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Case Report

Hemophagocytic syndrome, a rare variant of Still's disease

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ABSTRACT

Adult onset still's disease is a rare systemic inflammatory disorder of unknown etiology that is responsible for a significant number of cases of fever of unknown origin (FUO) and musculoskeletal diseases. The diagnosis in adult onset still's disease is mainly clinical and requires exclusion of other infections. Laboratory tests are nonspecific and treatment mainly comprises of corticosteroids, NSAIDS, immunosuppressive drugs, iv gamma globulin, anti-tumour necrosis factor, anti-interleukin. AOSD (adult onset stills disease) is a diagnostic challenge. Discovery of new serological tests and a specific diagnostic criterion may help the clinician in faster diagnosis and better management of the disease.

Keywords: AOSD (adult onset stills disease), Fever of unknown origin (FUO)

INTRODUCTION

Adult Onset Still's Disease (AOSD), was first described by Waters in 1971, as an inflammatory disorder of unknown etiology and pathogenesis although the juvenile counterpart was described much earlier. There is no specific diagnostic test or pathognomonic histopathology. It is a rare (1 case in 1-2 years at tertiary referral centers) rheumatological condition accounting for nearly 5% cases of PUO. A large proportion of patients have suffered from extended delays in diagnosis due to protracted expensive and often costly efforts to exclude occult infection or neoplasm.

The characteristic manifestation of AOSD is triad of fever (quotidian), rash (evanescent) and arthritis; other features include antecedent sore throat, polyserositis, hepatosplenomegaly and lymphadenopathy.[1]

AOSD as a part of differential diagnosis of PUO is uncommon with some peculiarities.[2,3] Although rare, this diagnosis can always be kept in mind as a differential, while dealing with a case of PUO.

HPS is a clinico-pathologic entity characterized by increased proliferation and activation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system manifesting as fever, hepatosplenomegaly and pancytopenia. However, pancytopenia is usually not seen in AOSD associated HPS. Uncontrolled T-lymphocyte activation is responsible for increased T(H)1 cytokines secretion. HPS may be secondary to malignancy, infection or autoimmune disease, and mechanisms involved are poorly understood.[4]

CASE REPORT

22 years old lady presented on 15 Aug 2016 with 10 days history of fever, arthralgia, skin rash, nausea and abdominal pain, was found to have high grade fever, tachycardia, active arthritis (ankles and wrist joint) maculopapular erythematous eruptions over back and legs, splenomegaly and few non-specific cervical lymph nodes. Investigations revealed polymorphonuclear leukocytosis, raised ESR, sonologically evidence of hepatosplenomegaly and negative work up for typhoid

and malaria. Empirical treatment with antimalarial and antibiotics did not show any response. Patient continued running intermittent high-grade fever with toxemic features.

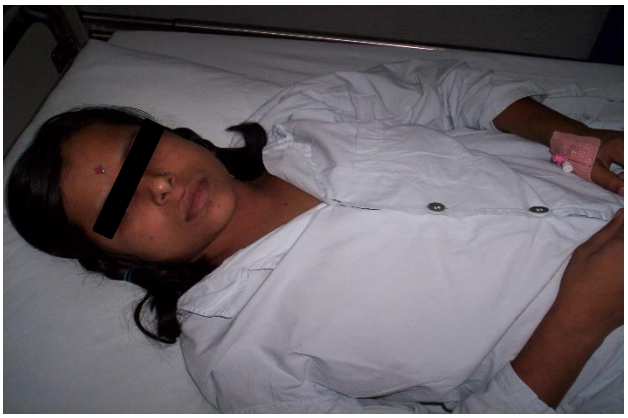

Figure 1: Clinical appearance.

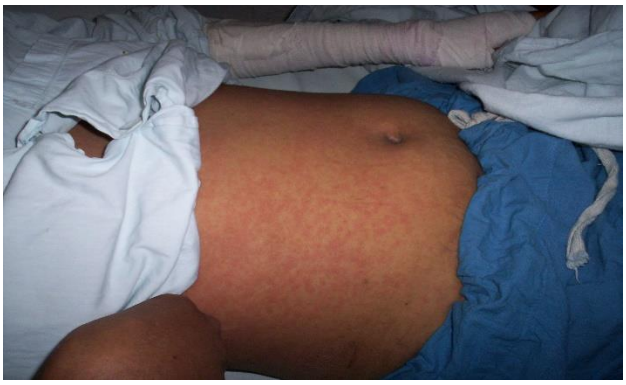

Figure 2: Cutaneous manifestation.

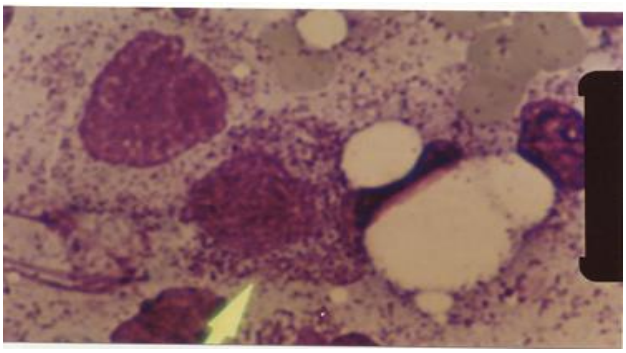

Figure 3: Pathologic slide.

Further assessment and evaluation revealed positive aldehyde test and bone marrow smear showed "numerous macrophage stuffed with intracellular LD bodies, some of which also seen lying extracellularly and a diagnosis of visceral leishmaniasis was offered. Managed with anti-leishmanial drugs (sodium stibogluconate followed by amphotericin) in adequate dosages. But the patient did not show any response. Instead she developed iatrogenic hepatitis, hypokalemia and hypotension which was managed accordingly. Her serum markers for RA Factor, ANA and dsDNA were negative. On 18 September 2016, strong suspicion of Adult Onset Still's disease was made and Serum ferritin level estimation was done and it was found to be grossly elevated with a value of 27252.8 ngm/ml (normal level is < 300 ngm/ml) clinching the diagnosis of AOSD. All the previous drugs were stopped and the treatment was revised. She was started on indomethacin and steroids to which she showed dramatic improvement. Presently doing well on maintenance with NSAIDs and DMARDs.

DISCUSSION

Unless a condition is thought of as a differential we cannot reach a diagnosis for specific treatment. Hence, a high index of suspicion is mandatory. A few points about the condition as a review of literature for practicing physicians are mentioned.

The supporting lab investigations are raised ESR, leukocytosis, serological silence for RA factor, ANA and dsDNA, and elevated levels of acute phase reactants, especially ferritin levels. The diagnostic criteria (Yamaguchi, 1992) are mentioned below. A score of 5 (including 2 major) is required to make the diagnosis:

- 4 major criteria: Fever>39C, arthralgia>2weeks, Still's rash and neutrophilic leukocytosis
- 4 minor criteria: Sore-throat, lymphadenopathy or splenomegaly, liver dysfunction and negative RF and ANA.

Macrophage activation syndrome, hemophagocytic syndrome (HPS)[4,8]

Reactive HPS may be primary (familial autosomal recessive) or secondary to some underlying disorders (viral infections, neoplasms or immune mediated disorders).

HPS is a clinico-pathologic entity characterized by increased proliferation and activation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system manifesting as fever, hepatosplenomegaly and pancytopenia. However, pancytopenia is usually not seen in AOSD associated HPS. Uncontrolled T-lymphocyte activation is responsible for increased T(H)1 cytokines secretion. HPS may be secondary to malignancy, infection or autoimmune disease, and mechanisms involved are poorly understood. However, in AOSD, juvenile chronic arthritis and probably systemic lupus erythematosus, IL-18 might play a role in initiating macrophage activation. Very high levels of ferritin (4000 to 30,000ng/ml) seem to correlate well with the presence of haemophagocytosis and are a possible marker for an early diagnosis.[5] The ferritin levels tend to shoot up with flare-ups and regress with therapy. Increased ferritin levels can be attributed to acute phase reaction (ferritin being one of the acute phase

reactants) and necrosis of hepatocytes which is seen in acute stages of AOSD. These two mechanisms can account for at the most moderate elevation of ferritin levels (500-1000ng/ml). However, when grossly elevated ferritin levels are encountered (4000-30000ng/ml), they are almost consistent with HPS, RBC's being engulfed by histiocytes/macrophages give rise to a histological picture similar to intracellular LD bodies (as happened in this case) resulting in diagnostic dilemma but also leads to very high levels of serum ferritin due to release of ferritin from phagocytized RBC's. The histological picture from the bone marrow aspirate of the patient under discussion showing haemophagocytosis is as shown.

A circadian cytokine pattern[6,7]

Sequential analysis of IL-6 production has shown diurnal variation, with peak levels between 1800 and 2200 hour, and lowest levels approximating the early morning surge of endogenous cortisol. IL-6 levels parallel the febrile spikes. Many data have suggested that in STILL'S disease, the diurnal alteration in fever and inflammatory symptomatology including evanescent rash are paralleled by the increase production of IL-6 and possibly other unidentified pyrogens or cytokines. Factors responsible for circadian production of cytokines are unknown but may relate to host susceptibility and immunologic reactivity to viral antigens (e.g. rubella), sequestered within monocytes, macrophages and another immunocompetent cell.

Presence of HPS indicates aggressive form of disease and is associated or may herald disease flare ups. While primary HPS carries unfavourable prognosis, the secondary form seems to have a favorable course (amenable to steroids and immunosuppressant drugs). Due to relatively refractory nature of primary HPS, curative method is transplantation of hemopoietic cells. The other advances in the therapeutic modalities are, intravenous immunoglobulins, plasmapharesis, cytostatic drugs such as etoposide and cyclosporine A and anti TNF-α (infliximab and etancercept). [9,10]

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REFERENCES

1. Giampietro C, Fautrel B. Anti-interleukin-1 agents in adult onset Still's disease. Int J Inflammation. 2012;2012.
2. Jose CC. Martinez-Banos D, Alcocer-Varela J. Adult-onset Still disease as the cause of fever of unknown origin. Medic. 2005;84(6):331-7.
3. Arnow PM, Flaherty JP. Fever of unknown origin. Lancet. 1997;350(9077):575-80.
4. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19(3):424-30.
5. Olive A, Junca J, Tena X. Ferritin and adult Still's disease. Br J Rheumatol. 1991;30(2):158.
6. Arvidson NG, Gudbiornsson B, Elfman L, Ryden AC, Totterman, TH, Hallgren R. Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. Ann Rheum Dis. 1994;53:521-24.
7. David J, Davies U, Rooney M. Cytokine measurement in juvenile chronic arthritis (JCA). Arthritis Rheum. 1990;33(9):S118-99.
8. Owlia MB, Mehrpoor G. Adult- onset Still's disease: a review. Indian J Med Sci. 2009;63(5):207-21.
9. Elliott MJ, Woo P, Charles P, Long-Fox A, Woody JN, Maini RN. Suppression of fever and the acute-phase response in a patient with juvenile chronic arthritis treated with monoclonal antibody to tumour necrosis factor-alpha (cA2). Br J Rheumatol. 1997;36(5):589-93.
10. Cavagna L, Caporali R, Epis O, Bobbio-Pllavicini F, Montecucco C. Infliximab in the treatment of adult Still's disease refractory to conventional therapy. Clin Exp Rheumatol. 2001;19:329-32.

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