A rare presentation of adult onset Still's disease in an elderly patient

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Abstract

Adult onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology that usually affects young adults. Very few patients older than 70-year-old have been reported. Clinical features include quotidian fevers, arthralgias, arthritis, pharyngitis, lymphadenopathy and an evanescent rash. AOSD should be considered in the differential diagnosis of fever of unknown origin. Early diagnosis is often difficult since it is a diagnosis of exclusion and the presence of infectious, neoplastic and autoimmune conditions needs to be ruled out before the diagnosis is made. No specific laboratory tests are available to aid in the diagnosis of AOSD. As a result, a set of diagnostic criteria that define the clinical features of this condition, termed the Yamaguchi criteria, have been most commonly used to establish the diagnosis. We describe the case of a 72-year-old Caucasian male with past medical history significant for generalized anxiety disorder, depression, BPH, and hypertriglyceridemia, ho was evaluated at a tertiary institution for profound generalized weakness and weight loss that started three weeks prior to his initial presentation. Initial laboratory studies showed leukocytosis, elevated ESR, CRP, ferritin and liver dysfunction. Cultures, ANA and rheumatoid factor studies were negative. The patient underwent further extensive workup that excluded the presence of infectious, neoplastic and autoimmune disorders and was subsequently diagnosed with AOSD and new onset diabetes mellitus. For the management of AOSD he was started on prednisone with significant improvement in markers of inflammation, symptoms and level of function.

Case Report

A 72-year-old Caucasian male with past medical history significant for generalized anxiety disorder, depression, BPH, and hypertriglyceridemia presented with profound generalized weakness, significant weight loss of 30 lbs, fever and arthralgia of three weeks duration. Physical exam was significant for apparent muscle weakness, lethargy, 2 + edema of the hands and 1+ edema of the lower extremities. Initial vital signs included temperature 38.2 C, pulse 95 beats/min, respiratory rate 16 breaths/min, blood pressure 103/67, oxygen saturation 97% on room air. Blood cultures obtained upon admission showed no growth. Chest X-ray revealed no acute cardiopulmonary process. Urinalysis revealed trace bacteria, WBC3-4 HPF, glucose >1000 mg/dL, protein 30 mg/dL, rare epithelial cells. Laboratory studies included sodium 132 mEq/L, potassium 3.8 mEq/L, chloride 95 mEq/L, carbon dioxide 26 mEq/L, glucose 384 mg/dL, BUN 20 mg/dL, creatinine 0.9 mg/dL, calcium 8.6 mg/dL, GFR 83 mL/min, albumin 2.4 gm/dL, lipase 125 IU/L, amylase 162 U/L, WBC 23.2 thou/cumm, 91% polys, RBC 4.32 mill/cumm, Hgb 13 gm/dL, Hct 39%, MCV 89 FL, platelet count 365 thou/cumm. EBV IgG level was 4 and EBV IgM level was 0.1, suggestive of latent infection. CMV IgG results were also elevated, again suggesting latent exposure. Liver function tests on admission were within normal limits with the exception of elevated AST level at 56 IU/L. Sedimentation rate was elevated at 59 mm/hr. Rocephin treatment was initiated upon presentation but was discontinued on day three since it was speculated that the presence of an infectious process was not likely. Two days after discontinuation of the antibiotic, repeat blood cultures were drawn and showed no growth. Due to the elevated lipase and amylase levels an ultrasound of the abdomen was performed and revealed normally defined and homogeneous pancreas, with no edema or enlargement to suggest pancreatitis. The liver appeared slightly heterogeneic, with a prominent gallbladder wall thickening ranging between 4-9mm. No stones, sludge or debris were noted. The biliary tree appeared normal. To rule out an intra-abdominal source of infection a Computed tomography (CT) of the abdomen was performed and showed cholelithiasis and multiple calcifications within the spleen likely related to granulomatous changes. The liver, pancreas and the adrenal glands appeared unremarkable. There was mild distention of loops of small bowel. CT pelvis showed inflammatory changes at the level of the presacral fat and a small amount of free fluid which was thought to present proctocolitis. The patient later underwent flexible sigmoidoscopy which showed diverticulosis and no evidence of colitis. Due to episodes of hypoxemia, a CT thorax was obtained and showed no evidence of pulmonary embolism. Small bilateral pleural effusions with associated compressive atelectasis were present. CT head showed no intracranial hemorrhage. Cerebral atrophy and chronic white matter microvascular ischemic changes were appreciated. Four days after admission the patient's liver function started to deteriorate. Labs revealed alkaline phosphatase 238 IU/L, total protein 5.2 gm/dL, AST 111 IU/L, ALT 88 IU/L, direct albumin 2.2 gm/dL. At that time WBC and platelet count continued to trend up. Peak WBC level was at 34.2 thou/cumm, and maximal platelet count of 792 thou/cumm. Hepatitis panel showed no active infection. Complement C3 and C4 levels were within normal limits. Plasma cryoglobulin levels were negative. Peripheral blood smear showed normocytic, normochromic anemia, with left shift and thrombocytosis. In the absence of inflammatory condition myeloproliferative disorder had to be excluded. Protein electrophoresis was noncontributory. No abnormal proteins were detected on immunofixation for IGG, IGA, IGM, Kappa or Lamda-type proteins. There was no evidence of monoclonal gammopathy. WBC alkaline phosphatase was elevated at 378. Folate and B12 levels were within normal limits. Bone marrow biopsy showed hypercellular marrow with myeloid hyperplasia and mild plasmacytosis. Flow cytometry did not detect any monoclonality in the plasma cells, thus the plasmacytosis was consistent with reactive finding. The myeloid hyperplasia was consistent with reactive pattern as well. No BCR/ABL transcripts or JAK2 mutation were detected. Rheumatoid factor and anti-nuclear antibody screen were negative. Ferritin level was significantly elevated at 2368 ng/mL. LD level was 175 IU/L. ANCA panel for vasculitis, Cyclic citrullinated peptide and Aldolase results were noncontributory. Echocardiogram revealed well preserved global and regional left and right ventricular systolic contractile function with a new onset pulmonary hypertention. High-resolution CT chest revealed moderate-sized bilateral pleural effusions which had increased in size. Pleural fluid examination revealed reactive mesothelial cells and mixed inflammatory cells. After the above mentioned laboratory and imaging studies aided in excluding the presence of neoplastic, autoimmune and infectious process the patient was diagnosed with AOSD. After the initiation of corticosteroids the parient's clinical condition and markers of inflammation dramatically improved.

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Discussion

AOSD is a systemic inflammatory condition of unknown etiology. It has been hypothesized that infections agents could trigger the condition. A number of viruses, including Epstein-Barr virus, cytomegalovirus, hepatitis B, C and parvovirus B19 have been implicated.[1-5] In the case that we describe, even though EBV and CMV titer results showed the presence of latent infection, no causal relationship could be established. AOSD predominantly affects young adults between 16 and 35 years of age.[1,5] A limited number of cases in the elderly have been reported.[6-8] Patients often present with fever (usually higher than 39C), evanescent rash, lymphadenopathy, sore throat, arthralgia, myalgia, arthritis and serositis.[1-4,9] In contrast, our patient presented initially with profound fatigue and weight loss.

There are no definitive laboratory tests available to aid in establishing the diagnosis of AOSD. Liver abnormalities have been described in up to75% of cases.[3] Rheumatoid factor and antinuclear antibody tests are usually negative.[1,5,9] Just as in the case that we describe, markers of inflammation such as ESR and CRP are often elevated.[1-4,9] White cell counts greater than 20×10^9 cells/L are observed in only close to 1/3 of the patients.[1] Anemia of chronic disease and thrombocytosis have also been reported.[1-3] Ferritin levels of 1000 ng/mL and above in combination with other clinical criteria have been used to imply the diagnosis of AOSD.[1] Glycosylated ferritin fraction has been reported to be an even more specific marker of disease than ferritin level.[1] The level of glycosylated ferritin usually drops to <20% in patients with AOSD.[1,2,7] Pleural effusions and respiratory failure have been observed in patients with AOSD.[1,8] In the case that we describe, CT of the thorax revealed bilateral small pleural effusions. AOSD is a clinical diagnosis. Neoplastic, infectious and autoimmune conditions need to be ruled out before the diagnosis is reached. The Yamaguchi criteria have been used to aid in the diagnosis (Table 1). Their sensitivity is above 93% and their specificity is approximately 92.1%.[1-5,9] Their sensitivity is above 93% and specificity 92.1%.[1,2] The clinical course of the disease can be grouped into a self-limited, intermittent or chronic articular pattern.[1,2] The self-limited pattern is characterized by one disease flare and a remission within a year from that episode. The intermittent pattern involves recurrent flares with remission between flares that can last up to several years. The chronic articular pattern involves articular manifestations that could lead to joint destruction.[1,2] Even though the prognosis is generally favorable, cases of AOSD leading to multiorgan failure and death have also been reported.[4,8,9]

No guidelines for the treatment of AOSD have been established due to the rarity of the condition and the lack of clinical trials. Treatment modalities available include the use of NSAIDS, steroids, immunosuppressants and biological agents.[1,4,9] The use of NSAIDs alone in the treatment of AOSD is effective in a limited proportion of patients. Most patients are placed on steroids at some point in the course of their disease. Prednisolone should be considered initial treatment choice in patients with elevated liver enzymes, pericarditis, serositis and persistent anemia.[3] The patient in our case responded to prednisone within two days of administration. He was able to ambulate, his fevers resolved and his markers of inflammation improved. Patients who do not respond to treatment with NSAIDs or steroids are often placed on antirheumatic drugs. DMARDs that have been used include methotrexate, cyclosporine and azathioprine. In the event of failure of the above mentioned drugs, biologic agents such as infliximab, etanercept, anakinra and rituximab have been used by some clinicians.[3,4]

Table 1. Yamaguchi criteria.

Major criteria	
	WBC > 10,000 (>80% granulocytes)
	Arthralgia, >2 wks
	Rash-nonpruritic, maculopapular
	Fever >39C, intermittent >/= 1 wk
Minor criteria	
	RF and ANA negative
	Lymphadenopathy and/or splenomegaly
	Abnormal liver function test
	Sore throat

Before establishing diagnosis exclude inflammatory disease, infection, neoplasm, autoimmune conditions; need 5 criteria for diagnosis (at least 2 major criteria).

Conclusions

AOSD is an uncommon systemic disorder that primarily affects young adults. The classical disease presentation includes evanescent rash, sore throat, fever and arthritis. Herein we have described an unusual presentation of AOSD in an elderly male. The diagnosis is that of exclusion. The presence of a constellation of clinical criteria along with elevated ferritin levels can aid in the diagnosis of this entity. Treatment options include NSAIDS, steroids and antirheumatic drugs.

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