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Adult Onset Still's Disease with Bisitopenia and Very High Ferritine: A Review on Differential Diagnosis and Diagnostic Criteria

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Abstract

Adult Onset Still Disease (AOSD) is the adult form of systemic juvenile arthritis. It is also one of the important reasons of the unknown fever that is a rare inflammatory disease and causes chronic arthritis. Diagnosis of the disease is made by exclusion of infection, malignancy and rheumatologic diseases. Increased ferritin level is very important to predict the disease. We present a 36-year-old male patient with a history of high fever, sore throat, knee pain, lower extremity rash. As opposed to leukocytosis, leukopenia and thrombocytopenia and a high level of ferritin as high as 15,000 were determined and diagnosed as AOSD according to Yamaguchi criteria. We reviewed the literature and presented it with clinical manifestations and differential diagnoses.

Keywords: Adult onset still's disease; High ferritin; Leukopenia; Thrombocytopenia; Negative rheumatoid factor; Negative anti-nuclear antibody

Introduction

AOSD is a rare systemic disease with unknown etiology. It is an inflammatory disease with high spiking fever, arthralgia, transient skin rashes, pharyngitis, lymphadenopathy and nonspecific hematologic findings. It is usually an inflammatory disease with a negative rheumatoid factor and anti-nuclear antibody. The level of ferritin, which is five times higher than the upper limit of the disease, and the glycosylated ferritin level is <20% due to defective glycosylation [1-3]. The annual incidence of AOSD was found to be 0.16 in 100.000 people and it shows distribution including (15 to 25) years and (36 to 46) years of age [4-6]. Although it has been suggested that genetic factors and infections such as *Yersinia enterocolitica* and *Mycoplasma pneumoniae* may be responsible, it is not clear yet which factors or factors are responsible for any patient [7,8]. In one of the previous studies, Human Leukocyte Antigen (HLA) was associated with B17, B18, B35 and DR2, but not in other studies [9,10]. However, twin cases have been reported [11]. First, it is described as Still's disease in children by George Still in 1896, it has become the nominative term for systemic juvenile idiopathic arthritis [12]. Since the features of the disease were similar to those in children with systemic juvenile idiopathic arthritis, it was first described in 1971 as "adult Still's disease" [13]. Clinically, the disease manifests itself in three forms: Monocyclic, intermittent, and chronic. Monocyclic type; it lasts weeks or months and recovers completely within a year. In this process; fever, rash, serocytis and hepatosplenomegaly are seen in patients. Intermittent type; disease can last for weeks and recovers completely in one or two years. Articular symptoms may not present in all AOSD. Chronic type; Articular symptoms are predominant and destructive arthritis may develop through active disease progression [14]. Corticosteroids, Disease-Modifying Anti Rheumatic Drugs (DMARDs) such as Methotrexate (MTX), polyvalent Intra Venous Immunoglobulins (IVIg), biological agents of anti-TNF agents (infliximab, etanercept, and adalimumab), and recombinant antagonist of the IL-1, IL-6 and IL-18 receptor can be used for the treatment of the disease [1].

Case Presentation

A 36-year-old male patient was admitted to the emergency department with high spiking fever, chest and back pain for approximately two weeks and he had mild macular rash that started to fade under his left knee and arthralgia in both knees. Cervical lymphadenopathy was not detected during the physical examination. In respiratory and cardiac examination, respiratory rate was 24 breaths per minute, heart rate was 98/min and blood pressure was 120/75 mmHg (Figure 1). The patient had no remarkable personal or familial history of drug use. In addition, the patient had diffuse

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Table 1: Adult onset Still disease two days after starting, prednisone treatment and some laboratory results for three months.

Laboratory parameters and its normally value	Results before Prednisolone treatment			Results after prednisolone (60 mg) treatment	Results 1 month after discharge
	First day	Second day	Third day		
Leukocyte (3700-10400 cells/microL)	4000	3200	2100	8900	8500
Neutrophil (40%-75%)	71%	-	-	72%	75%
Lymphocytes (16%-49%)	21%	-	-	19%	18%
Eosinophil (0.8%-7.3%)	1.50%	-	-	0.70%	0.80%
Hemoglobine (g/dL)	15.2	14.8	13.6	13.2	18
PLT (149-371 × 10^3 cells/microL)	58 × 10^3	68 × 10^3	78 × 10^3	155×10^3	218 × 10^3
Ferritine (24-336 ng/mL, for man)	15000	-	-	958	120
CRP (0-0.5 mg/dL)	14.7	-	-	1.3	0.03
D-Dimer (0-500)	78900	13200	-	4570	-
CPK (0-190, IU/L)	1084	-	-	185	53
Fibrinogen (180-450 mg/dL)	226	-	-	-	-
LDH (135-225 u/L)	1918	-	-	727	222
Albumin (3.5 -5.2 g/dL)	3.9	-	-	3.5	5.3
AST (0-40 u/L)	228	-	-	98	25
ALT (0-41 u/L)	93	-	-	93	41
RF (0-14, IU/mL)	11	-	-	12	6
ANA (negative)	negative	-	-	negative	negative
GGT (8-61 u/L)	64	-	-	67	19
ALP(40-130 u/L)	62	-	-	56	57
Ürea (10-71 mg/dL)	39	-	-	38	42
Sedimentation (0-20 mm/hour, for male)	31	-	-	25	6

CRP: C-Reactive Protein; CPK: Creatine Phosphokinase; LDH: Lactate Dehydrogenase; AST: Aspartate aminotransferase; ALT: Alanine Aminotransferase; RF: Rheumatoid Factor; ANA: Antinuclear antibodies; GGT: Gamma Glutamyl Transferase, ALP: Alkaline Phosphatase

muscle pain and tenderness, pain and mild swelling in both knees were revealed during the musculoskeletal examination. In abdominal examination, there was no additional finding except that the traube's space was closed. C-Reactive Protein (CRP) was 15 mg/dL (normal: 0 mg/dL to 0.5 mg/dL), Erythrocyte Sedimentation Rate (ESR) was 31 mm/hour, Aspartate Transaminase (AST) was 228 u/L, Alanine Transaminase (ALT) was 93 u/L, glucose was 78 mg/dL, albumin was 3.9 g/dL, Alkaline Phosphatase (ALP) was 62 u/L (40-130), urea was 39 mg/dL (10-71), creatinine was 0.8 mg/dL and Gamma-Glutamyl Transferase (GGT) was 64 mg/dL (8-61), Lactate Dehydrogenase (LDH) was 1918 u/L (135-225) in the patient who transferred from emergency department to internal medicine. The patient was not anemic and had hemoglobin of 15 g/dL, white blood cell count of 3200 cells/microL but platelet count of 58 cells/microL × 10^3 cells/microL was low. Blood, throat and urine cultures were obtained and sultamicillin was started (Table 1).

According to the recommendation of the infectious diseases consultation of the patient whose fever persists; HIV, anti-HCV, HBsAg, brucella (with rose bengal and coombs anti serum), Epstein Barr Virus (EBV) Ig-M and IgG, Parvovirus B-19, rubella IgM and Anti-Cytomegalo Virus (CMV) Ig-M were negative. In addition, Antinuclear Antibody (ANA), anti-ds-DNA, Rheumatoid Factor (RF), anti-SSA and SSB, anti-SCL-70, cANCA, pANCA and Cyclic Citrullinated Peptide (Anti-CCP), HLA-B27, Anti Mitochondrial Antibody (AMA), Liver Kidney Microsomal antibody (LKM), anti-β2-glycoprotein, anticardiolipin antibody and Anti-Smooth Muscle Antibody (ASMA) test results were negative.

The patient had chest pain, nausea and dyspeptic complaints. The D-dimer level was 78,900 (normally range: 0-500 ng/mL) and the ferritin level was 15000 (23 ng/mL to 336 ng/mL) and it was found almost 45 times the upper limit. It was found that there was no feature other than hepatomegaly (180 mm) and minimal splenomegaly (140 mm) when thorax CT, portal vein Doppler USG and abdominal CT were performed in terms of probability of pulmonary embolism, portal vein thrombosis, and endocarditis. Echocardiography results were found within normal limits. The patient had a low white blood cell count for the first two days and β2-microglobulin level was 2259

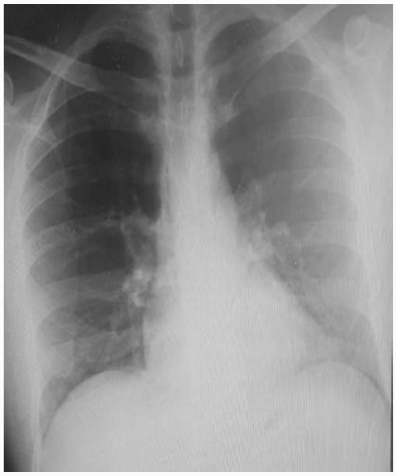

Figure 1: Lung X-ray graphic of the patient within normal limits.

Table 2: Diagnostic criteria for adult onset still's disease.

Yamaguchi criteria	Fautrel's criteria	Cush's criteria
Major criteria	**Major criteria**	(**2 points**)
- Fever >39°, intermittent, >1 week - Arthralgia for at least 2 weeks - Salmon colored rash (trunk/extremities) - Leukocytosis >10 000 (80% granulocytes)	- Spiking fever ≥ 39°C - Arthralgia - Transient erythema - Pharyngitis - Granulocytes ≥ 80% - Glycosylated ferritin <20%	- Fever >39°C - Transiet rush - Leukocytosis >12000+ - ESR >40 mm/hour - Negative RF and ANA - Carpal ankylosis
Minor criteria	**Minor criteria**	(**1 points**)
- Lymphadenopathy - Hepatomegaly or splenomegaly - Abnormal liver function tests - (-) tests for RF and ANA	- Macular or papular rash - Leukocytosis ≥ 10000/mm^3	- Onset age <35 - Prodromal sore throat - RES involvement or abnormal liver function - Cervical or tarsal ankylosis

Yamaguchi's criteria: Five or more criteria are required, of whom two or more must be major. Fautrel's criteria: 4 major criteria or 3 major + 2 minor.
Cush's criteria: Probable AOSD: 10 points with12 weeks' observation, definite AOSD: 10 points with 6 months observation (RES: Reticuloendothelial System)

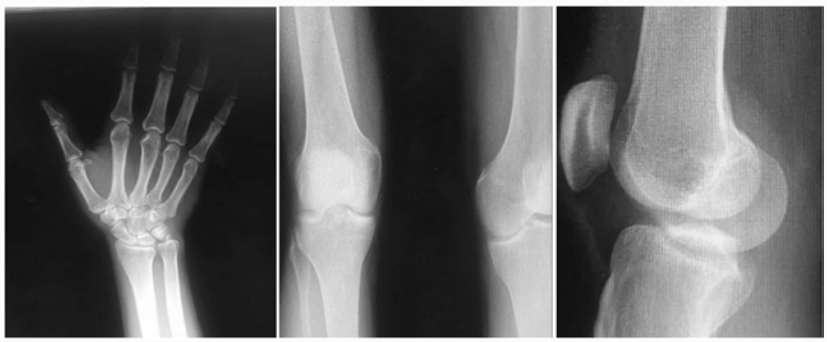

Figure 2: X-ray graphic of the wrist and knees of the AOSD patient (no narrowing of the joint spaces).

(normally range: 604 ng/mL to 2286 ng/mL). Blood smears were normal in white blood cell series, erythrocytes were normocytic normochromic, and platelets were low. The throat, blood and urine cultures were also negative two days later. Eye examination was performed and no pathology was detected in the eye examination. On the following day, the white blood cell and platelet count were again at the lower limit of normal. However, the patient, who had fever persisted, was diagnosed with AOSD according to Yamaguchi criteria on the fourth day of his admission due to lack of positive findings for infections, collagen tissue and other autoimmune diseases and hematological malignancies, and negative ANA and RF (Figure 2). The patient weighed 75 kg and was prescribed only prednisone 60 mg/day since his symptoms were relatively mild. The number of white cells was 8900 cells/microL, LDH was 727 u/L, D-dimer was 13200, ferritin 1410 was ng/mL, AST and ALT were 98 u/L and 93 u/L respectively, platelet count was 155 cells/microL × 10^3 cells/microL and fever regressed to normal levels and knee joint pain was alleviated after 48 h of treatment. The patient was stabilized and followed-up for three days without fever. The steroid dose was planned to be gradually decreased to 16 mg within one month and the patient was discharged. In the first control, it was found that the number of white cells was 8500 cells/microL, ESR was 6 mm/hr, CRP was 0.03 mg/dL, ferritin was 120 ng/mL, platelet count was 218 cells/microL × 10^3 cells/microL, LDH was 167 u/L, AST and ALT were respectively 25 u/L and 41 u/L, and hemoglobin was 17 g/dL. The blood smear was within normal limits and white blood cell was 59%, platelets were normal and clustered, erythrocytes were normochrome normocytic. The patient's hemochromatosis (HFE gene), MEFV gene mutation analysis for FMF, anti β2 glycoprotein, anti-cardiolipin and lupus anti-coagulant test results were found negative. Since the patient had mild left knee pain and hepatosplenomegaly, 15 mg methotrexate was added to the treatment. Methotrexate was used for long-term management and prevention of joint and other organ injury. In addition, the patient had no intolerance such as steroid-induced gastrointestinal system and hypertension, and 8 mg steroid treatment was planned.

Discussion

Genetic factors, infections and environmental factors are suggested to play a role in the pathogenesis of AOSD [7-11]. For the differential diagnosis of the AOSD with various clinical presentations, infections, leukemia, lymphoma, angioblastic lymphadenopathy, autoimmune diseases and neoplastic diseases should be excepted. For the diagnosis of AOSD; cultures, serological tests, hematological profile, radiological imaging and sometimes bone marrow and lymph node biopsy may be required [15]. Although activation of numerous cytokines such as TNF-α, IL-1, IL-6, IL-8 has been suggested in pathogenesis, IL-1β is thought to have the most important role among them [16,17]. In recent years, it has been suggested that CD 64 up regulation and interleukin-18 (IL-18) related macrophage and neutrophil activation have been predictors in the pathogenesis of the disease [18,19]. Commonly, high spiking quotidian fever, which is ≥ 39 degrees fever in the evening and falls in the morning, was seen in AOSD. It can also be accompanied by arthralgia, macular or maculopapular rash and sore throat [20]. Non-pruritic mild macular rash began to fade when patient admitted to the hospital. Our patient had sore throat, and his throat culture was negative. Sore throat is caused by cricothyroid perichondritis [21]. Throat culture and viral serological analyzes are negative in AOSD cases and do not respond to antibiotic therapy [22,23]. AOSD is a non-rash, non-pruritic, transient macular, maculopapular or proximal extremity with koebner's phenomenon known as pressure and trauma [24]. Joint involvement can involve knees, ankles, elbows and wrists. When the hand joints

were affected, carpometacarpal narrowing occurs characteristically. When the fluid of these joint is examined, it carries neutrophilic characters [9,25,26]. In our patient, there was mild pain in both knee joints and wrist and there was no pathology on wrist radiography. In our patient, there was mild pain in both knee joints and wrist and there was no pathology on wrist radiography. Lymphadenopathy, which was reported in 44% to 90% of the lymphoma, was not found in our patient. Hepatomegaly and splenomegaly, which are commonly detected in AOSD, were also present in our patient, 180 mm and 140 mm in dimensions, respectively. Some patients may be accompanied by fever, abdominal pain and mesenteric lymphadenopathy requiring exploratory laparotomy for diagnosis. In the abdominal CT of our patient, hepatosplenomegaly was seen as in previous study [9]. AOSD may be confused with Kikuchi's syndrome, Sweet's syndrome, Familial Mediterranean Fever (FMF) and TNF Receptor Associated Periodic Syndrome (TRAPS) and vasculitis [1]. Especially in the cervical posterior nodes were seen in almost 100% of patients with Kikuchi syndrome and nodes were also seen in axillary, mediastinal, mesenteric, inguinal, celiac, and peripancreatic region [27,28]. Sweet's syndrome includes inflamed papules, plaques, nodules, leukocytosis with fever and edema in the face, arms and legs. However, in our patient, there was no leukocytosis and no skin findings were seen in this syndrome. On the other hand, FMF is a disease with a familial history of acute synovitis with abdominal pain, peritonitis, pleuritis, and fever persists for 1 to 3 days. In addition, MEFV genetic analysis of the patient was negative. A TRAP is usually a childhood disease with ocular involvement and persistent fever [1]. ESR and ferritin levels are elevated in AOSD that accompanied by neutrophil-dominated leukocytosis and more than 400,000 PLT counts. In the present case, there was leukopenia and thrombocytopenia and no anemia. This finding suggests Macrophage Activation Syndrome (MAS) in the first step. Although bone marrow aspiration and biopsy were required to determine whether the patient has MAS or not, the patient had no anemia, lymphadenopathy, coagulopathy and absence of pulmonary and renal involvement, and leukocyte and PLT counts were below normal limits for the first three days but responded to prednisolone treatment so bone marrow aspiration and biopsy were not needed. RF and ANA test were negative in the present case. In AOSD, the ferritin level, which is generally expected to be more than five times higher than the upper limit, was 15000 (range: 23 ng/mL-336 ng/mL) which was not common in AOSD. This ferritin level decreases as disease activity decreases. Ferritin levels may also increase in hemochromatosis, leukemia, lymphomas and infections. Therefore, a glycosylated ferritin level of <20% is a more specific marker for AOSD diagnosis. However, we could not do this marker because there was not marker in our central laboratory. Although, Glycosylated ferritin level is 20% to 50% in infections, this level decreases under 20% in patients with AOSD [1]. In our patient, cultures and serological tests were negative in terms of infection, and all exons of the HFE gene for hemochromatosis were normal, and no pathology could be detected in abdominal CT that could indicate both hemochromatosis and malignancy. It is well known that Radiographs may not be very illuminating in the acute phase of the disease. The evaluation of the knee and hand radiographs of our patient as normal shows that the joints were not radio graphically affected yet. The classic radiographic findings about AOSD, which can progress to ankylosis, are nonerosive narrowing of the carpometacarpal and inter carpal joint spaces. Radiographic abnormalities are generally seen in about 40 percent of patients. Early in AOSD, the radiographs are typically normal or shows soft tissue swelling and sometimes joint effusions [9,29]. The diagnosis of AOSD is difficult as it has various nonspecific symptoms. AOSD can be diagnosed after exclusion of infections mentioned above (such as Cytomegalovirus, Epstein-Barr virus, HIV, and Parvovirus), malignancies, connective tissue diseases (such as systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, and Takayasu's arteritis) and granulomatous diseases (such as Crohn's disease and Sarcoidosis). Although the diagnosis is mostly made according to Yamaguchi criteria, it is also diagnosed according to the Fautrel and Cush criteria [1,30] (Table 2).

The patient we presented according to Yamaguchi criteria had 2 major criteria (fever and arthralgia) and other minor criteria except lymphadenopathy. Corticosteroids, Disease Modifying Anti Rheumatic Drugs (DMARDs), such as Methotrexate (MTX), azathioprine, cyclosporine, and cyclophosphamide are used in the treatment of the disease. In addition, anti-TNF agents (infliximab, etanercept, and adalimumab), recombinant antagonist of the IL-1, IL-6 and IL-18 receptor can be used [1].

Conclusion

AOSD is a disease that is difficult to diagnose and can be confused with many diseases, and it may accompany with leukopenia and thrombocytopenia as in the presented case. It should be considered that the early diagnosis is very important.

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