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Clinical Case Report

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Hemophagocytic Lymphohistiocytosis and Diagnostic Difficulties

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Abstract

Familial haemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive disorder of immune dysregulation associated with uncontrolled T cell and macrophage activation and hypercytokinaemia. HLH affects primarily pediatric population, mainly infants of less than 3 months of age. It is important to have a high index of suspicion for diagnosis since an early diagnosis is crucial to decrease the significant mortality associated the disease. This article gives a case historie and review the varied clinical presentations, pathophysiology, prognosis and treatment of the entity.

Keywords: Cytopenia, Fever, Consanguinitie, Macrophage activation, Childhood

Introduction

Familial haemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive disorder of immune dysregulation associated with uncontrolled T cell and macrophage activation and hypercytokinaemia. The incidence of FHL is 0·12/100·000 children born per year, with a male to female ratio of 1:1 [1]. Familiar HLH cases usually present in the first years of life, but cases in adolescents and young adults have also been reported [2, 3]. The disease is classified into six different types based on genetic linkage analysis and chromosomal localization; five specific genetic defects have been identified, which account for approximately 90% of all patients [4]. The major immune dysfunction is an absence of down-regulation of abnormally activated lymphocytes and macrophages [5]. Macrophages become activated and secrete cytokines, leading to tissue damage and a

severe inflammatory reaction. At same time, cytotoxic T cells and NK cells are unable to eliminate the over activated macrophages leading to their further activation, associated with increased levels of interferon gamma and other cytokines: Tumor Necrosis Factor Alpha (TNF a), soluble receptor of Interleukin (IL) 2 or CD25, IL-6 and IL-10 [6]. Patients with F-HLH have defects in this perforin-dependent and granzyme-dependent pathway, resulting in the inability of the NK cells or CTLs to down-regulate the immune response [7, 8]. Genetic testing is also commonly used for siblings and to confirm a suspected diagnosis; it is important to distinguish HLH from sepsis. In secondary, or reactive, HPS there is often an associated "predisposing condition" causing immune dysregulation, such as malignancy (particularly lymphoma), immunodeficiency, or autoimmune disease, and/or a "trigger", most commonly infection such as Epstein–Barr virus (EBV) [8]9 . In some cases, an associated disease process is not identified [10].

Case Presentation

Child girl of 03 years resulting from a consanguin marriage 2nd degree, without particular antecedents, patient since 15 days, admitted to our service for an infectious and tumoral syndrome. The clinical examination at his admission found a febrile girl at 40 °, with intense cutaneous mucosa, cutaneous haemorrhagic syndrome (made petechiae in the abdomen), the Abdomen was ballooned, Transit preserved. The liver was hyertrophied with a hepatic area as 12 cm, with splenomegaly type IV. Neurological examination was normal, we did not find abnormal movements. Biologically there was pan cytopenia with hemoglobin at 6.6g/dl, leukocyte and platelet levels was 0. We found macrophage activation syndrome with hyperferiitinemia at 17621,27 ng/ml without associated hypertriglyceridemia, normal fibrinogen level, moderate hepatic cytolysis, and positive inflammatory status with serum hypergammablobulinemia. The serology HIV, HBS, HCV were normal, Syphilis TPHA and Cmv serology blood test were negative. Leishmanian serology: HAI (-), Western Blot: (-), PCR (k13): EBV serology was also normal. All our blood cultures were negative. The blood smear had not visualized blasts, the medullogram found a poor marrow with lymphocytic hemophagocytosis. The genetic study confirmed the abnormal expression of perforin (PRF1) .The treatment appealed to ciclosporin and high doses of corticosteroids.

Discussion

HLH is caused by a defect in inflammatory signals that results in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway. Untreated, approximately 95% of children will die of the disease [11, 12]. Our patient had hyperinflammatory syndrome classically described to include the development of fever, splenomegaly, and cytopenias. The serum ferritin was altrough 17621,27 ng/ml compared to that of the literature that retains 7485 ng/ml [13]; over 10,000 mg/l have sensitivity and specificity of 90% and 96%, respectively, for diagnosis of HLH2. We have found no hypertriglycedemia and no hypofibrinogenemia in our case. However a high percentage (up to 24%) of FHL cases are associated with parental consanguinity [14]. In the present study it was present. A recent study in India [15] showed that 36% of patients had CNS symptoms at the time of the presentation, which were eventually diagnosed with HLH. However, our patient had no CNS involvement at diagnosis. The specific treatment for HLH is mainly based on the HLH-94 protocol, or a list of clinical trials rather than treatment based on the HLH-2004 protocol. Therapy Based on the HLH-94 protocol includes weeks of treatment for induction on etoposide and dexamethasone, with a intrathecal treatment for those who reach from SNC.

For intrathecal therapy with methotrexate Hydrocortisone are generally used. Dexamethasone is the preferred corticosteroid because it can cross the blood-brain barrier. It is administered by intravenous or oral route and tapered during the induction of eight weeks [16]. The HLH-2004 protocol was initiated by Histiocyte Society in 2004 and closed in December 2011 and the results of the study are expected. Major changes were added simultaneously with cyclosporine topside. For our patient, the decision to put boluses of corticosteroids and to take over with ciclosporin was a collegial decision (in collaboration with experts) considering the clinical state of our patient and the severity of the cytopenias. The median of survival in patients with HLH is around 40% with treatment based on HLH-94 guidelines. Poor prognosis includes younger age, CNS involvement, and failure of treatment induces remission before bone marrow transplantation remains the only curative therapy [17].

Conclusion

In children presenting with prolonged fever, organomegaly and cytopenia, suspected HLH must be asked for early diagnosis and appropriate therapy. Molecular diagnostics should always be tried, and a bone marrow transplant offered every time an HLA compatible donor is offered.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethical committee of University Teaching Hospital, Belfort, Algier's, Algeria.

Informed consent

Informed consent has been obtained from the parents of case (3 year old girl) included in this study.

Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of interest

The authors declared no conflict of interest.

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