

Case Report

Hemophagocytic Lymphohistiocytosis Complicating the Clinical Presentation of Adult-Onset Still's Disease

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life threatening condition. It is usually secondary to infections, malignancies or autoimmune diseases. HLH is a common complication of Adult-onset Still's Disease (AOSD) and when present together poses diagnostic difficulty due to overlapping clinical features. We present a case of a young male who presented with the complaints of intermittent, moderate grade fever and symmetrical large joints polyarthralgia for the last four years. Clinical examination revealed lymphadenopathy and mild splenomegaly. Subsequent investigations revealed pancytopenia, hypertriglyceridemia and many fold increased serum ferritin. Bone marrow aspiration and biopsy showed granulohistiocytic predominance with hemophagocytosis suggestive of secondary HLH (sHLH) due to AOSD. The patient was treated successfully with systemic steroids. A high index of suspicion is required to avoid delay in the diagnosis of HLH and increased morbidity and mortality.

Key words: Hemophagocytic lymphohistiocytosis, AOSD, HLH.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life threatening condition caused by unrestrained immune activation. In adults, it is usually secondary to viral infections, malignancies or autoimmune conditions. ^[1] HLH is not uncommon in Adult-onset Still's Disease (AOSD) and has been reported to be present in 12% of patients. ^[2] The clinical presentation of both diseases are non-specific, mutually overlapping and similar to that of various infections, autoimmune conditions and malignancies especially lymphomas. ^[3] This causes delay in the diagnosis leading to increased morbidity and mortality. We present an interesting case of secondary HLH with AOSD who had, coincidentally, cholecystitis and

developed generalized maculopapular rash, posing a diagnostic dilemma and therapeutic challenge.

CASE PRESENTATION

A 25 year old male was referred to our hospital with complaints of moderate grade, intermittent fever and arthralgia for the last four years along with colicky upper abdomen pain for the last one week. Arthralgia was present in knee, elbow and wrist joints which was symmetrical in distribution. With these complaints, the patient consulted nearby physician on several occasions and was prescribed NSAIDs and oral steroids which resulted in partial improvement in arthralgia but fever persisted. Subsequently, he developed acute

pain in abdomen along with fever with chills and was referred to our hospital.

At the time of presentation, he was febrile and had severe colicky pain in abdomen. On examination, he appeared toxic and dehydrated with stable vitals. He had moderate grade fever, pallor and multiple tender cervical, axillary and inguinal lymphadenopathy. Abdominal examination revealed tenderness in right hypochondrium with mild hepatosplenomegaly. Other systemic examination was unremarkable. With this presentation, possibilities of liver abscess or acute cholecystitis were considered. Symptomatic and supportive treatment with IV fluids, antipyretics and broad-spectrum intravenous antibiotics were started.

Initial haemogram showed moderate anemia (Hemoglobin: 8.0 g/dl), leucopenia with relative monocytosis (TLC: 2800/ μ l, N57 L21 M20) and raised ESR (50 mm in 1st hour). Liver function was grossly deranged (ALP: 920 IU/l, SGOT: 958 IU/l, SGPT: 181 IU/l, Total protein 4.7g/dl, albumin 2.3 g/dl) with reversal of albumin-globulin ratio. Urine examination revealed mild proteinuria (800 mg/dl/day) without casts, dysmorphic RBCs or active sediments. Blood and urine cultures were sterile. Ultrasonography of abdomen suggested acute cholecystitis. The patient was managed conservatively with adequate hydration, antibiotics and antipyretics. His abdominal pain gradually subsided over the next three days. However, fever persisted and patient developed extreme maculopapular erythematous rash all over the body with gradual worsening of general condition. Cutaneous drug reaction (rash) was suspected and the antibiotics were changed with concurrent local steroid ointment application but there was no improvement. Thus, a multisystem inflammatory condition with cutaneous manifestations was considered and he was further investigated to evaluate for the cause.

The haemogram showed bicytopenia and biochemical investigations revealed

raised serum TG (269 mg/dl) and high serum ferritin levels (2100 μ g/l) which raised the suspicion of HLH. Bone marrow aspiration and biopsy was performed which showed granulohistiocytic predominance with hemophagocytosis (Figure 1). Thus, a diagnosis of secondary HLH was made based on HLH 2004 criteria. [2]

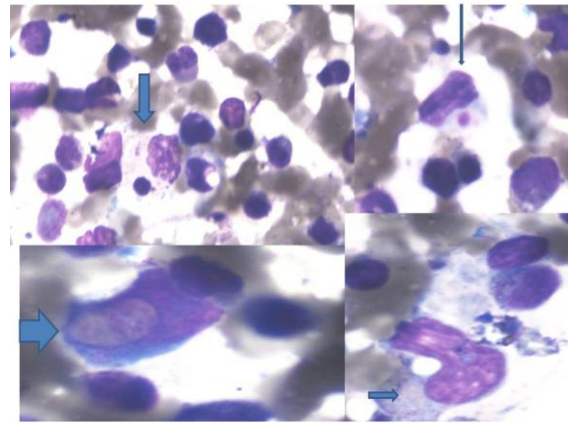


Figure 1: Thick Arrows points towards a histiocytic cell with phagocytosed erythroid cell. Thin arrows points at a histiocyte with engulfed platelet

He was further worked up for primary cause. Viral markers (HIV 1 and 2, HBsAg, anti HCV antibodies, EBV serology, and CMV pp65 antigen) and autoimmune markers (RF, ANA, ANCA) were found to be negative. Sputum AFB and serum rk-39 were also negative. Serum galactomannan level was mildly raised (Index: 0.5) but repeated fungal cultures were sterile. Whole body FDG PET scan was performed to screen for any malignancy which showed increased uptake in inguinal lymph nodes. Excision biopsy of this lymph node with histopathological examination showed features suggestive of reactive lymphadenitis.

Finally, in view of presenting history, a clinical diagnosis of AOSD associated with secondary HLH was made based on Yamaguchi's criteria [4] and HLH 2004 Criteria. [2] Inj. Dexamethasone (15mg/day) in divided doses was started and the patient was followed up with serial serum ferritin and TG levels.

The patient showed both subjective and objective improvement with gradual decrease in serum ferritin and TG levels. Within a week, he became afebrile with

normalization of liver enzymes and blood counts. Maculopapular erythematous rash gradually healed with scaling and hyperpigmentation. The patient discharged from hospital and kept under OPD follow-up with gradual tapering of oral steroids which was stopped after six weeks.

DISCUSSION

The diagnosis in this patient was challenging because of non-specific signs and symptoms. The patient presented with pain in joints, fever, splenomegaly, pancytopenia and acute cholecystitis. Subsequently, he developed generalized maculopapular erythematous rash which that was initially suspected to be “drug reaction”. However, the patient’s condition did not improve on discontinuation of the drug which raised the possibility of any other inflammatory condition. It is important to note that fever, splenomegaly, pancytopenia and cutaneous manifestations occur in around 65% of HLH cases. [5]

In such cases, serum ferritin is an important marker. Markedly raised serum ferritin is found in four rare conditions like AOSD, HLH, Catastrophic Antiphospholipid syndrome and septic shock. [6] Serum ferritin is reported to be 90% sensitive and 96% specific in diagnosing HLH when cut off level is >10,000 µg/l and 82% sensitive and 42% specific for cut off level >500 µg/l. [7] The raised serum ferritin level of 2100 µg/l in the patient raised the doubt of sHLH that was confirmed by bone marrow examination.

In case of secondary HLH, the patient is extensively worked up for primary etiology and treated accordingly. In untreated cases, relapse of HLH is common with significant treatment resistance and high mortality. [2] In our patient, infective causes, autoimmune conditions and malignancies were reasonably ruled out after extensive investigation and a clinical diagnosis of AOSD was made based on history of high spiking fever with arthralgia.

High dose corticosteroid is first line approach for treatment of sHLH especially with AOSD because of excellent response. [8,9] Other, treatment for HLH includes etoposide, dexamethasone and cyclosporine A and use of intrathecal methotrexate and corticosteroids in CNS involvement especially in familial HLH cases. [2]

CONCLUSION

HLH secondary to AOSD often poses diagnostic difficulty due to overlapping and nonspecific clinical features. A high index of suspicion is required to avoid delay in the diagnosis. Estimating serum triglyceride and ferritin levels can be useful initial investigation.

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