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Case Report

Haemophagocytic Lymphohistiocytosis Syndrome Following Influenza A Infection a Rare and Fatal Complication

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is not rare but may be fatal. It may be complication that can progress when Influenza A confounds immunocompromised children [1]. We report a case of Hemophagocytic lymphohistiocytosis complicating an influenza A infection in a one year and 4 months old well thriving girl. The child had come with simple influenza infection which soon progressed to ARDS and multi organ failure when HLH was suspected and bone marrow was done which conformed and the other criteria were met for the diagnosis of HLH. The child was appropriately treated and supported by ECMO and could be discharged home.

Keywords: *Hemophagocytic Lymphohistiocytosis (HLH); Influenza A; Haemophagocytic Lymphohistiocytosis Syndrome (HLHS)*

Introduction

Haemophagocytic Lymphohistiocytosis Syndrome (HLHS) can be primary which may have genetic predisposition or secondary that is acquired later [9]. Secondary HLHS may be secondary to either infections or malignancies. HLH complicating influenza A infection in well thriving children is quite rare. We report a one year and four-month old girl who presented with high fever, cough diagnosed to have influenza A infection later developed HLHS. Clinicians should be aware that HLHS may be a serious complication of influenza A infection.

Case Report

One year four months old female child, second by order of birth, born of non-consanguineous marriage with family history of paratyphoid and Influenza A+ in sibling was brought with history of high grade fever, cough, vomiting, poor oral intake since 3 days.

On examination child was sick looking, febrile, dehydrated, and drowsy. Throat was congested and chest had bilateral crepitation and rhonchi. Investigations at admission showed Hb 9.1, WBC 8590, N 45, L 53, Platelets 340000 and CRP of 6.5; Influenza A was positive.

Child was admitted and treatment started with IV fluids, Tamiflu and nebulization. Fever spikes persisted. IV antibiotic Ceftriaxone was added. In view of drowsiness, MRI brain and Lumbar Puncture was done. Repeat blood test showed decrease in Hb, WBC, and Platelets. (Hb 8.7 mg/dl, WBC 6180, N 58, L 39, platelets 2.36). Peripheral Smear showed microcytic hypochromic anemia, anisopoikilocytosis, elliptocytosis and pencil cells. Lumbar puncture showed RBCs. Second line investigations were sent. Inj. Acyclovir and Vancomycin were added.

Fever spikes persisted. Child developed generalized tonic clonic convulsions and was loaded with Phenytoin. In spite of these, fever persisted and developed respiratory distress and desaturation. Oxygen therapy started. Chest x-ray showed pleural effusion. Pleural tapping done. Investigations showed falling Hb and dropping WBC and platelets (Hb 8.1, WBC 2480, with N 37%, Platelets 1.47lac). In view of increase in distress with suprasternal retractions and increased requirement of oxygen, she was intubated and put on ventilator. 2D-ECHO was done to rule out pulmonary hypertension. Ventilator settings had to be increased and chest X-ray showed ARDS. She had to be put on high frequency ventilator and nitric oxide therapy was started. For refractory hypotension inotropes and hydrocortisone were added.

Fever spikes persisted and investigations showed further fall (Hb 7.1, WBC 2250, N 38, L 58, Platelets 1.44). Blood culture sent several times were sterile.

On ventilator she developed pneumothorax. ICD was inserted. Because of persistent fever, Hepatosplenomegaly, Anaemia, Leukopenia along with Thrombocytopenia with normal CRP we thought of Haemophagocytic Lymphohistiocytosis and hence ferritin and lipid profile was sent. Ferritin was 5000, and she had high triglycerides. To confirm we decided to do bone marrow aspiration.

Bone marrow aspiration showed marked increase in histiocytes, phagocytes suggestive of Haemophagocytic Lymphocytosis Syndrome. We could not do the HLA testing. She was started on pulse methylprednisolone. She required ECMO, steroids and got better after 2 months of hospital stay.

Parameters	Day 1	Day 3	Day 6	Day 7	Day 8	Day 9	Day 11
HB	9.1	8.7	8.4	8.1	7.1	12.5	11.6
WBC	8590	6180	3860	2480	2250	3040	5700
Neutrophil	45	58	42	37	38	28	45
Lymphocytes	53	39	55	57	58	65	31
Platelets (lac)	3.39	2.36	2.06	1.47	1.44	1.15	1.11

Table 1: *Lab parameters.*

Discussion

Influenza A virus infection are generally mild and patients mostly recover completely [2]. Some H1N1 patients may have hematological findings like leucopenia, neutropenia, and idiopathic thrombocytopenic purpura [3,4]. Very rarely, HLH has been observed [3]. HLHS presents as febrile disorder along with multiple organ involvement. Differential diagnosis are infections, prexia of unknown origin, liver failure, macrophage activation syndrome, or encephalitis. In a study conducted on HLH patients 94 of 249 patients had prominent clinical signs like Hepatosplenomegaly (95%), Lymphadenopathy (33%), Neurologic symptoms (33%) and Rash (31%) [5].

The diagnosis of HLH is established if five of the following eight findings are present: Fever 38.5°C, Splenomegaly, Peripheral blood cytopenias with at least two of the following: Hb < 9 g/dL, Platelets < 100,000/microL, ANC < 1000/microL, Hypertriglyceridemia (fasting triglycerides > 265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL), Hemophagocytosis in bone marrow, spleen, lymph node or liver, Low or absent NK cell activity, Ferritin >500 ng/mL only 80% specificity (ferritin >3000 ng/mL more indicative of HLH), Elevated soluble CD25 (soluble IL-2 receptor alpha) two SD above normal [6,7].

The differential diagnosis can include Macrophage activation syndrome (MAS), Infection/sepsis, Liver disease/liver failure - Multiple organ dysfunction syndrome, Auto-immune lymphoproliferative syndrome (ALPS), Encephalitis, Drug reaction with eosinophilia and systemic symptoms (RESS), Child abuse, Kawasaki disease, Cytophagic histiocytic panniculitis, Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or drug-induced thrombotic micro angiopathy (DITMA), Transfusion-associated graft-versus-host disease (ta-GVHD) [6-9].

Our patient had prolonged fever, fatigue, pneumonia, ARDS, pancytopenia, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia, and hemophagocytosis at bone marrow aspiration. Using criteria of HLH 2004 we could fit the diagnosis of HLH in our case [10,11].

A case in 17-year-old female patient with H1N1 influenza A related HLH who completely recovered with steroid and oseltamivir treatment was the first to be reported [12]. Following this report, 23 more patients were reported of various ages between 2 months and 61 years old [13-19]. In most of the cases, pancytopenia, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia and hemophagocytosis at bone marrow aspiration were detected [13-19].

Mc Clain., *et al.* had shown association of HLH with EBV virus in immune deficient children [20]. Harms., *et al*. confirmed in eight patients H1N1 association with HLH in autopsy [21]. There is only one case report as per our knowledge by Mou SS of influenza A infection complicated by HLH in a three-year-old girl [22].

Potter., *et al.* looked into deaths during epidemics of H1N1 in 2009 and speculated that those may be due to HLH and found 36% had developed HLH and 89% of them died [23]. Steven., *et al.* described HLH complicating influenza A in a 3-year-old child leading to death in spite of ECMO [24].

One retrospective study which included 18 pediatric cases showed 88.9% cases were previously healthy and the case fatality rate was 61.1%, and all fatal cases died within 2 months of disease onset. The infectious agents associated with HPS were identified in 11 cases (61.1%), and (82.7%) of them had evidence of Epstein-Barr virus (EBV) infection or reactivation [25].

As the management of HPS includes intravenous immunoglobulin and steroids as the first-line agents, these were administered in 16 cases and 11 cases, respectively, while etoposide was administered in 5 cases which were refractory to immunoglobulin and steroids during the late phase of disease. We also treated our patient with immunoglobulin and steroids [25].

As per our knowledge goes this is the only case, which survived after Influenza A, complicated by Haemophagocytic lymphohistiocytosis and ARDS. Most probably it could happen due to early suspicion and intervention.

High mortality has been reported in patients with HLH if diagnosis is delayed. Patients with early diagnosis and treatment have favorable outcomes. It also leads to prolonged viral load clearance and cytokine response.

Conclusion

We report a previously healthy child with influenza associated with HLH. Our patient met criteria of HLH and started early treatment. HLH complicating Influenza pathogenesis is not completely understood. One should have high suspicion whenever we deal with babies with high fever, deranged blood counts not explained by infection or other cause and rule out HLHS.

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