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Case Report

Cytomegalovirus Infection Induced Hemophagocytic Syndrome in Infant with Hyper Ige Syndrome -

Mohamed Sellouti[1]*, Ilyas El Kassimi[2], Abdelhakim Ourrai[1], Amale Hassani[1], Rachid Abilkassem[1] and Aomar Agadr[1]

[1]Department of Pediatrics, Mohammed V Military teaching Hospital, Mohammed V University, Souissi, Rabat, Morocco
[2]Department of Internal Medicine, Mohammed V Military teaching Hospital, Mohammed V University, Souissi, Rabat, Morocco

***Address for Correspondence:** Mohamed Sellouti, Department of Pediatrics, Mohammed V Military teaching Hospital, Mohammed V University, Souissi, Rabat, Morocco, Tel: +212660627466; E-mail: msellouti@gmail.com

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ABSTRACT

Hemophagocytic syndrome is a rare and life-threatening disease. It is characterized by the combination of clinical features, (fever, hepatosplenomegaly and lymphadenopathy), biological abnormalities (cytopenias, liver cytolysis, high plasma triglycerids, and coagulopathy) and hemophagocytosis involving numerous organs preferentially bone marrow, caused by a dysregulation in cytokine secretion and benign proliferation of lymphocytes or histiocytes.

This case report presents a 2 month-old girl who presented with Hemophagocytic syndrome and concurrent Cytomegalovirus infection, and was subsequently diagnosed with Hyper IgE syndrome.

To our literature review, this is the first case of Hemophagocytic syndrome and CMV infection in the setting of Hyper IgE syndrome. Although this association is likely to be entirely coincidental, clinicians should be aware of this rare clinicopathologic entity. Complementary investigations and accurate diagnosis are important strategies to confirm this association urgently for initiate appropriate treatment.

Keywords: Cytomegalovirus; Hyper-IgE syndrome; Hemophagocytic syndrome; Immunodeficiency

BACKGROUND

Hemophagocytic syndrome is a multisystemic disease that results from an intense activation of the immune system characterized by uncontrolled proliferation of macrophages and oversecretion of cytokines [1]. This disease was described by Risdull in 1979 in a group of patients receiving immunosuppressive drugs for renal transplantation [2]. This syndrome is classified into 2 groups. Primary Hemophagocytic syndrome is a hereditary immune disorder that is associated with an inherited genetic abnormality or secondary Hemophagocytic syndrome when the disease occurs with systemic infection, immunodeficiency, or underlying malignancy [3]. It's characterized by persistent fever, cytopenias, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia with hemophagocytosis in the bone marrow liver, or lymph nodes [4].

Hyper-IgE Syndrome (HIES) is a primary immunodeficiency syndrome resulting in elevated serum IgE levels and typified by the development of recurrent staphylococcal skin abscesses, eczema, and recurrent pulmonary infections with pneumatocele [5]. Autosomal Dominant HIES (AD-HIES) have been found to be due to mutations in STAT3 although DOCK8 (Dedicator of cytokinesis 8) mutations have been identified in patients with Autosomal Recessive HIES (AR-HIES). The signal transducer and activator of transcription 3 gene (STAT3), is involved in protein production regulating genes, which impact T-cell maturation [6]. HIES predisposes affected patients to frequent infections and higher risk for facial, dental, skeletal, and connective tissue abnormalities. Hemophagocytic syndrome occurs after strong immunologic activation, often related to an infectious etiology.

In this case we describe, an unusual case of secondary Hemophagocytic syndrome following cytomegalovirus infection in a tow month old baby subsequently diagnosed with IgE syndrome.

CASE PRESENTATION

A two month five days old female infant was admitted to pediatric department with a 10 days history of fever and lethargy. The fevers were associated with disseminated maculopapular rash and abdominal distention. The girl was delivered by cesarean section, with a birth weight of 2.9 kg. Postnatal period was uneventful. The baby was on exclusive breast feeding, had no developmental delay, and was fully immunized for age.

On examination she looked pale with no facial dysmorphism. She was alert but febrile. Maculopapular rash were noted all over body (Figure 1). She had hepatosplenomegaly, bilateral leg oedema but had no lymphadenopathy or focal neurologic deficits.

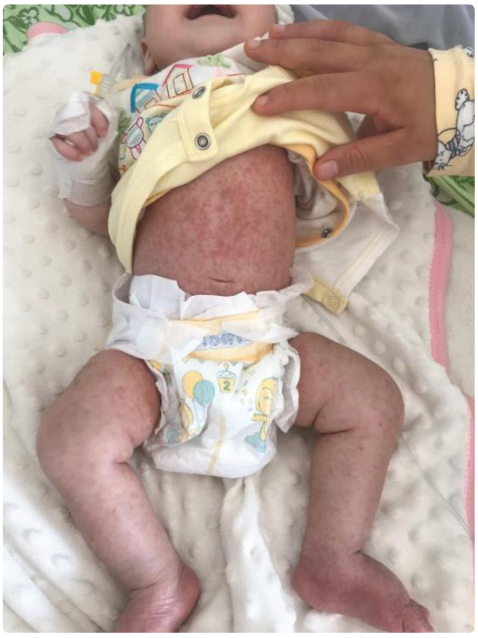

Figure 1: Characteristic crusted papulopustular eruption.

Biological assays showed pancytopenia, with hemoglobin 8.6 g/dl (NR :13-17g/dl), total leukocyte count 22000/mm3 (with 25% neutrophils, 70% lymphocytes, 5% monocytes), platelet count 119000/mm3 (NR :150000-400000 /mm3), and an erythrocyte sedimentation rate at 31mm the first hour. Alanine aminotransferase was 765 IU/L (NR : 5–50 IU/L), Aspartate aminotransferase was 1606UI/l (NR : 7–40 IU/l), triglyceride at 343 mg/dl (NR: < 150 mg/dL), and the ferritin level was at 3246 ng/ml (NR: 30-400 ng/ml), C- reactive protein 327 mg/dL (NR: < 5 mg/dL). IgA, IgM, IgG and IgG subclasses were within normal range. A number of $CD4^+$ and $CD8^+$ T lymphocyte in serum were in normal range. However, serum IgE level was markedly elevated at 4823 IU (NR: 0-50 IU).

Chest computed tomography scan showed right pneumatocele. Abdominal ultrasonography revealed hepatosplenomegaly. Quantitative PCR examination of blood, and urine was highly positive for CMV with 10549 copies/ml. Bone marrow biopsy revealed moderate hemophagocytosis. With a high suspicion HIES, genetic testing was sent which detected an autosomal dominant (c.1909G > A) at DNA-binding domain of STAT3 gene.

The patient was put on intravenous gancyclovir at a dosage of 10 mg/kg/day was for three weeks followed by gancyclovir 5 mg/kg/day for three weeks. Intravenous immunoglobulin was administered on two successive days in order to treat Hemophagocytic syndrome. The evolution was marked by clinical and biological improvement.

DISCUSSION

Hemophagocytic syndrome characterized by an uncontrolled accumulation of activated T-lymphocytes and activated histiocytes derived from unregulated cytokine storm with numerous possible etiologies, including genetic predisposition, autoimmunity and immunodeficience. [7,8]. A key factor that causes Hemophagocytic syndrome manifestations can be the failure of normal negative feedback from cytotoxic T cells and natural killer, resulting in the overwhelming activation of hemophagocytic monocytes [9-10]. Primary Hemophagocytic syndrome is an autosomal recessive disease. It is also called familial HLH. It's can appear sporadically as familial hemophagocytic lymphohistiocytosis. Secondary Hemophagocytic syndrome is a reactive disorder causing strong immunologic activation, often triggered by systemic infection, malignancy, use of drugs or immunodeficiency [11]. Diagnostic criteria for Hemophagocytic syndrome include fever, splenomegaly, cytopenia that affects 2 cell lines, coagulopathy, hypertriglyceridemia and/or hypofibrinogenemia and hemophagocytosis in bone marrow [8]. In our case, the patient had hepatosplenomegaly, bicytopenia (anaemia and thrombocytopenia), haemophagocytosis in bone marrow, hyperferritinaemia and hypofibrogenaemia.

Serological investigation confirmed CMV infection. As the patient is just two month old, we could not determine whether it is a congenital or acquired CMV infection. It is the most common congenital infection in humans and also an etiology of Hemophagocytic syndrome in infants or immunosuppressed population. The clinical spectrum of congenital CMV infection varies widely. CMV infection may manifest with no clinically apparent symptoms, however, 90-95% of infants manifests with symptoms such as generalized petechiae, direct hyperbilirubinemia, hepatosplenomegaly, purpuric rash, microcephaly, seizures, focal or general neurologic deficitis, retinitis and intracranial calcifications [12].

HIES was first defined by Davis in 1966 in patients who suffered from recurrent infections and severe dermatitis with "cold" abscesss [13], and it was reported by Buckley in 1972 as "eczematous eruptions" beginning early in childhood, presenting symptoms may be as recurrent bacterial and fungal infections [14]. It is a rare immunological disorder with two types of HIES have been reported, autosomal dominant and recessive forms [13,15]. Autosomal dominant HIES, caused by mutations in the Signal Transduction And Activation Of Transcription 3 gene (STAT3) identified in 2007 presents with skeletal, connective tissue, and pulmonary abnormalities [13,16,17]. Autosomal recessive HIES, caused by mutations In Dedicator of Cytokinesis 8 (DOCK8) gene identified in 2009 manifests as severe eczema, recurrent bacterial and viral skin infections [15,7]. HIES is associated with the STAT3 mutation. STAT3 mutations result in failure of differentiation of Th17 cells and subsequent failure of IL-17 secretion [18-20]. Because the STAT3 protein plays an important role in signal transduction induced by many cytokines, including interleukin (IL)-6, IL-10, IL-17, IL-21 and IL-22, its deficiency results in upregulation and downregulation of proinflammatory and anti-inflammatory proteins as well as important in the regulation of CD8 T-cell responses [18,21]. This explains part of the increased susceptibility to infection seen in AD-HIES. Clinical HIES scoring system gives an estimate of HIES's likelihood with more than 40 suggestive points [15,20]. However, a genetic mutation responsible of this disease remains the clef of diagnosis confirmation.

CONCLUSION

The aim of this article is to aware clinicians of the possible association between Hemophagocytic syndrome and HIES during infancy. This is coincidence or causative relationship, however more studies are needed to explore this association. A vigilant eye and suspicion at a younger age might benefit patients and effective and rapid therapy can be started early which could decrease morbidity and mortality.

CONSENT

The authors certify that they have obtained all appropriate patient consent forms for publication of this case report.

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