Case Profile

A Case of Adult Onset Still's Disease complicating with Macrophage Activation Syndrome (MAS) and Myocarditis

Name of the Patient: Anuja Nawamal

Age: 20 years

Gender: Male

Date of Admission: 06/07/2018

Date of Discharge: 28/07/2018

BHT Number: 116311/18

Ward: 43, NHSL

Name of the Supervising Consultant: Dr(Mrs). F.G. Sivagnanam

Signature: .....

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A Case of Adult Onset Still's Disease complicating with Macrophage Activation Syndrome (MAS) and Myocarditis.

Abstract

Adult onset Still's disease (ASOD) is a relatively uncommon condition which is categorizing under connective tissue diseases. It is an inflammatory condition[1] and the exact pathogenesis is still unknown. The disease is characterized by quotidian fever, arthritis, and an evanescent rash typically found on the trunk[5]. A wide range of systemic manifestations also can occur. Macrophage Activation Syndrome is a well-recognized serious complication of the disease. It occurs in about 10%[2] of patients with Adult Onset Still's Disease, developing which potentially life is threating. Here I describe a 20 years old male student, who was previously investigated for a possible arthritis six months ago and lost to follow-up following a short course of treatment, currently presenting with a febrile illness with generalized weakness for a duration of one week followed by a two days' history of polyarthralgia. Examination revealed posterior cervical lymphadenopathy and a hepatomegaly. Investigations revealed a leukocytosis with neutrophil predominance, very high inflammatory markers but a negative septic screening. He had a very high serum ferritin level but autoimmune panel was negative. Investigations did not have evidence of a hematological malignancy. With Yamaguchi criteria, the diagnosis was made as adult onset Still's disease after excluding other conditions and started on non-steroidal anti-inflammatory drugs and oral prednisolone but after a period of mild clinical responsiveness for two days there was a recurrence of high grade fever with tachycardia. The diagnosis of macrophage activating syndrome with myocarditis was made and started on intra-venous methylprednisolone initially and converted to oral prednisolone. Methotrexate was started later due to persistent joint symptoms. Currently the patient is on rheumatology clinic follow up.

Keywords

Macrophage Activation syndrome, Adult Onset Still's Disease, Myocarditis. Methylprednisolone, Methotrexate

Introduction

Adult onset Still's disease is a state, which is categorized under inflammatory conditions that clinically manifests with fever, arthralgia, skin rash and systemic involvement. It is described as the adult form of systemic juvenile idiopathic arthritis and it does not satisfy the criteria for classic rheumatoid arthritis. Haemophagocytic lymphohistiocytosis (HLH) is a life threatening syndrome which is due to excessive activation of the immune system. Macrophage activation syndrome describes the same clinical entity which occurs in association with adult onset Still's disease. It is potentially life threatening.

Patient Information

Mr. C, a twenty-year-old student at a private institute who had been investigated for a joint disease six months ago and lost to follow-up, presented with a history of febrile illness for one-week duration and polyarthritis for two days' duration. He had generalized weakness and myalgia associated with these symptoms. At the beginning of the symptoms there had been a sore throat but no other upper respiratory tract symptoms. From the beginning the fever was high grade and intermittent with one or two daily spikes. He had experienced severe worsening of myalgia during the spikes of fever. His joint symptoms had started from bilateral knee joints and gradually progressed to involve wrist joints, elbow joints and small

joints of the hands in a symmetrical manner. There had been a significant rest induced stiffness lasting about one hour. He denied any symptoms suggestive of axial skeletal involvement or enthesitis. There was no history of urethritis or altered bowel habits. He complained of significant loss of appetite during the period of illness but had not experienced any appetite loss or weight loss prior to this disease. There was no contact history of leptospirosis or no recent contact history of fever.

Six months ago he has had an episode of arthralgia involving bilateral knee joints and wrist joints symmetrically with a significant rest induced stiffness for two weeks' duration but he denied recurrent oral ulcers, photo-sensitivity rashes or other symptoms suggestive of a connective tissue disease. He had undergone several investigations including rheumatoid factor but had lost the records. He had defaulted the follow-up after two weeks of treatment. Other than this systemic inquiry was unremarkable. He denied high risk sexual behaviors. There was no history of intravenous drug abuse, blood transfusions, or tattooing and he had not travelled abroad.

Clinical Findings

On examination he was thin built and had a BMI of 19 kg / m^2. He was febrile with a temperature of 102 F but he was not pale or icteric. There was an anterior cervical lymphadenopathy with the largest node 1cm in size, which were soft and tender but no enlarge lymph nodes in other groups. On the day of admission there was a non-itchy erythematous rash in his abdomen and upper thighs noted during the spike of fever. There were tender bilateral wrist joints and knee joints with restricted movements due to pain but without significant joint effusions. Examination of the cardio vascular system revealed a mild tachycardia but blood pressure was normal. His first and second heart sounds were normal, no murmurs and there was no pericardial rub. Respiratory examination revealed bilateral vesicular breathing with no added sounds. There was a mild non tender soft hepatomegaly of 3cm below the

right costal margin was palpable and there was no splenomegaly. He did not have ballotable masses or free fluids. His neurological examination was unremarkable. During the ward stay, after a period of responding to treatments, he started to deteriorate with a second phase of the illness where he had again developed high spiking fever and became restlessness. He was tachycardic and developed mild bilateral pitting edema.

Differential Diagnosis

Viral fever / Dengue fever

Leptospirosis

Post streptococcal arthritis

Systemic lupus erythematosus

Adult onset still's disease

lymphoma

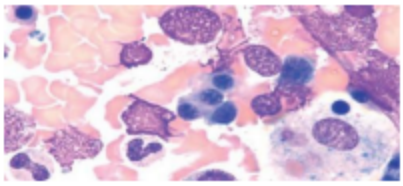
Diagnostic Assessment

His full blood count revealed a neutrophil leukocytosis with a WBC count of eighteen thousand and elevated inflammatory markers. C reactive protein was 120 ml/dl and ESR was 96 mm/hr. His screening for common infections in the setting including dengue antibodies, leptospirosis microscopic agglutination test (MAT) were negative. Urine full report, urine cultures, blood cultures, sputum cultures were not suggestive of an infection. Livers function test revealed a transaminitis with a aspartate aminotransferase of 128 U/L and alanine aminotransferase of 104 U/L, bilirubin was elevated with a level of 51 µmol/L (direct 32 µmol/L) and alkaline phosphatase of 440 U/L (40-160 U/L). Coagulation profile was normal.

Blood picture was showing a neutrophil leukocytosis with toxic changes with normal two other cell lines. There were no abnormal cells. Serological investigations for cytomegalo virus Epstein Barr virus, Retro viral infection, syphilis screening were negative.

Chest x-ray revealed no significance abnormality. His ultrasound scan of the abdomen showed a hepatomegaly of 3cm with mildly increased echogenicity. His serum LDH level was 152 U/L (40-160 U/L). Since he had past history of a possible arthritis we went ahead with Rheumatoid factor and ANA but both investigations were negative. His serum ferritin level was 8000U/L.

With the changing clinical picture after starting treatments, there were significant changes in certain investigations as well. His hemoglobin level started to drop from 12g/dl to 10g/dl over a period of two days and there was a developing thrombocytopenia as well. ESR dropped to 22mm/hr and his repeat serum ferritin rose up to 115,000 U/L. He had an elevated fasting triglyceride level of 290mg/dl as well. Bone marrow showed increased cellularity, increased histiocytes with haemophagocytic activity (Figure 1). His electrocardiogram had evidence of elevated of wide spread T-inversions with a negative troponin I. 2D Echo cardiogram had mild global hypokinesia with an ejection fraction of 40% suggestive of possible myocarditis. Given the clinical picture we made the diagnosis of adult onset Still's disease complicated by macrophage activating syndrome and myocarditis.



(Figure 1 – Bone Marrow Biopsy showing Haemophogocytes)

Therapeutic Intervention

Broad spectrum antibiotics were started initially with a tentative diagnosis of a bacterial infection depending on the early investigations but there was no clinical or hematological response after 48 hours of treatments. All the serological tests and cultures were negative for bacterial or fungal infections. With positive clinical and suggestive investigation findings the diagnosis of adult onset Still's disease was made and he was started on IV methyl prednisolone for three days with ibuprofen by the rheumatology team and he achieved a good clinical response. 2 days after being converted to oral prednisolone, the change in his clinical picture had occurred. With the diagnosis of macrophage activation syndrome, again he was stared on IV methylprednisolone for 5 days followed by oral prednisolone 1mg/kg per day. For possible myocarditis with mild stable heart failure with reduced ejection fraction he was treated with a carvedilol 3.125mg twice daily dose and a low dose of frusemide. NSAIDs were discontinued for a period of 2 weeks.

Follow-up and Outcome

With that treatment he achieved a good clinical and biochemical response other than persisted joint symptoms. With the rheumatology opinion he was started on a weekly 20mg dose of methotrexate with folic acid.

Timeline


01/2018
Investigated for a possible arthritis
28/06/2018
Onset of febrile illness
Sore throat
Arthritis
06/07/2018
Admission
Significant arthritis
Skin rash
Hepatomegaly
High serum ferritin
Elevated transaminases
High inflammatory markers
10/07/2018
Diagnosed as Still's disease and started on
IV methylprednisolone
Ibuprofen
13/07/2018
Started on oral prednisolone
15/07/2018
Recurrence of high fever
Bicytopenia
Very high serum ferritin
High fasting triglyceride
Bone marrow – haemophagocytes
Diagnosed as macrophage activation syndrome
Started on IV Methylprednisolone
06/08/2018
Started on methotrexate and folic acid –persistence joint symptoms

Discussion

Systemic juvenile idiopathic arthritis was first described in children in 1896 by George Still. So the condition is also used to be termed as "Still's disease" as well. Later in 1970 a clinical entity similar to that was identified in adults as well and it is termed as adult onset still's[6] disease. Classically the condition did not fulfill the criteria of rheumatoid arthritis. The exact aetiology of the condition is still unknown but several factors were identified as possible predisposing conditions. Although in several studies genetic factors have been proposed, none of them were confirmatory. Involvement of interleukin I (IL I) and IL VI have been shown in the process pathogenesis[3,9]. Certain infectious also have been proposed in some other studies including *Yersinia entercolitica* and *Mycoplasma pneumonia.* The condition has shown two peaks, one around 20 years and another peak around 40 years of age. Clinically adult onset Still's disease has fever, rash, and arthritis as major features and our patient had high fever from the beginning with a late onset joint symptoms and a skin rash. The fever is usually quotidian and high grade. The classical skin rash is a salmon-coloured, evanescent, non-pruritic, macular- papular which appears at the height of the fever spike.

Adult onset Still's Disease is basically a diagnosis of exclusion. There are no specific diagnostic tests available to confirm the condition. So over a period of time there had been various criteria used to diagnose this condition. Among those Yamaguchi's criteria[7] is widely accepted currently. It has four major criteria and five minor criteria of which five features should be fulfilled including 2 major criteria to diagnose the condition. Major criteria are

a. Arthritis /Arthralgia for more than two weeks.
b. Leukocytosis (more than 10,000/ μ L with 80% of granulocytes).
c. Salmon coloured rash which is non-pruritic appearing during fever.
a. Fever more than 39°C (102.2^{O}F) which has to be lasting at least a week duration.

Minor criteria are as follow:

a. Negative tests for RF and ANA

b. Hepatomegaly or splenomegaly

c. Sore throat.

d. Abnormal liver function tests particularly AST, ALT or LDH.

e. Lymphadenopathy.

Our patient fulfilled all these major criteria as well as minor criteria and we made the diagnosis after excluding other possible differential diagnoses as well. The treatment is based mainly on the initial disease activity and the severity of the internal organ involvement. Initially the mild disease with fever, rash, mild degree of arthritis can be treated with non-steroidal anti-inflammatory drugs (NSAIDs). 80% of patients are not responsive to NSAIDs alone. In those patients it is recommended to add a low dose of glucocorticoids. (Oral prednisolone 0.5-1mg/kg). In patients who do not control with glucocorticoids and predominant symptom is arthritis, the recommended treatment is weekly methotrexate[10]. Biological disease modifying anti-rheumatic drugs (DMARDs) like anakinra (IL-1receptor antagonist[4]) can be used in patients who have predominant rash and systemic symptoms rather than arthritis. Patients who do not respond to anakinra can be changed to tocilizumab(IL-6 receptor antagonist[8]). Infliximab (TNF inhibitor) can be used in patients who respond poorly to a course of methotrexate for two months.

Macrophage Activation Syndrome (MAS) is a well-recognized complication of adult's onset still disease which is potentially fatal. Although the exact pathophysiology of the condition is not well recognized, it is thought to be due to an over-whelming inflammatory reaction due to excess cytokine and lymphocyte activation. As seen in our patient laboratory studies predominantly show cytopenias as well as very high serum ferritin levels. Additionally, when they go in to MAS, there will be a noticeable reduction in ESR and elevation in fasting

triglycerides which were evident in our patient as well. To diagnose MAS either identification of a mutation of HLH gene or fulfilment of 5/8 criteria of HLH 2004 trail is necessary.

Those criteria are as follow:

a. Splenomegaly
b. Cytopenia in atleast two cell lines evidenced by haemoglobin < 90g/L , platelet < 100000 μ /L, or absolute neutrophil count <1000 μ /L
c. Fever ≥ 38.5°C
d. Ferritin >500 ng/mL
e. Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
f. Low or absent NK cell activity
g. Hemophagocytosis in bone marrow, spleen, lymph node, or liver
h. Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms

Identifying and treating the underline figuring condition is the main stay of management in MAS.patients who deteriorate may need transfusion of red cells , platelets , fresh frozen plasma or fibrinogen. Patients with refractory symptoms can be treated with steroids , emapalumab (Interferon gamma inhibitor) or alemtuzumab (anti – CD 25).

Conclusion

Adult onset still's disease is a condition which can involve multiple systems .It is necessary to diagnose and start on treatments as well as to identify complications like macrophage activation syndrome. In refractory patients biological agents can be used with close monitoring. There was no conflict of interest in this case report.

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