

# Hemophagocytic Lymphohistiocytosis in a Patient with Adult-Onset Still's Disease – a Diagnostic Dilemma

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## Abstract

*Hemophagocytic lymphohistiocytosis (HLH) is a serious complication of Adult-onset Still's Disease(AOSD) and because of their overlapping clinical features, there will be delay in the diagnosis leading to increased morbidity and mortality. Here we present a case report of 61 years old female patient who were diagnosed with AOSD associated with secondary HLH, which despite treatment, led to fatal outcome.*

**Keywords** – Hemophagocytic lymphohistiocytosis, Adult-onset Still's Disease, Ferritin

## I. INTRODUCTION

Adult-Onset Still's disease (AOSD) is a rare, immune-mediated, multisystem inflammatory disorder characterized by quotidian spiking fevers, evanescent rash, and arthritis. [1] Life threatening conditions such as hepatic involvement, cardiac tamponade, disseminated intravascular coagulation (DIC), respiratory distress syndrome or pancytopenia were occasionally developed in the course of AOSD [2], and in some cases were often associated with hemophagocytic syndrome (HS) [3-5].

Hemophagocytic lymphohistiocytosis (HLH) is not uncommon in AOSD and has been reported to be present in 12% of patients [6]. HLH is a life threatening condition characterized by uncontrolled hyperinflammation on the basis of various inherited or acquired immune deficiencies [7]. The clinical presentation of both diseases are non-specific, mutually overlapping and similar to that of various infections, autoimmune conditions and malignancies especially lymphomas [6]. This causes delayed recognition in the diagnosis leading to increased morbidity and mortality. We present a case of secondary HLH in a patient with AOSD who had presented with inflammatory arthritis of Right knee with elevated ferritin, LDH and Triglycerides levels and subsequently this was associated with fever, pancytopenia, coagulopathy, altered liver function tests, and hepatomegaly, posing a diagnostic dilemma and therapeutic challenge.

## II. CASE PRESENTATION

A 61 year old female was referred to our hospital with complaints of Right knee reactive arthritis for the last one year along with fever of unknown origin since one week. For knee reactive arthritis, the patient consulted nearby physician on several occasions and was prescribed antibiotics, NSAIDs and oral steroids which resulted in partial improvement in arthralgia.

She had leucocytosis with elevated inflammatory markers (ESR, CRP & Ferritin). The knee aspirate was inflammatory in nature and sterile on culture. PET scan shows increased uptake in the right shoulder, left knee joint and in the bone marrow. Suspecting Adult onset Still's disease, she received hydroxychloroquine, sulfasalazine and steroids.

Subsequently, there was a progressive increase in the ferritin to 20000, elevated serum LDH levels to 4459mg/dl, elevated serum triglycerides to 444 mg/dl and decrease in fibrinogen from normal to 170 mg/dl. This was associated with continuous fever, pancytopenia, coagulopathy, altered liver function tests and hepatomegaly. Bone marrow aspiration and biopsy were performed and revealed nonspecific changes and no features of hemophagocytosis despite a detailed examination (Fig. 1 and 2). These atypical findings on bone marrow biopsy results in diagnostic confusion.

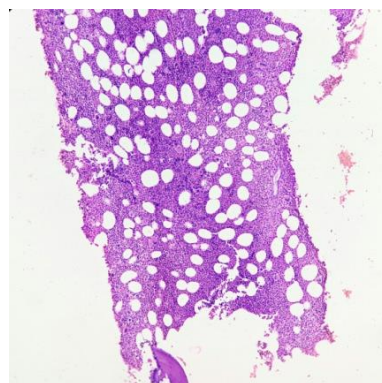
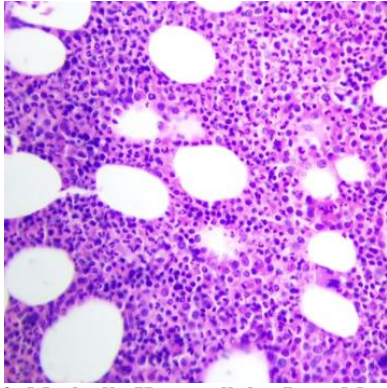


Fig.1: Markedly Hypercellular Bone Marrow. Hematoxylin and Eosin Stain, Low Power.



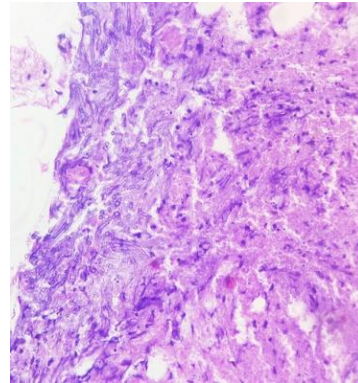
**Fig. 2: Markedly Hypercellular Bone Marrow. Hematoxylin and Eosin Stain, High Power.**

The complete workup for any infective etiology (viral, bacterial and fungal) and autoimmune cause was done. Repeat bone marrow study with biopsy confirmed that there was macrophage activation syndrome. Finally, a clinical diagnosis of AOSD associated with secondary HLH based on Yamaguchi's criteria [8] and HLH 2004 Criteria [9]. IV Immunoglobulin therapy, pulse methyl prednisolone followed by dexamethasone maintenance therapy was started along with broad spectrum antibiotics support but there was no response, hence she was started on Etoposide with due risk of its complications. She received total four doses. She was supported by packed cell and platelet transfusions, G-CSF, Etoposide and cyclosporine. She also had Axillary folliculitis and accelerated hypertension. Over next few weeks, she gradually improved. She was hemodynamically stable, HLH parameters decreased (Hb: 9, TLC: 11,000/mm<sup>3</sup>, platelets: 309, Ferritin: 2940, LDH: 724, Fibrinogen: 351, Triglycerides: 313). She was discharged on oral weekly Etoposide, tapering dose of Dexamethasone, Cyclosporine, Hydroxychloroquine and Cotrimoxazole.

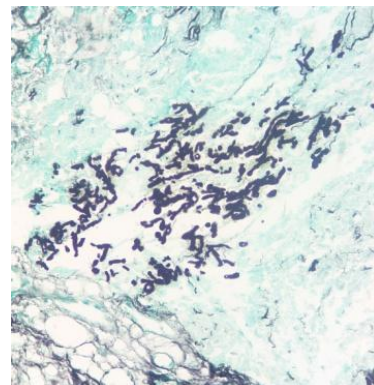
After three months, she was readmitted with sepsis and multiorgan failure. She also developed axillary and perianal ulceration, flare of HLH, Acute kidney injury (AKI), liver abscess, urinary infection, encephalopathy, back pain with right lower limb radiculopathy and also developed herpes zoster in the right of L1-L2 segments. The immunosuppressants (Etoposide) were temporarily withheld and she was treated with Meropenem, Clindamycin as per antibiotic sensitivity. The ulcers and abscess improved. AKI and oligouria was responds to diuretics and noninvasive ventilation. Lower limb radiculopathy was controlled with analgesics and gabapentin. She was mobilized and discharged but the parameters of HS remained unchanged. At home, she was doing reasonably well.

She was re-admitted in hospital again due to acute pain and swelling in the right knee after one

month. There was neutrophilic leukocytosis and purulent knee aspirate that grew *Aspergillus fumigatus* on culture (Figure 3 and 4). She also underwent arthroscopic knee debridement of the knee joint. She received Voriconazole inj. for one month along with antibiotic support. HLH parameters were still elevated; Sr. ferritin: 4960, Sr. Triglycerides: 249, Sr. fibrinogen: 348, LDH: 680. Recurrent anemia requiring blood transfusion. HLH markers were remain same after one month. Antifungal, antibiotic support and low dose steroids were continued.



**Fig. 3: Fungal Colonies and Branching Hyphae. Hematoxylin and Eosin Stain, High Power.**



**Fig. 4: Fungal Colonies and Branching Hyphae. Gomori's Methenamine Silver Stain, High power.**

She later suffered with septic shock with septic encephalopathy with right sided empyema thoracis for which ICD insertion was required. After few weeks, she went into cardiac arrest which led to death.

### III. DISCUSSION

HS is a rare and fatal syndrome that is characterized by multiple organs failure and hemophagocytosis [10]. HLH occurring in the course of adult systemic disease has rarely been reported. Immunosuppression induced by the systemic disease itself and exacerbated by immunosuppressive therapies may result in HLH, with or without an associated infection. The most frequently reported

systemic diseases associated with HLH are systemic lupus erythematosus (SLE) and AOSD [11].

HS shares similar clinical and laboratory features with AOSD [10]. Emmenegger et al. [11] pointed out that 40 percent of patients with HS shared similar clinical features with AOSD. The main differences between the two diseases are cutaneous, articular involvement and different hematological findings [10]. Thrombocytosis and leukocytosis are present in AOSD but pancytopenia is present in HS. The development of cytopenias is an important feature of this syndrome. Ferritin is an acute phase reactant, and hyperferritinemia shows acute disease activation of AOSD. In our case, we made a differential diagnosis between leukemias, lymphomas, drugs, and infectious diseases that originated from viruses. There were no blastic cells of leukemias and lymphomas in the bone marrow puncture-biopsy or any isolated lymph node enlargement in our patients. The serological cultures were sterile so we did not think any viral infectious and neoplastic diseases were triggers of HS in our patient. In our patient, hemophagocytosis was indicated by repeat bone marrow study with constellation of signs, symptoms, and laboratory abnormalities, including fever, hepatomegaly, pancytopenia, hypofibrinogenemia, hypertriglyceridemia, and an elevated serum ferritin levels. We finally showed in our patient AOSD triggered HLH.

Corticosteroid alone has been successfully administered for treatment of macrophage activation syndrome or adult onset Still's disease. However, some patients seem to be resistant to steroids (12), as seen in our case. Although various immunosuppressants have been used, there is no established treatment for ASOD accompanied by macrophage activation syndrome. Chang-Bum Bae et.al [13] study showed that cyclosporine, etoposide, and high-dose steroids were used as the main chemotherapy agents in HLH patients (47.1%). Therefore, we used Etoposide and Cyclosporin A in addition to corticosteroid because our patient was resistant to corticosteroid alone. Later, patient was presented with fungal infection of knee and multiorgan failure, which was treated with antifungals, antibiotics and the immunosuppressive treatment of the underlying disease decreased as described in literature [14].

Furthermore, more than half of the HLH patients (52.9%) died although aggressive chemotherapy and prophylactic antibiotics were used [13]. In previous studies, the overall mortality associated with HLH was reported to be 46% (range 22–60%) [14]. In this study, factors associated with a higher risk of mortality were low hemoglobin levels, a low platelet count, high alkaline phosphatase, high

bilirubin, high ferritin concentrations, older age, secondary infection, and may be aggressive chemotherapy.

#### IV. CONCLUSION

The presented case report shows that HLH occurring in the course of AOSD is an underdiagnosed complication but important clinical entity in terms of patient prognosis. The non-specific and overlapping clinical presentation of both the diseases, causes delay in the diagnosis leading to increased morbidity and mortality.

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