ejpmr, 2023,10(9), 184-188

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

IS STILLS DISEASE STILL HARD TO DIAGNOSE? - A RARE ENTITY(CASE REPORT)

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Article Received on 05/07/2023 **Article Revised on 25/07/2023** **Article Accepted on 15/08/2023**

ABSTRACT

We present here a 31 years FA, Para 3, who presented with fever, sore throat, polyarthritis and pinkish maculopapular evanescent rash for last 4 weeks. Patient was diagnosed as pyrexia of unknown origin in a tertiary care hospital in HP and referred to IGMC on empirical Anti tubercular treatment (ATT) and multiple higher order antibiotics. Work up for underlying infection, malignancy and connective tissue disease was inconclusive. Empirical antibiotics and Anti tubercular therapy at peripheral centre did not relieve symptoms. Laboratory analysis showed anaemia, neutrophilia predominant leukocytosis, transaminitis, hypertriglyceridemia and disproportionately high serum ferritin. Bone marrow biopsy showed haemophagocytosis raising suspicion towards Still's disease. Skin biopsy was consistent with Adult onset Still's disease (AOSD). There was dramatic response to NSAIDs and Steroids, while Methotrexate was used as steroid sparing agent. AOSD, although uncommon, presents with characterstic clinical and biochemical features in the differential diagnosisof PUO, high index of suspicion is required to diagnose this disease.

INTRODUCTION

Adult onset stills disease is auto inflammatory syndrome that most commonly affects young adults. It typically presents as a triad of high spiking fever (usually > 102 degree F), arthritis and maculopapular salmon pink evanescent rash but pleiotropic presentations often lead to diagnostic and therapeautic delays. Milder to overt life threatening macrophage activation syndrome (MAS) may complicate 10-30% cases.

Case discussion

We present here a 31 years FA, who presented to our ED with fever, sore throat, polyarthritis and pinkish maculopapular evanescent rash for the last 4 weeks ***Figure 1.1*** With these complaints patient had visited a tertiary care hospital in HP. Patient was put on empirical ATT and antibiotics for managing a suspected infectious etiology of the disease by the physicians and referred to our hospital for further work up and management of the patient with a differential diagnosis of Pyrexia of unknown origin. Patient had high grade fever (104 deg Fahrenheit) with evening rise of temperature, associated with chills and sore throat without night sweats and relieved on taking antipyretics. She also developed joint pains involving large joints bilaterally (knee, ankle, elbows) associated with swelling of B/L knee joints, associated with stiffness throughout the day, not associated with redness. 2 weeks after the onset of fever and joint pains, patient developed maculopapular skin rash over extremities and trunk, not associated with pruritus, non scaly, not associated with pain or photosensitivity. Rash initially started in the lower limbs and gradually progressed to the upper limbs over 6-8 days. Work up received from periphery was inconclusive, with an ANA titre of 1:40 speckled type. On examination patient was febrile to touch, with BP - 94/70 mmHg, PR - 138/min, SpO2- 91% at Room Air, Temp- 104 degrees F, RBS- 98 mg/dl, with significant pallor, but no lymphadenopathy was found on palpating. On local examination skin rash was noticed which was red in colour, raised to flat lesions present over bilateral hand and feet and around mouth and trunk. B/L knee joints were swollen and tender, warm to touch without erythema. Joint movements were painful. The possibility of Infective endocarditis was ruled out as there were no peripheral signs of Infective endocarditis, with normal cardiovascular exam.

Other systemic examination was within normal limits, with a liver span of 16cm (just palpable beneath the right costal margin on deep inspiration). Keeping a possibility of PUO with Maculopapular erythematous rash with hepatomegaly and polyarthritis, investigations were sent keeping possible differentials of Infectious arthritis, Disseminated Tuberculosis, Connective tissue disease(CTD), or Viral Exanthem. On Day 1, Hb -10.2g/dL(11.5-15.5 g/dL), TLC-14.30 thou/microL, Platelet- 253, ESR-70, qCRP-138, HIV/HBsAg/HCV Nonreactive, LFT (ALT- 228 U/L, AST- 140 U/ L, Total Bilirubin-1.17mg/dL(0.2-0.8

mg/dL),Conjugated Bilirubin - 0.20 mg/dL, RFT, electrolytes and urine analysis were within normal limits. Blood and urine cultures were sent for analysis.

Patient was started empirically on broad spectrum antibiotics (Vancomycin, Meropenem), IV fluids, cold sponging, while ATT was withheld. Cardiology consult was taken revealing normal examination clinically and no evidence of infective endocarditis / any valvular abnormality on 2D Echo. On day 2, patient was febrile, labs revealed normal study for IgM Scrub, IgM Brucella, IgM Typhidot, VDRL, P/S for Malaria, Dengue NS1 antigen and serology, COVID 19 RTPCR, rk39 antigen. Urine and blood cultures were obtained to be sterile, and serum procalcitonin was found to be <0.2 mcg/L. CECT Chest and abdomen was done which revealed mild hepatomegaly(***Figure 1.2***). During this period patient remained febrile despite being on antipyretics, having two spikes of fever of 101-102 degree Fassociate with chills and prominence of rash was seen with each febrile episode. Synovial fluid aspiration was done on Day 5, and was sent for cytology, Gram's and ZN staining, and culture/ sensitivity, reports received on Day 7. Joint aspirate was sterile, acellular and non infective. On Day 6 and 7, patient remained afebrile. Routine investigations were sent showing persistent anaemia and leukocytosis with a raised LDH (619 U/L)

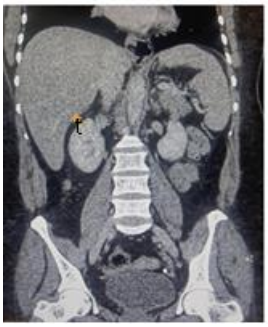

***Figure 1.2*: Coronal section suggestive of hepatomegaly (orange arrow).**

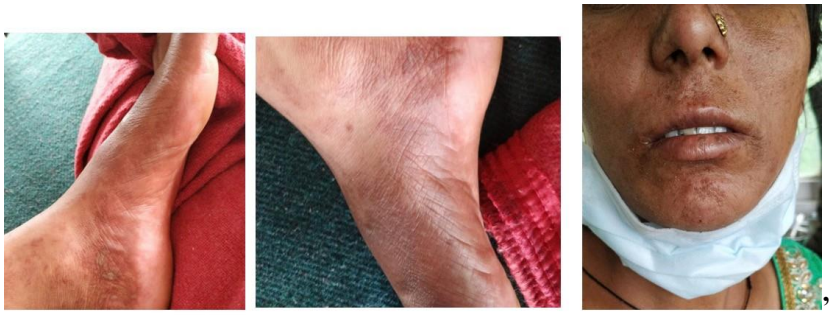

***Figure 1.2*: Patient on presentation with evanescence rash progressing from left leg to periorallesions**

Peripheral smear of the patient revealed mild anisopoikilocytosis, predominantly normocytic and normochromic. Iron studies and ferritin revealed Iron of 12 mcg/dL , TIBC of 212 mcg/dL, TSAT of 6%, serum ferritin of > 2000 ng/mL - Suggestive of anemia of chronic disease.

On Day 8, patient was again febrile with pinkish-red rash which characteristically appeared during the episodes of fever. Work up of vasculitis, and ANA reflux was found to be negative. Rheumatology consult was taken, the presence of evanescent rash appearing with fever spikes , negative work up for infectious etiology, and negative urine and blood cultures raised strong suspicion towards AOSD(Adult onset Still's disease). As the patient's fever was non resolving despite 8 days of broad spectrum antibiotics, antipyretics along with development of transaminitis and thrombocytopenia (Fig 4), the patient now fit 4 major and 3 minor Yamaguchi criteria for AOSD (***Figure 2)***. Thereafter a revised diagnosis of AOSD was kept with possibility of secondary Macrophage activation syndrome(to be confirmed on Bone marrow biopsy). Skin consultation was taken, planning skin biopsy from the left leg (***Figure 4***); and Bone marrow biopsy was also planned. On adding NSAIDs (T. Naproxen) to the current regimen , patient improved drastically and remained afebrile. Labs showed normalisation of LFTs and platelet count. Bone marrow biopsy revealed Haemophagocytosis (***Figure 5***), Skin biopsy revealed focal hyperkeratosis, mild acanthosis. Papillary dermis showed moderate mixed inflammatory infiltrates of lymphocytes, neutrophils, few plasma cells and eosinophils in the interstitium and perivascular region. Deeper dermis showed mild perivascular lymphoid, mononuclear cell infiltrates confirming the diagnosis of AOSD.

Clinical, biochemical and histopathological correlation led to the diagnosis of AOSD. Patient was discharged on steroids and NSAIDs. Patient is currently asymptomatic, doing well and parameters on Day 1, Day 7 and Day 30 are attached(***Figure 3)***.

YAMAGUCHI

Major criteria	Fever 39°C lasting ≥ 1 week
	Arthralgia or arthritis lasting ≥ 2 weeks
	Typical nonpruritic salmon-colored rash
	Leukocytosis ≥ 10,000/mm^3 with granulocytes 80%
Minor criteria	Sore throat
	Lymphadenopathy
	Splenomegaly
	Abnormal liver function tests
	Negative tests for antinuclear antibody and rheumatoid factor
Exclusion criteria	Infection
	Malignancy
	Other rheumatic disease (vasculitis)
Criteria for diagnosis of AOSD	≥ 5 criteria are present with ≥ 2 being major criteria and no exclusion criteria.
Sensitivity and specificity	Sensitivity 96.2% and specificity 92.1%

Figure 2: **Yamaguchi criteria with a proposed Sensitivity of 96.2 % and Specificity of 98.9 % >= 5 criteria are present with >= 2 being major criteria and no exclusioncriteria.**

Parameters	Day 1	Day 7	Day 30
Hb	10.2	9.8	12.2
TLC	14,30	13.4	9
PLT	253	88	180
Blood urea	12	8	19
Serum creatinine	0.2	0.59	0.30
ESR	70	88	5
qCRP	138	112	1.8
Sputum AFB and GS	Negative	Negative	-
Sputum CBNAAT	Negative	Negative	-
MANTOUX TEST	Negative	Negative	-
Serum TSH	0.9	0.87	-
Na/K/Cl/Ca/P	135/3.96/102/8.2/3.8	138/3.64/100/8.6/3.6	136/3.7/102/8.8/3.6
ALT/AST/ALP	228/140/280	236/134/296	18/22/100
Bilirubin (Total/Conjugated)	1.17/0.20	1.3/0.26	1.2/0.4
pH/HCO3/Lac	7.41/16.4/0.93	7.36/16/1.01	7.42/23.1/0.6
Viral markers	Non reactive	Non reactive	-
Urine r/m	WNL	WNL	-
Blood and urine C/S	Negative	Negative	
Synovial fluid aspirate		Acellular,sterile and GS/AFB neg	
Iron studies with s. Ferritin	Iron - 12 mg/dL, Ferritin - >2000	% TSAT - 6 %, TIBC - 212	Iron -24mg/dL, Ferritin 100
CPK/s. LDH		63/619	WNL
D dimer		0.7	<0.5
2 D Echo		Normal study	
RA factor and ANA	RAfactor-neg;ANA hep 2 is 1:40	ANA Reflux negative panel	
Triglycerides		234	
Fever w/u		WNL	

Figure 3: **Trend of labs from the day ofadmission till Day 30(full recovery) Fever w/u includes screening for tropicalinfections to rule out infectious etiology.**

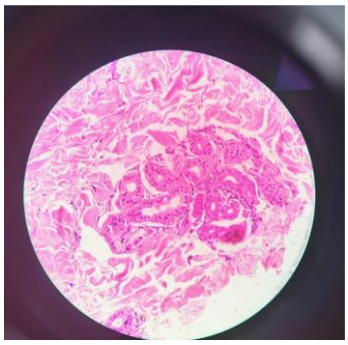

Figure 4: **Skin biopsy from Left leg of the patient showing epidermal infiltrates with perivascular lymphohistiocytic infiltrates.**

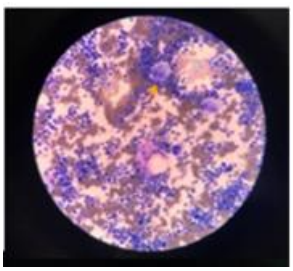

Figure 5: **Bone marrow biopsy suggestive of hemophagocytosis withemperipolesis(orange arrow).**

DISCUSSION

AOSD presents with a classical triad of fever, rash and arthritis. Patient undergoes a battery of investigations and is usually a diagnosis of exclusion due to no gold standard test. Skin rash is predominantly found over limbs and trunk appearing during the febrile phase. Biopsy from rash shows hyperkeratosis, dyskeratosis and mixed inflammatory infiltrate around the vessel and dermalappendages. MAS has been reported in 15-20 % AOSD patients. Our patient fulfilled Yamaguchi Criteria(4 major and 3 minor) which is the most sensitive and specific criteria for AOSD and was started on NSAID, showing dramatic response with resolution of skin lesions and normal laboratory findings.

Although AOSD is considered to be equally distributed among genders, some series claim that it is more commonly seen in women, as in our case. It usually affects young people with a bimodal peak at ages 15-25 and 36-46 years.

It may be categorised as a multigenic autoinflammatory disorder at the crossroads of auto inflammatory and autoimmune diseases, due to its complex pathogenesis, involving both innate and adaptive immune system.

Although a familial trend has not been reported in AOSD, some genetic studies showed an association of the disease with different susceptibility genes. Some associations between AOSD and HLA antigens have been reported, including HLA-B17, - B18, -B35, -DR2 and -DR4. A possible infectious etiology of AOSD has been proposed due to the similarity between AOSD clinical presentations and infections. A possibility of Still's disease was only kept in our case after ruling out infectious etiology.

Seasonality has also been reported in AOSD and these variations have been reported as an argument for an infectious trigger. More recently, both solid cancers and haematological malignancies have been proposed as possible triggers of AOSD, via the same pathogenic pathways reported for macrophage activation syndrome (MAS) development, a severe life-threatening complication of AOSD. However, it must be pointed out that, no unique pathogenic trigger has been clearly defined, suggesting the possibility that multiple environmental triggers may be a role in AOSD.

AOSD accounts for 10-20% of pyrexia of unknown origin and almost all patients experience high spiking fever. Fever generally exceeds 102 degree F and is transient, lasting under 4 h. It shows commonly a quotidian or twice quotidian pattern with the highest temperatures observed in the late afternoon or early evening. The fever usually shows an abrupt onset resembling an infectious syndrome often preceeding the onset of other systemic manifestations.

Arthralgia and arthritis mainly involving wrists, knees and ankles are frequently reported in AOSD. At the start of the disease, these symptoms may be mild and transient often progressing to symmetrical polyarthritis. After months of disease progression, from joint narrowing to ankylosis mainly involving carpal joints it has been reported that the joint fluid aspiration be performed and itoften shows neutrophilic predominance. Myalgia is also common.

Evanescent salmon-pink erythema which may be associated with an erythematous maculopapular eruption, predominantly found on the proximal limbs and trunk, appearing during the febrile attacks. Some patients, with usually more severe outcome. may experience this eruption for many weeks. The histopathology of this rash shows a mixed inflammatory infiltrate. surrounding the perivascular areas and without epidermal changes, strongly differs from the persistent rash, in which the eruption shows2 main findings: 1) A pattern of dyskeratosis in the superficial layers of the epidermis without accompanying basilar dyskeratosis; 2). a sparse superficial dermal infiltrate often containing neutrophils but without vasculitis.

Both splenomegaly and mild-severe enlargement of cervical lymph nodes (LNs) are frequently observed in AOSD patients and lymphoma should be always considered in the differential diagnosis.

In our case the patient had characteristic clinical and biochemical findings; albeit rare in occurrence with classical clinical features- the disease poses a challenge because of its inherent nature to mimic an infectious etiology. In case the disease presents with MAS, Disseminated intravascular coagulation, diffuse alveolar haemorrhage - can prove to be fatal.

Often managed with steroids and NSAIDs as first line. It is managed with steroids with clinical response seen in around 60 % patients. DMARDs are used as second line therapy and 69% attain complete remission. New insights in the pathogenesis of AOSD has highlighted new therapeutic targets like biologics (anakinra, tocilizumab, infliximab) in the management of refractory AOSD.

CONCLUSION

High index of suspicion, detailed history and work up , along with physical examination are required in diagnosing a case of AOSD.

Disease may present with MAS, Disseminated intravascular coagulation, diffuse alveolarhaemorrhage - and thus can prove to be fatal.

Often managed with steroids and NSAIDs as first line

with clinical response seen in around 60 % patients. DMARDs are used as second line therapy and 69% attain complete remission. New insights in the pathogenesis of AOSD has highlighted new therapeutic targets like biologics (anakinra, tocilizumab, infliximab) in the management of refractory AOSD.

The independent risk factors for predicting AOSD mortality have been proposed to be age at onset ≥50, coexisting infection, hepatomegaly and MAS; however additional studies are required to confirm these findings.

Early diagnosis and initiation of treatment is paramount as it can prevent development of fatal complications.

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