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Work up of Fever of Unknown Origin: A case of Adult Onset Still's Disease

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ABSTRACT

Fever of Unknown Origin (FUO) is frustrating for both patient and physician because the diagnostic workup involves numerous noninvasive and invasive procedures that sometimes fail to explain the fever. The condition is a diagnostic challenge and results in significant number of referrals to tertiary care centers. We report here a case of 53 years old male who had continuous fever for 5 months which remained undiagnosed despite thorough investigations. The clinical picture evolved in to a constellation of clinical and laboratory findings which fit Yamaguchi's criteria for Adult Onset Still's Disease. Extremely high levels of serum ferritin (> 16,500 ng/mL) helped us diagnose the condition with confidence. Our patient responded to naproxen. This case highlights the importance of keeping all the differentials in mind and giving due consideration to the evolving clinical features while treating a patient of FUO.

Keywords: Adult-Onset/diagnosis, Diagnosis, Differential, Fever of Unknown Origin, Still's Disease.

INTRODUCTION

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3°C (100.9 °F) on several occasions and lasting longer than 3 weeks, with a diagnosis that remains uncertain after one week of investigation in a hospital or outpatient setting[1]. FUO can be frustrating for patients and physicians because the diagnostic workup often involves numerous noninvasive and invasive procedures that sometimes fail to explain the fever. The condition is a diagnostic challenge and result in a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the FUO to be mainly secondary to infectious, neoplastic or inflammatory diseases[2,3].

Adult Onset Still's disease (AOSD), an important cause of FUO, lacks specific clinical or laboratory findings. Therefore AOSD warrants high level of suspicion on the part of the treating physician. Moreover AOSD is a diagnosis of exclusion and demands thorough work-up of the patient for various infections, inflammatory conditions and malignancies. We present one such patient which was evaluated as FUO and eventually diagnosed as AOSD.

CASE REPORT:

A 53 years old male presented with sore throat and moderate grade fever (up to 103°F) of 2 weeks duration. He had no other complaints and his past medical history was insignificant. His general and systemic examinations were unremarkable for causes of fever. Routine investigations results were as given in Table 1. Chest x-ray was normal, blood culture was sterile and Montoux Test was negative (8mm). He was treated with combination of cefpodoxime and ofloxacin with anti-pyretics. After a week, there was slight improvement in general condition, with fever occurring only in the evening every day. Ultrasonography of the abdomen revealed enlarged fatty liver. The same

treatment was continued for the next week after which the patient was discharged.

On second follow-up few weeks later, the patient continued to have moderate to high grade fever with chills and increasing exhaustion. He also reported body pains, bilateral knee pain with left knee swelling, stiffness and pain in wrist joint and fingers, difficulty in buttoning and unbuttoning of his shirt, difficulty to sit on the toilet seat. Anti-streptolysin titer and rheumatoid factor were negative. He was prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. Fever persisted up to 102^0F.

The patient lost follow-up to come back after three and half months with toxic looking appearance. He was hospitalized with fever going up to 103^0F with chills and rigors, anorexia and weight loss, pain over knee and shoulder joint, pain left temporal region and left ear. General physical examination revealed bilateral axillary lymphadenopathy more on left side and bilateral inguinal lymphadenopathy, liver enlarged 3cms below the right costal margin and spleen tip was felt. No evidence of skin rash, clubbing or bony tenderness was found. Widal test showed no increase in titers on serial estimations. Cardiovascular and respiratory examination were normal. Joint examination revealed mild swelling of left elbow joint with local tenderness. No clinical signs suggestive of infective endocarditis were found. Peripheral blood film for malarial parasite, anti-Human Immunodeficiency Virus antibody 1 and 2, Hepatitis B surface antigen, anti-Hepatitis C viral antibody and dengue serology were negative. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibody were negative with serum adenosine deaminase 27.50 U/l (normal <15 U/l). The only abnormality seen on ultrasound abdomen was enlarged fatty liver, as was seen previously as well. Computed tomography (CT) head to look

especially for petrous temporal bone revealed no abnormality. Electrocardiogram showed sinus tachycardia and 2 dimensional-echocardiography was normal with no signs suggestive of infective endocarditis.

Serum protein electrophoresis showed raised alpha-1 and alpha-2 globulins, suggestive of acute/subacute inflammation. CT chest was normal. CT abdomen showed mild hepato-splenomegaly (liver span 15.5 cm and spleen span 12.3 cm), few periportal, precaval, para-aortic and bilateral inguinal lymphadenopathy and a small left renal calculus. Left axillary lymph node biopsy had features suggestive of reactive proliferative changes. Bone marrow examination was performed next which showed a normoblastic marrow with mild myeloid hyperplasia.

Our patient satisfied six of the Yamaguchi's diagnostic criteria for AOSD, with three of them being major. Serum ferritin was >16,500 ng/mL. As a result all antibiotics were stopped and the patient was treated with naproxen 500 mg and other supportive care. The patient gradually recovered from his fever and articular symptoms with increasing sense of well being. After 6 months of treatment his serum ferritin value fell to 262.90 ng/mL and had no symptoms of fever.

DISCUSSION:

AOSD is a rare inflammatory disorder of unknown etiology characterized by high spiking fever, evanescent rash, arthritis, and multiorgan involvement[4]. The diagnosis is that one of exclusion and differential diagnosis includes infections, neoplastic, and autoimmune disorders. Although there are several sets of diagnostic criteria for AOSD, Yamaguchi's criteria present with the highest sensitivity (93.5%)[5]. (Table 2) The annual incidence is approximately 0.16 cases per 100,000 person-years and is slightly higher in women[6]. A retrospective

analysis by Mert et al of all FUO patients admitted in a hospital over a period of 18 years found 15% of FUO patients eventually being diagnosed as AOSD[7]. In the study 100% of AOSD diagnosed patients had fever, 90% had arthralgia, 85% had rash and 75% had sore throat[7].

The classic rash of AOSD is an evanescent, salmon-colored, macular or maculopapular eruption that tends to occur with the fever, involving primarily the trunk and extremities. This rash may be difficult to appreciate in patients with darker skin color, probably the reason why this rash has been less frequently reported in India as compared to patients in the west[8]. Athralgia, arthritis and myalgia are very commonly seen in AOSD with symptoms starting mildly, progressing over months and sometimes progressing to destructive polyarthritis. Knees, wrists, ankles and elbows are the most commonly involved joints and the synovial fluid is usually inflammatory. Hepatic abnormalities seen in patients with AOSD may be confused with salicylate toxicity as many of these patients receive salicylate therapy. However, elevated liver enzymes have been reported prior to the use of salicylates in AOSD patients[9]. Lymphadenopathy is seen in half of the patients and the clinical picture with fever and high white cell count may create a diagnostic confusion with lymphoma. Lymph node biopsy is helpful in these cases. Reactive hemophagocytic syndrome (RHS) is a rare, life-threatening, and little-known complication of AOSD which is characterized by fever, pancytopenia, liver failure, coagulopathy, and neurologic symptoms[10]. RHS is diagnosed by the presence of bone marrow full of numerous, well-differentiated macrophages (histiocytes) that are engaged actively in the phagocytosis of hematopoietic elements[11]. RHS when happens in the setting of AOSD is termed macrophage activation syndrome.

A variety of laboratory findings are seen in AOSD but none are specific to the

disease. However, a constellation of laboratory findings with abovementioned clinical features should alert a physician of a possibility of AOSD. Elevated erythrocyte sedimentation rate, leucocytosis with high neutrophil count, hypoalbuminemia, normocytic normochromic anemia, elevated liver enzymes are some of the commonly seen laboratory abnormalities[12].Although serum ferritin is an acute phase reactant, high levels of seru, ferritin has been strongly associated with AOSD[13]. The combination of glycosylated ferritin level 20% or less with ferritin five times normal produced a sensitivity of 43% and specificity of 93% in the diagnosis of AOSD[14]. We could not obtain glycosylated ferritin levels in our patients due to the lack of laboratories performing this investigation. Rheumatoid factor and anti-neutrophilic antibody are usually negative in AOSD. Radiographic abnormalities are seen very late, if at all, in the course of the disease, most commonly being nonerosive narrowing of the carpometacarpal and intercarpal joint spaces of the wrist.

Initial therapy should be based upon the degree of disease activity, including the extent and severity of organ system involvement. Patients with mild disease such as fever, rash, arthralgias are treated with NSAIDS[15] Patients not responding to NSAIDS alone should receive corticosteroids[15].

Steroids should be the first line drug if the initial presentation of the patient includes high grade fever, arthralgia or multiple organ involvement. Gradual tapering of steroids to a lowest minimal dose should be attempted once remission has been achieved. Disease modifying antirheumatic drugs (DMARD) has been shown to be effective when AOSD is not controlled with at least two months of steroid therapy.[15] Biological agents like infliximab (anti-tumor necrosis factor-α antibody), etanercept (tumor necrosis factor-α receptor blocker),

tocilizumab (interleukin-6 receptor antibody), canakinumab (interleukin-1 beta inhibitor) have recently been shown to be effective in patients with disease that is refractory to usual therapies include rituximab (anti-CD20 monoclonal antibody), rilonacept (interleukin-1 inhibitor), intravenous immune globulin, and cyclosporine[15].

Table 1. Results of investigations of patient done on presentation and on subsequent visits.

Investigation	On presentation	After 1 week	After 2 weeks	After 3 months
Hemoglobin (gm%)	11	11	11	10
Total leucocyte count ($x10^3$/cumm)	20	18.7	17	25.3
Percentage of neutrophils	83%	70%	90%	90%
Platelets ($x10^5$/cumm)	2.7	2.5	2.6	2.8
Peripheral blood film	Microcytic, hypochromic RBCs, Neutrophilia with no toxic granulation, platelets normal	Not performed	Not performed	Normochromic, microcytic picture with leucocytosis.
Erythrocyte Sedimentation Rate (mm 1^{st} hr)	90	95	90	110
C-reactive protein (mg/l)	Negative	Negative	Negative	110
Urine routine examination	NAD	NAD	NAD	NAD
Renal function test	NAD	NAD	NAD	NAD
Liver function test	NAD	NAD	NAD	NAD
Malaria parasite	Negative	Negative	Negative	Negative
Chest x-ray	NAD	NAD	NAD	NAD
Blood culture	Sterile	Sterile	Sterile	Sterile
Montoux test	Negative	Negative	Negative	Negative

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

Major	Minor
Fever of at least 39 °C for at least one week	Sore throat
Arthralgias or arthritis for at least two weeks	Lymphadenopathy or splenomegaly
Nonpruritic salmon colored rash	Abnormal liver function tests
Leukocytosis (10,000/microL or greater), with 80% polymorphonuclear cells	Negative tests for antinuclear antibody and rheumatoid factor
(Diagnosis: Any five should be present; atleast two should be major.)	

CONCLUSION

This case report highlights the difficulty experienced by internists and rheumatologists in reaching a conclusive diagnosis of AOSD. AOSD is an important cause of FUO and early diagnosis is possible if the treating physician can join different pieces of the puzzle.

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