CHRONIC FEVER WITH SEVERE WEAKNESS - A CASE REPORT

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Abstract:

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown etiology and pathogenesis that presents in 5 to 10% of patients as fever of unknown origin (FUO) accompanied by systemic manifestations. We report an interesting case of a 63-year-old Bangladeshi male who presented with one-month duration of FUO along with, severe weakness, oral thrush, high WBC count, low RBC count and low hemoglobin concentration. After extensive workup, potential differential diagnoses were ruled out and the patient was diagnosed with AOSD based on the Yamaguchi criteria. The case history, incidence, pathogenesis, clinical manifestations, differential diagnoses, diagnostic workup, treatment modalities, and prognosis of AOSD are discussed in this case report.

Key word: *High fever, Neutrophilic leukocytosis , ferritin ,steroid, Adult onset Still's disease*

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Introduction

Fever of unknown origin (FUO) is a clinical picture worldwide which needs both knowledge and experience to determine its etiology. It was first described by Petersdorf and Beeson in 1961.[1] This definition requires a fever higher than 38.3C on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week's investigation in hospital.[2] The main etiologic categories of FUO are infections, neoplasm, connective tissue diseases, miscellaneous diseases and undiagnosed.

Adult-onset Still's disease (AOSD) is a rare auto inflammatory disorder of unknown etiology, which was initially described in adults by Eric Bywaters in 1971, who also coined the term (AOSD) due to the disease's close resemblance to a pediatric syndrome described by Dr. George Still in 1899, currently known as systemic juvenile idiopathic arthritis (sJIA)[3] AOSD is characterized by high spiking fever, arthralgia or arthritis, sore throat, transient maculopapular rash, lymphadenopathy, hepato-splenomegaly, and serositis. Patients may or may not have all of the above symptoms at initial presentation. AOSD is one of the most frequent aetiologies of FUO. The disease has non-specific clinical features and mimics bacterial infections. It's mysterious and found worldwide. It can appear and disappear suddenly. It is difficult to diagnose. The purpose of this case report is to describe the FUO that can initially mislead diagnosis and to review the literature about AOSD from a primary care perspective.

A medical bill was sent to me for verification. There was a disparity between patient's statement and hospital discharge letter. Hospital discharge letter write down Enteric fever as diagnosis but patient state that his fever continued despite treatment in hospital for 15 days. So I went through the case to find out the cause of fever.

Case Report:

A 63 years old man presented with low grade fever for one month. Fever rises in the evening and low in day time and he was taking conventional antipyretic medicine. But fever continued and one month later it suddenly goes up. He became unconscious and admitted in nearby hospital under supervision of a medicine specialist. At the time of admission he also complained of anorexia, profound weakness, vertigo, tinnitus, muscle cramp, oral ulceration, profuse productive cough and constipation. But he has no headache, neck

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rigidity, joint pain, rash, rigor, shivering, night sweating, loin pain or dysuria. General examination revealed normal blood pressure, pulse 76/min, weight 59kg, tongue coated and ulcerated. Many medical tests were done repeatedly to find out the cause of pyrexia. His cardiac, pulmonary, and abdominal examinations were normal and there was no evidence of arthritis or rash. The patient's past medical history were unremarkable.

Initial complete blood picture (CBP) analysis performed before hospital admission and demonstrated neutrophilic leukocytosis (total white blood cells $15x10^9/\mu L$; 70% Neutrophils, 16% Lymphocytes, 14% Monocytes, hemoglobin 12.6 gm /dl, ESR 92/1st hour, RBC 4.42/µL, total platelet count $480X10^9$ /µL). Ten days after admission, laboratory tests showed that hemoglobin 10.9 gm /dl, total leukocytes $33.2 \times 10^9/\mu l$, Neutrophils 80%, platelets $599 \times 10^9/\mu l$, ESR 110 mm/1st hour, Na^+ 134 mmol/l, K^+ 3.8 mmol/l, AST 38 U/l, ALT 14 U/l, serum creatinine 0.89 mg/dl. Thyroid profile was normal. He was empirically treated with intravenous Ceftriaxone, tablet Chloroquine and Doxycycline after cultures of blood, urine, and cough were obtained. Extensive investigations were done to exclude an infectious cause. All were negative including a normal x-ray chest. Sputum for acid-fast and gram stains were negative (2 times). Serological tests for Enteric fever, Q fever, spotted and typhus fever and influenza found negative. ICT for Malaria was negative. Table (1,2,3,4) showed the test report serially.

USG of abdomen and pelvis showed mild hepatomegaly and enlarged prostate. He stayed in hospital for 15 days and treated with Mebendazole, Clonazepam, Montelukast, Levo salbutamol and intravenous infusion of normal saline. Despite extensive medical treatment his fever remained as before. He became weaker and exhausted. His hemoglobin level went down from 12.6mg/dl to 9.4mg/dl. His ESR, WBC count, total platelet counts progressively increased. After consultation with the internist he was discharged from the hospital and remain drug free for 4 days. He was instructed to return to internist for follow- up.

He was readmitted after 4 days with persistent fever for 45 days that did not respond to acetaminophen. He lost 6 kg weight within 15dys, persistent high total WBC count, severe generalized weakness, occasional dry cough, anorexia and oral thrush. Physical examination did not reveal any new findings. At this stage an autoimmune disorder was considered and serum ferritin was measured.

The list of laboratory tests performed during the second admission are shown in Table (1,2,3,4) . His hemoglobin level was 10.8gm/dL and serum ferritin level was 1490ng/ml (normal value is 32-501ng/ml). Urine sent for Ziehl–Neelsen staining and acid fast bacillus not found. No growth found in urine culture. After admission in hospital, he was treated with intravenous Ceftazidime 1gm and Amikacin 500mg 8 hourly, Inj. Betamethasone, cap. Fluconazole. Fever subsided. He was transfused 2 units fresh cross matched human blood for anemia. After blood transfusion his hemoglobin level raised from10.9gm to 12.2gm /dl, WBC count came down from $40x10^9/\mu L$ to$16.2x10^9/\mu L$. Serum TSH is 1 µgm/dl. No abnormality detected in routine urine examination. USG showed enlarged prostate, calyectasia (left), extra renal dilated pelvis. X-ray KUB region found normal. After 7days, serum ferritin level was 1350 ng/ml. After an extensive negative infectious disease evaluation, a diagnosis AOSD was made. [4] Chronic low grade fever, cough, extreme fatigue, oral ulceration with high fever spikes, neutrophilic leukocytosis, high ESR and elevated ferritin level fulfilled the Yamaguchi criteria for AOSD [3]and criteria proposed by Pouchot [5] in 1991. Initially Betamethasone was given intramuscularly, later on therapy was switched over to oral Betamethasone. For oral thrush, fluconazole 150mg daily for 5days. The patient was discharged 8 days after hospitalization on a steroid Betamethasone 15 mg over a 5 days' period. He noted some degree of weakness at the time of discharge. Patient came in follow up visit and found well.

Laboratory evaluation:

Table-I

Serial change in complete blood picture

Blood analysis	Before admission	After 12 days	Day 15	Day 18	Day 22	Day 23	Day 24	Day 25	Day 26
Hb%	12.6g/dl	10.9	9.5	9.4	10.8				12.2
ESR	92	110	97	110	65	Steroid			76
t WBC*	15000	33200	36100	36000	40000				16200
t RBC*	4.42	3.65	3.3	3.4			Blood	Blood	
TPC*	480000	599000	707000	597000	300k/		transfused	transfused	688k/l
Nutrophil	70%	80%	84%	79%	80%		1unit	1unit	89%
Eosino	14%	12%	9%	14%	2%				0%
HCT	39.2%	32.5%	30%	28%	34%				37%

*total WBC count, total RBC count, total Platelet count, Nutrophil, Eosinophil

Table-II

Results of Biochemistry & Immunological test

Name of test	Before admission	Day of Admission	Day 4	Day 17	Day 23
Triple antigen test					
Widal test	NAD				
Weil Felix test	NAD				
Brucella	NAD				
ICT for Malaria			Negative		
Sputum for AFB	No found (1st sample)	No found (2nd sample)			
Serum Electrolytes	Na+ 133 K+ 5.1 Cl - 95 Co2 28			Na+ 126 K+ 4.5 Cl - 90 Co2 27	
Serum bilirubin	12 µmol/L				
Serum TSH	1.95 µIU/ml				1 µIU/ml
SGPT	38 U/L				
Serum Creatine	0.89mg/dl			1.2	
Serum Ferritin				1490 ng/ml	1350 ng/ml

Table-III

Serial change in urine analysis.

Name of test	Before admission	Day 12	DAY 18	Day22	Day26
Urine RME	4-6/HPF	20-25/HPF		10-15/HPF	3-4/HPF
Culture		No growth		No growth	
Blood culture	No growth				
Urine for ZN stain			AFB not found		

Table-IV

Serial change in imaging tests

Name of test	Before admission	Day 8	Day 21	Day 23
X-ray chest	NAD			
USG		Hepatomegaly, enlarged prostate	Calyectasia, Extra renal dilated pelvis(right)	
X-ray KUB				NAD

Table-V

*Yamaguchi criteria**

Major Criteria	Minor Criteria	Exclusion Criteria
• Arthralgia, >2 weeks	• Sore throat	• Infection, especially sepsis
• Fever, >39°C, intermittent ≥1 week	• Lymphadenopathy	• Epstein-Barr infection
• Typical rash (macula popular, nonpruritic)	• splenomegaly or hepatomegaly	• Malignancy
• WBC >10,000 (>80% granulocytes)	Abnormal liver function test	• Inflammatory disease
Elevated ferritin level	• Rhematoid factor and ANA negative	

Discussion:

Adult-onset Still disease (AOSD) is a rare systemic inflammatory disease that usually affects young adults,[2,6] although it can also be seen among the geriatric population.[2,5-7] The annual incidence is estimated at 0.16 cases per 100,000 population.[5] It affects women [2,6] more often than men. Prevalence is estimated at 1.5 cases per 100,000-1,000,000 population.[6] There is a bimodal age distribution with one peak incidence between ages 15–25 and a second peak between ages of 36–46 years.[7]

The exact pathogenesis of AOSD is unknown. Several factors such as genetics, infectious (bacterial and viral) agents, and environmental factors have been thought to play a causative role.[8] But there are no strong evidences to suggest their causal relationship with the disease. An important step in the pathogenesis of AOSD is interleukin-18 (IL-18) mediated macrophage and neutrophil activation (evidenced by upregulation of CD 64 in patients with active disease) [9]

Clinically, most of the patients with AOSD present with fever, sore throat, arthralgia, arthritis, and/or skin rash but some patients may also have lymphadenopathy, hepatosplenomegaly and /or serositis.[8] The fever, typically higher than 39°C, starts suddenly and could present as FUO alone.[2,6,7]

Our patient present with Extreme fatigue with accompanying waves of high fevers that rise daily to 102^0 F (39^0 C) or even higher and rapidly return to normal levels or below. Fever spikes often occur at approximately the same time every day. But there is no joint pain or no skin rash. The patient did not meet the criteria for any other systemic illness either tuberculosis or malaria or urinary tract infection. But his productive cough, oral ulceration, muscle cramp, weight loss (10.15%) indicate inflammatory process continued and release of inflammatory mediators.[10] Of all patients with Still's disease, 100% patient have high intermittent fever, 40-45% have hepatosplenomegaly[5,8,10], 85% have a marked

increase in the white blood cell count [5] 69% percent have sore throat [5,7],60% have inflammation of the lungs (pleuritis), and 40% have severe anemia. Poor appetite, nausea, and weight loss are common.[5,11] Patient with Adult-onset Still's disease usually report extreme fatigue.

The diagnosis of AOSD continues to be a clinical one and, in the absence of a definitive diagnostic test, often necessitates the arduous exclusion of potential mimickers, that is, infectious, neoplasm tic, autoimmune, and other auto inflammatory diseases and can be facilitated by the use of one of several validated diagnostic criteria, that is Yamaguchi's, Cush's, or Fautrel's [4,16,17]

Leukocytosis, hepatomegaly, progressively rising erythrocytes sedimentation rate and ferritin level appears to correlate well with the activity of illness. [8,10,15] The underlying mechanism of this is probably continuation of inflammatory process. A hallmark of AOSD is neutrophil [10] and macrophage activation[15] possibly under the effects of the proinflammatory interleukin-18 (IL-18) signalling.[9,10,14,15] Patients with AOSD often show hypercomplementaemia, and serum levels of IL-1â, IL-6, IL-18, TNFá, IFN " and macrophage-colony stimulating factor (M-CSF) have been found to be considerably higher [10,13] than compared with controls. [14,15] These cytokines also appear to share a role in increasing the production of ferritin. [10,15]

The laboratory investigations can show an increased systemic inflammatory response[12], such as high white blood cell count (usually 10,000 to 15,000 with more than 80% granulocytes), thrombocytosis, low hemoglobin, ESR and significant increase in serum ferritin level.[2,6,9] ESR level could be >100 mm in some cases. A high level of ferritin seems to be characteristic of AOSD and is seen in nearly 70% of cases.[6-9] Our patient's thrombocytosis and markedly elevated serum ferritin are reactive changes.[6]The serum ferritin level has been suggested as a predictive marker for AOSD as it is invariably elevated and often higher than levels found in other autoimmune or inflammatory diseases, with a five-fold increase in serum ferritin being 41% specific and 80% sensitive as a diagnostic test. [15] The markedly high ferritin level in AOSD has been attributed to hyper-production by the reticuloendothelial system or hepatocyte damage,[6,10,13] and is unrelated to iron metabolism. [18] The patient's blood results illustrated a microcytic anemia, although the iron studies point towards an inflammatory reaction.[12] Serum ferritin levels are typically increased during disease flares and this finding is useful for diagnosis and monitoring of AOSD .[8,10,13,15] Elevated ferritin level is a nonspecific but common finding [8]

For diagnosis requires at least five features, with at least two of these being major diagnostic criteria.[3] Rapid diagnoses of AOSD is difficult because of non-specific clinical and laboratory features.[2,8] Our patient had high fever, productive cough Leukocytosis, progressively rising erythrocytes sedimentation rate, hepatomegaly and increased ferritin level confirm the diagnosis of AOSD. [8,10,13,15]

The clinical course of AOSD is heterogeneous, with patients falling into one of three clinical patterns.[2,4,8,11,15] (1)Monocyclic or self-limiting pattern, which has a single episode of systemic disease of variable duration followed by complete remission.(2)Polycyclic or intermittent pattern, where 2 or more episodes of systemic disease are separated by symptom-free remission period lasting for a minimum of 2 months.(3) Chronic articular pattern, which is characterized by the severe articular manifestations causing joint destruction. Our patient falls under monocyclic group.

In our patient, causes of fever of unknown origin without rash were considered, such as endocarditis, hematological malignancies and systemic vasculitides and antibiotics were given. In the absence of solid data in regard to the underlying pathogenic mechanisms, treatment of AOSD has been for years largely empirical.[15] Corticosteroids remain the first-line treatment for AOSD, regardless of the clinical presentation.[11] Disease modifying ant rheumatic drugs (DMARDs), such as methotrexate (MTX), azathioprine, cyclosporine, and cyclophosphamide, are often

used for maintenance therapy of the disease.[8,11] Our patient responded well after addition of corticosteroid[13].

In conclusion, AOSD is not an uncommon etiology of FUO. Over the past forty years, AOSD still remains as a diagnostic dilemma for physicians as it presents with a combination of nonspecific symptoms that can be caused by a wide variety of diseases. However, the key point to remember is that, for patients who present with prolonged and unexplained fever combined with cough, the differential diagnoses should include AOSD. Timely diagnosis and treatment of the disease can prevent complications, save cost and lead to a favorable prognosis with improved quality of life.

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Competing interests: I declare that I have no conflict of interest.

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