 mmol/l	8,5-11,0 mmol/l
Ferritin	>15 00 ng/ml	23,9-336,2 ng/l

AST	96 U/l	<50 U/l
ALT	95 U/l	<50 U/l
GGTP	222 U/l	<55 U/l
PCT	0,77 ng/ml	<0,05 ng/ml

The poor prognosis of the disease is due to the severe symptoms that occur as complications of AOSD. One of them is reactive hemophagocytic lymphohistiocytosis (RHL), which occurs as a complication of AOSD with a frequency of 12-17% [25], which should be suspected in a constantly feverish patient with initially increased levels of neutrophils and leukocytes. Its development is associated with a cytokine storm.
Another complication is coagulation disorders: disseminated intravascular coagulation (DIC) and thrombotic macroangiopathy. They can complicate the course of the disease mainly in the acute phase. DIC is a complication with a frequency of 1-5% and is manifested by thrombotic events and bleeding from mucous membranes and skin, while the diagnosis of thrombotic microangiopathy suggests a stroke or multiple organ failure. [26]
Lung involvement occurs in up to 53% of AOSD cases [27] and the most common complications associated with this organ are pleural effusion and transient pulmonary infiltrates. [28] There is also pulmonary arterial hypertension and involvement of the heart and liver [26]
Due to the high percentage of side effects in patients, the use of NSAIDs is not recommended, but it is useful for diagnostics. Indomethacin (150–250 mg/day) is considered as the most effective drug in this case. [29]
First-line drugs include high-dose corticosteroids along with adjuvants, and are used in patients with most systemic symptoms. This provokes a clinical response in approximately 60% of patients. [25] Usually they are used at a dose of 0.5-1 mg / kg / day. It should be mentioned that patients treated with prednisone 0.8 mg / kg / day achieve better treatment effects and fewer relapses [29]. Unfortunately, 45% of cases are steroid dependent which can cause serious side effects.
Disease-modifying anti-rheumatic drugs (DMARDS) such as cyclosporine A, methotrexate and leflunomide have been shown to be effective in some cases, but their positive effects are described in too few cases to make them a first-line drug. They are only used when life-threatening complications are present and other medications have failed. [29]

Conclusion

Adult-onset Still Disease to this day poses as a difficult one to be diagnosed. Its symptoms overlap with several other inflammatory diseases with or without infectious origins. This should encourage scientists to seek for proper methods for diagnostics, that could potentially

reduce the amount of misdiagnosed patients, trigger mechanisms and direct methods of treatment.

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