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CASE REPORT

Synchronous brain and intravascular B-cell lymphoma after remission of an adult hemophagocytic syndrome

Válter R. Fonseca[1,2], Eduardo Espada[2,3], Ruth Geraldes[2,4], Santiago Ortiz[5], Rita Sousa[6], Dolores Lopez[5], Marisa Teixeira Silva[1] & Rui Victorino[1,2]

[1]Serviço de Medicina II, CHLN – Hospital de Santa Maria, Lisboa, Portugal
[2]Faculdade de Medicina da Universidade de Lisboa, Instituto de Medicina Molecular, Lisboa, Portugal
[3]Serviço de Hematologia e Transplantação de Medula, CHLN – Hospital de Santa Maria, Lisboa, Portugal
[4]Serviço de Neurologia, CHLN – Hospital de Santa Maria, Lisboa, Portugal
[5]Serviço de Anatomia Patológica, CHLN – Hospital de Santa Maria, Lisboa, Portugal
[6]Serviço de Imagiologia Neurológica, CHLN – Hospital de Santa Maria, Lisboa, Portugal

Correspondence
Válter R. Fonseca, Clínica Universitária de Medicina II, Av. Professor Egas Moniz – Hospital de Santa Maria, 1649 – 028 Lisboa, Portugal. Tel: +351 217805051; Fax: +351 217805610;
E-mail: vfonseca@fm.ul.pt

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Key Clinical Message

Hemophagocytic lymphohistiocytosis (HLH) should be considered in the differential diagnosis of adult patients with white matter disease. Brain involvement can be life-threatening and should prompt aggressive therapy. Even after HLH remission, the possibility of subsequent deterioration due to emergence of an aggressive intravascular lymphoma is highlighted here.

Keywords

Brain lymphoma, hemophagocitic lymphohistiocytosis, intravascular lymphoma, white matter abnormalities

Introduction

Hemophagocytic lymphohistiocytosis (HLH) [1] is a rare and life-threatening hyperinflammatory syndrome caused by genetic mutations (primary HLH) or systemic acquired conditions (secondary HLH) which in adults is most commonly associated with hematological malignancies [2, 3]. Although primary and secondary HLH have usually been considered distinct entities, recent evidence has pointed to an increase in the frequency of heterozygous mutations in *PRF1*, *UNC13D*, and *STXBP2* genes, suggesting an increased overlap between the two forms of the disease [4].

The central nervous system (CNS) is commonly affected in children with HLH where white matter abnormalities are characteristic [5]. In adults, neurological manifestations have been reported in up to 25% of cases [1, 2], although HLH is not usually considered in the differential diagnosis of white matter abnormalities in this age group.

We report an adult hemophagocytic syndrome presenting like a primary HLH with a good response to therapy that evolved subsequently to a unique form of diffuse large B-cell lymphoma with fulminant CNS involvement and concomitant intravascular lymphoma (IVL).

Case Report

A 47-year-old healthy woman, with no significant family history, was admitted with a 4-month history of fever, anorexia, and loss of 10% of body weight. Physical examination was unremarkable. Blood tests showed normocytic anemia and thrombocytopenia (35,000 platelets/μL), elevated C-reactive protein (23.6 mg/dL) and erythrocyte sedimentation rate (110 mm), hypertriglyceridemia (546 mg/dL), and hyperferritinemia (Fig. 1A). A full body CT scan revealed only a mild homogeneous splenomegaly. Additional evaluation, including extensive cultural, serological and molecular microbiologic tests, full autoanti-

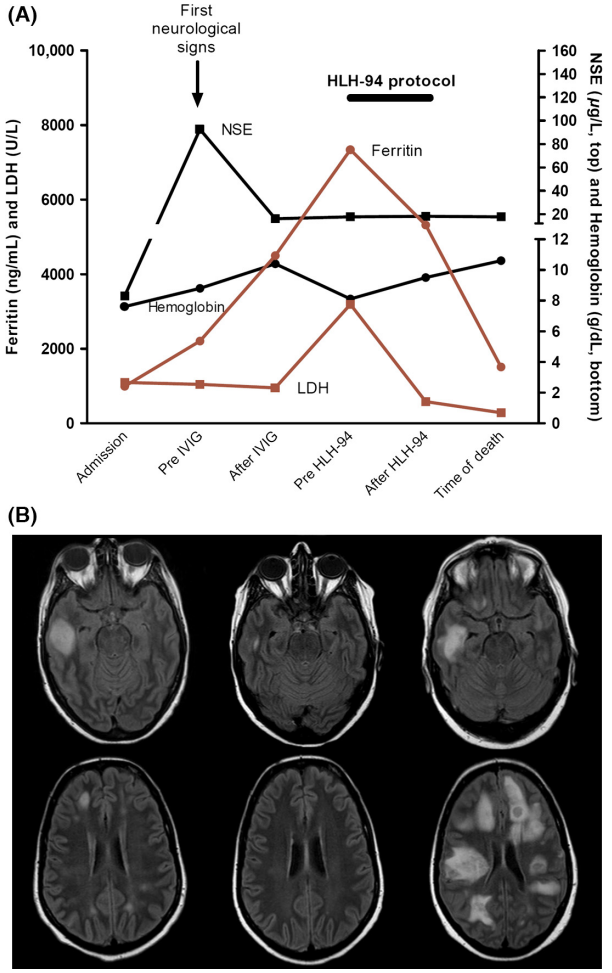

Figure 1. Clinical course and management during 5 months (A) and brain axial T2-Flair MRI images evolution (B). (A) Clinical course and treatment-induced remission with IVIG (400 mg/kg/day) plus IV methylprednisolone (1 g/day) and HLH-94 chemotherapy protocol (Dexametasone 10 mg/m^2, daily, during 2 weeks and then tapering plus Etoposide 150 mg/m^2, IV, twice-weekly for the first 2 weeks and weekly dosing thereafter during the following 6 weeks). HLH-94 protocol period was complicated by *Cryptococcus neoformans* fungemia and *Klebsiella pneumoniae* bacteremia. (B) (left): After seizure: right temporal subcortical lesion hyperintense on T2 FLAIR, with no restriction on diffusion and without gadolinium enhancement (not shown), with little mass effect, small supratentorial bilateral lesions hyperintense on T2 Flair. B (middle): After IVIg plus Methylprednisolone: decrease in volume and mass effect and resolution of gadolinium enhancement (not shown). B (right): During acute confusional state: multiple edematous lesions in basal ganglia and supratentorial white matter, with gadolinium enhancement (not shown), restriction on diffusion (not shown) and mass effect.

body serologic profile, cardiac ultrasound, upper endoscopy, colonoscopy, and bronchoscopy, were normal. Bone marrow biopsy showed a normocellular bone marrow tissue with normal counts of plasma cells and lymphocytes with no morphological changes. Liver and lung transbronchial biopsies showed a reactive inflammatory response, prompting a spleen biopsy which revealed an extensive histiocytosis with erythrophagocytosis.

Hemophagocytic lymphohistiocytosis was assumed and, accordingly, an increased level of soluble CD25 (7460 U/mL) was detected, fulfilling 7/8 of HLH diagnostic criteria [1]. An increased level of neuron-specific enolase (NSE) (92.7 μg/L) was also found. As no specific cause for HLH was identified, the possibility of a primary form was considered.

Four weeks after admission a complex partial seizure occurred with conjugate right eye deviation and left-sided hemiparesis. Her brain MRI showed right temporal subcortical lesion (Fig. 1B, left). Cerebrospinal fluid (CSF) examination showed six normal lymphocytic cells. CSF bacteriological and neurotropic virus studies were negative as well as were anti-neuronal antibodies. The patient refused a brain biopsy and was treated with levetiracetam 500 mg twice daily plus a 5-day course of intravenous methylprednisolone and IVIg (Fig. 1A). After a week a substantially improvement of her brain MRI lesions was attained (Fig. 1B, middle), but due to worsening of cytopenias and persistence of HLH markers, the HLH-94 chemotherapy protocol was initiated (Fig. 1A). There was a substantial response to treatment with ferritin levels lowering past 2000 ng/ml (Fig. 1A) and a full remission of symptoms allowing discharge after 6 weeks.

Two months after HLH-94 induction, she was readmitted because of acute confusional state and visual hallucinations. Brain MRI showed a significant lesion recrudescence (Fig. 1B, right), although all markers of HLH had improved (Fig. 1A). In less than 24 h, the patient suffered sudden clinical deterioration into coma and death, caused by diffuse brain edema with central transtentorial herniation.

Post-mortem brain pathology was consistent with a primary diffuse large B-cell lymphoma of the CNS with an angiocentric distribution associated with hemophagocytosis (Fig. 2A and B). The presence of an intravascular restricted infiltration by monoclonal CD20+ lymphocytes in all other tissues (Fig. 2C and D) led to the concomitant diagnosis of IVL. There were no known HLH-related mutations on *PRF1*, *UNC13D*, *STXBP2*, and *STX11* genes.

Discussion

Hemophagocytic lymphohistiocytosis truly remains a clinical challenge, particularly in adults who comprise around 40% of cases [1]. Hemophagocytic lymphohistiocytosis is usually suspected in a patient with fever, cytopenias, increased acute phase reactants, and altered liver tests. Soluble CD25 is used as a marker for the hyperinflamma-

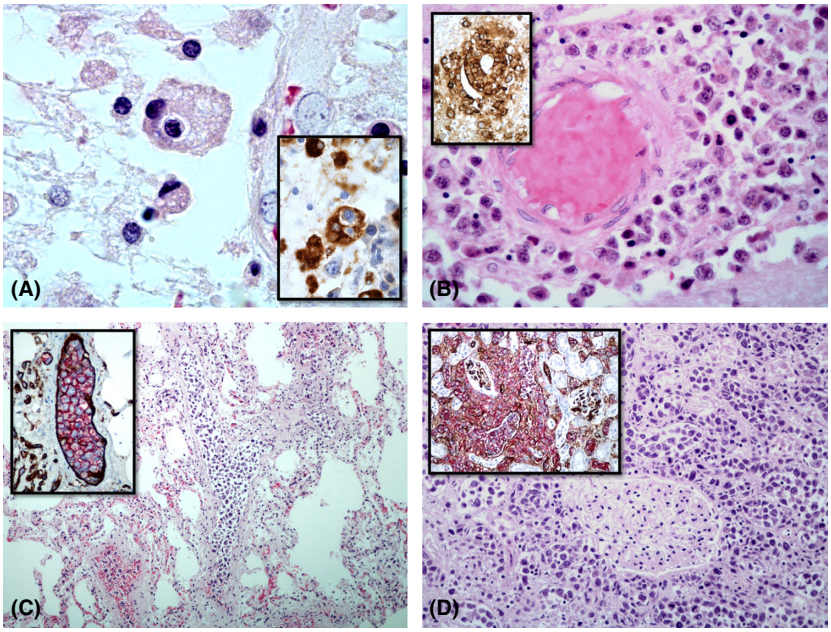

Figure 2. Post-mortem pathological diagnosis of primary B-cell lymphoma of the CNS (A and B) and intravascular lymphoma (C and D). (A) Numerous macrophages with ingested lymphocytic cells (hemophagocytosis) (H&E ×1000). These macrophages are CD68 positive (insert). (B) Primary diffuse large B-cell lymphoma of the CNS. Accumulation of tumor cells within the perivascular space, sparing vessel lumina (H&E ×400). Strong CD20 staining (insert). (C and D) Intravascular lymphoma cells are present in the sinuses of the lung (C, H&E ×100) and they fill the lumen of small vessels in the kidney (D, H&E ×200). The tumor cells are highlighted by staining for CD20 (red) and the endothelium is staining for CD34 (brown) (inserts).

tory state, although other markers such as NSE have been reported in pediatric HLH [6]. Interestingly, NSE was found increased in our patient, suggesting that NSE could possibly be also used in adults with HLH.

The CNS involvement in HLH is heterogeneous ranging from altered mental status to seizures and coma typically with CSF abnormalities [1]. Even though adult HLH has been better characterized in the last years, CNS involvement and MRI changes in adults are still poorly documented. In children, white matter abnormalities are characteristic of CNS involvement in HLH [5, 7]. On brain MRI, the lesions are usually multiple, asymmetrical and fuzzy, hyperintense on T2 with contrast enhancement, and a periventricular or juxtacortical distribution [5, 7]. These abnormalities are not usually considered a feature of adult HLH, although this case, like others [8], suggests that this may be a wrong assumption. Compared to other published cases of adult HLH [2, 8], our case has a detailed documentation of HLH neurological involvement and resembles a children primary HLH. Moreover, it has the particularity of remission of HLH markers after treatment with an almost complete resolution of CNS lesions, and the resurgence of CNS lesions without reappearance of HLH blood markers leading to death and the post-mortem diagnosis of IVL.

Usually the etiology of secondary HLH is identified during its clinical course. This case resembled a primary HLH clinical picture as no cause could be identified after extensive investigation. The remission of HLH markers after treatment with an almost complete resolution of CNS lesions would argue in favor of this possibility, but the subsequent emergence of an aggressive B-cell lymphoma during HLH remission questioned this initial interpretation. In this case, it is difficult to define whether the lymphoma was already evolving during initial months of HLH, or whether it developed after secondary immunodeficiency caused by HLH and its treatment, but the duration and type of immunosuppression does not favor this second possibility. Although, there was no evidence of lymphoma at presentation even after an extensive investigation (favoring the diagnosis of primary HLH), the exclusion of known HLH-related mutations clearly favors the diagnosis of secondary HLH. Thus, the possibility of a subclinical evolving lymphoma since the beginning of the clinical course seems to be the most plausible interpretation. It is well known that some hematological conditions, like autoimmune hemolytic anemia, can precede the emergence of non-Hodgkin and Hodgkin lymphomas, especially after immunosuppression for the presenting condition. It is possible that a HLH presenting as a primary-like form represents a similar phenomena.

The B-cell lymphoma diagnosed in this patient had intriguing and previously undescribed features. T-cell lymphoma and Epstein-Barr virus infection are the most common causes of adult HLH [1–3]. B-cell lymphoma presenting with HLH is less common and it is mostly seen in the Asian-variant of IVL [9], but not in western countries [9, 10]. Besides the unusual association of HLH with IVL in European patients, there are other features that do not favor a classical IVL in this case. In fact, brain pathology resembled primary diffuse large B-cell lymphoma of the CNS and while some cases of IVL have brain mass-like lesions [11], IVL with secondary CNS involvement usually have brain vessel and leptomeningeal infiltration [9] not seen in this case. It is thus plausible to assume a primary diffuse large B-cell lymphoma of the CNS with synchronous IVL.

In conclusion, we report a rare case of an adult hemophagocytic syndrome presenting as a primary-like HLH with a good response to therapy and a subsequent emergence of a unique form of diffuse large B-cell lymphoma with fulminant CNS involvement and concomitant IVL. This case highlights that CNS involvement can occur at early stage of HLH even in adults and that lymphoma can emerge even after remission of a HLH resembling a children primary HLH. Although in this case a brain biopsy could not be obtained, this should always be considered as it may prove crucial in diagnosis the underlying hematological disorder.

Acknowledgments

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Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

A written informed consent for patient information and images was provided by the patient's husband as this case reports on a deceased patient.

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