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Hemophagocytic Lymphohistiocytosis: A Case Series Over 4 Years in a Saudi Hospital

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare but rapidly fatal disorder. It is characterized by aggressive proliferation of activated macrophages and histiocytes which leads to the clinical manifestations of the disease. Although the mechanism is not entirely understood, a theory of inappropriate immune reaction is currently accepted. Presentation can be either primary (familial) which is an inherited form of HLH or secondary which is an acquired form that occurs in response to immunologic over-activation as seen in severe infections, immunodeficiency and malignancy.

Case Series: We retrospectively report a series of five cases who were diagnosed as secondary HLH or macrophage activation syndrome (MAS) between 2013 and 2017. These were Saudi Arabian patients fulfilled the criteria of diagnosis and were managed at our tertiary hospital that serves the northwestern region of Saudi Arabia. Three out of 5 patients have been managed successfully and currently alive, while the 2 other patients died of severe progressive disease. Effective early diagnosis and fast installation of treatment contributed to an instant clinical and laboratory improvement and success of management, whereas late diagnosis will inevitably lead to a progressive fatal outcome. Interestingly, tumor lysis syndrome was noticed in 3 patients after starting treatment, so it is advised to monitor this condition while treating this cohort of patients.

Conclusions: HLH is a rare and under-diagnosed disorder since it can mimic and overlap with other conditions. Prompt diagnosis and management is life saving and every effort should be done to differentiate it from other similar conditions that necessitate different pathways of management.

Keywords: *Hemophagocytic lymphohistiocytosis; macrophage activation syndrome; tumor lysis syndrome; Saudi Arabia*

Background

Hemophagocytic lymphohistiocytosis (HLH) is a rare fatal disorder due to histiocyte and lymphocyte overactivity. It is a non-malignant condition despite the uncontrolled growth nature of the inflammatory and immune cells that can be regarded as highly stimulated but ineffective [1].

Clinical presentation includes fever, pancytopenia, hepatosplenomegaly, lymphadenopathy and cutaneous manifestations. These manifestations can occur in association with different diseases, in particular; malignant disorders. Nevertheless, when combining a set of clinical features with laboratory data, an expert physician can competently come up with a definite and early diagnosis [2].

Mortality is inevitable without treatment especially in the familial form of the disease, and fortunately, chemotherapy and immunosuppressive agents have significantly reduced the mortality rate in such aggressive disorder [3,4].

Case Series

We retrospectively reviewed the medical records of pediatric patients in King Salman Armed Forces hospital (KSAFH). Target population is pediatric patients from 1 to 14 years of age. Data collected for patients under regular follow up in 4 years period from 2013 till 2017. Study location is KSAFH which is located in Tabuk (northwestern region) Saudi Arabia. Patients with confirmed diagnosis of HLH or MAS were retrieved and reviewed separately. All demographic and clinical and imaging data were collected and entered into SPSS v.20. Frequencies and percentages of the descriptive analysis of the data are presented in tabulated form.

Results

Five patients (4 females) fulfilled the criteria of HLH or MAS, age was 9 months to 8 years. All the patients presented with fever and splenomegaly, 3 presented with rash and hepatomegaly, 2 presented with bony aches and joint swelling and 1 patient presented with generalized lymphadenopathy (Table 1). Two patients were diagnosed as systemic onset juvenile idiopathic arthritis (SJIA) and started treatment on non-steroidal anti-inflammatory drugs (NSAID) after which they developed a picture of MAS manifested by coagulopathy, significantly low ESR and evidence of hemophagocytes in bone marrow (2 patients) and lymph node biopsy (1 patient). The three other patients were diagnosed as secondary HLH mostly due to an infectious cause. The three patients fulfilled at least 5 out of 8 of the diagnostic HLH-2004 criteria [5]. Bone marrow aspirate and biopsy was performed in all the patients and showed a picture of hemophagocytosis with no evident malignancy (Table 2).

Symptoms/signs	Number of patients = Total 5	Frequency
Fever	5	100%
Splenomegaly	5	100%
Hepatomegaly	3	60%
Skin rash	3	60%
Lymphadenopathy	1	20%
Jaundice	3	60%
Rheumatologic manifestations	2	40%

Table 1: *Main presenting symptoms and signs.*

Laboratory results	Number of patients = Total 5	Frequency
Cytopenia	5	100%
Elevated triglycerides	4	80%
Low fibrinogen	4	80%
Elevated ferritin	4	80%
Coagulopathy	4	80%
Low ESR	2	40%
Elevated liver enzymes	3	60%
Positive ANA, anti ds DNA	2	40%
Hemophagocytes in bone marrow	5	100%
Hemophagocytes in lymph node	1	20%

Table 2: *Main laboratory finding.*

Two patients with MAS were treated with steroids and etoposide according to the induction phase of HLH-2004 protocol and one of them received IVIG at day one of treatment [5]. Tumor lysis syndrome (TLS) occurred at the initiation of treatment and was managed successfully using iv hydration, recombinant urate oxidase and strict fluid balance, both patients went into remission post induction and were referred to rheumatologist to resume the management of SJIA.

One patient with secondary HLH was treated with induction phase of HLH-2004 protocol, went into clinical and laboratory remission and currently alive with regular follow up. While the 2 other patients with secondary HLH died of severe sepsis, disseminated intravascular coagulation and respiratory distress syndrome despite initiation of treatment.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a fatal hyperinflammatory condition with an incidence of 1.2 cases per million which is most probably an underestimate [6]. It can be classified into primary HLH which is familial and secondary acquired HLH. Secondary HLH can occur in association with severe infection, rheumatologic disorders, immunodeficiency and malignancy [7].

Macrophage activation syndrome (MAS) is a subset of HLH and is considered as a life-threatening condition that occurs secondary to treatment or a complication of rheumatologic disorders. It seen most frequently with SJIA and is characterized by impaired liver function, coagulopathy, pancytopenia and neurologic manifestations [8].

Our series of patients included those who were diagnosed as either secondary HLH or MAS, while no patient was proven to have familial HLH which might be attributed to missed diagnosis or lack of early advanced laboratory investigations.

Diagnosis of HLH depends on specific diagnostic criteria that were set up by the Histiocytic Society trials HLH-94 and HLH-2004 (Table 3). Despite the non-specificity of these criteria that might occur in association with different diseases, it's the only available and valid utility for diagnosis of HLH, hence; 5 out of 8 criteria are required to make a definite diagnosis [5].

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below): *
Fever
Splenomegaly
Cytopenias (affecting ≥ 2 - 3 lineages in the peripheral blood):
hemoglobin < 90 g/L
platelets < 100 x 10^9/L
neutrophils < 1.0 x 10^9/L
Hypertriglyceridemia and/or hypofibrinogenemia:
fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dL), fibrinogen ≤ 1.5 g/L
Hemophagocytosis in BM, spleen, or lymph nodes
Low or absent NK-cell activity
Ferritin ≥ 500 g/L
Soluble CD25 (i.e., sIL2r) ≥ 2400 U/mL†
*Supportive criteria include neurologic symptoms, cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia and transaminitis, hypoalbuminemia, hyponatremia, elevated D-dimers, and lactate dehydrogenase (see text for details). The absence of hemophagocytosis in the BM does not exclude a diagnosis of HLH.
†New data show normal variation by age. Level should be compared with age related norms.

Table 3: *HLH-2004 diagnostic criteria [5].*

Almost all of our patient in this series fulfilled the criteria, as they met both the clinical and laboratory requirements to make a definite diagnosis.

There is no need to distinguish primary or secondary HLH at treatment initiation, as both forms should be treated immediately without delay. Early and effective therapy improved the overall survival and decreased mortality rates from 95% to almost 30% [9].

While bone marrow transplantation is the mainstay of management in patients with primary HLH, those with secondary HLH respond significantly to a combination of immunosuppressive and chemotherapeutic agents; and only when etoposide was added to treatment regimen, a sustained remission was achieved [10].

Other agents include cyclosporin, steroids, immunoglobulins and intrathecal methotrexate. Patients with MAS may respond to steroids alone or combination of steroids and immunoglobulin and both MAS and secondary HLH will not require bone marrow transplant once achieved complete clinical and laboratory remission [11].

All the patients in our series were treated with steroids, immunoglobulins and etoposide. The three alive patients achieved rapid and complete remission during induction and thus didn't require further management. While those who didn't achieve remission had a progressive course of disease and died of severe infection, sepsis and DIC.

Interestingly, tumor lysis syndrome has been detected in 3 patients on initiation of treatment. This is a syndrome that is characterized by a group of metabolic and electrolyte abnormalities which may eventually lead to acute renal injury and failure. This was detected early in 2 patients and were managed successfully, while in the third patient, the delay in diagnosis and management contributed as one of the main causes of death in this patient [12].

Besides the natural course of the disease, we assume that mortality due to HLH can be attributed to several avoidable factors; these include: 1- delay or hesitancy in diagnosis, 2- similarity of the diagnostic criteria with other diseases, 3- lack of disease awareness and late referral and consultations, 4- un-anticipated TLS thus failure of early detection and management.

Unlike familial HLH, secondary HLH occurs as a consequence of an underlying condition. These includes malignancies, rheumatologic disorders, severe infections and immunologic conditions. Proper management and close follow up of these conditions will facilitate early recognition of HLH. Furthermore, HLH is a group of clinical features and laboratory findings, the best way to diagnose this disease is high level of suspicion and anticipation because the clinical feature may overlap significantly with other diseases.

Conclusion

Hemophagocytic lymphohistiocytosis is an under-diagnosed condition and every effort should be done to early detect, anticipate and manage this disorder accordingly. Special attention should be considered when initiating the management of rheumatologic disorders that may lead to MAS, also anticipation of tumor lysis syndrome should be kept in consideration when starting immunosuppressive therapy for HLH.

Ethics Approval and Consent to Participate

Not applicable.

Competing Interests

The author(s) declared no potential conflicts of interest.

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