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"Hemophagocytic Lymphohistiocytosis after EBV reactivation and ibrutinib treatment in relapsed/refractory Chronic Lymphocytic Leukemia"

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a rare syndrome characterized by ineffective T-cell and NK response. We report the clinical course of a patient with relapsed CLL who developed acute symptoms soon after starting ibrutinib. Hyperpyrexia, splenomegaly, hyperferritinemia, hypertriglyceridemia, cytopenias, and a typical cytokine pattern, i.e. high interleukin (IL)−6, IL10 and IL18, were consistent with a diagnosis of HLH. Coexistent Epstein Barr virus reactivation was documented. Ibrutinib-induced impairment of NK degranulation, associated with EBV reactivation and CLL-related immunodeficiency may have contributed to the development of HLH in our patient.

1. Case report

A 70 year old previously healthy man was diagnosed with Binet stage B Chronic Lymphocytic Leukemia (CLL) in 2008. The diagnostic work-up showed typical morphology and immunophenotyping with a 4/5 Matutes score [1], CD38+ and ZAP70+. Cyclin D1 was negative. The immunoglobulin heavy-chain variable (*IGHV*) gene was unmutated (UM), molecular cytogenetic analyses showed a chromosome 14q deletion. Serum β2-microglobulin and lactate dehydrogenase (LDH) levels were within the normal laboratory range. In 2010 he developed progressive lymphadenopathy and received 6 cycles of fludarabine, cyclophosphamide and rituximab without achieving a meaningful response. He was then treated by 6 cycles of bendamustine and rituximab (BR), attaining a < 50% reduction of lymphadenopathy, i.e. stable disease according to NCI criteria. In the absence of disease-related symptoms no further treatment was given until 2013, when symptomatic disease progression occurred. Retreatment with BR was stopped after 1 course, due to grade 3 cutaneous toxicity and the patient received 10 cycles of cyclophosphamide and prednisone (CP) without attaining a significant response.

In January 2015, after one month from the last CP course, the patient was enrolled on a named patient program (NPP) offering access to Ibrutinib treatment in refractory CLL in our country. The patients was in good general condition, with ECOG performance status 1. The lymphocyte count was 28×10^9/l with a normal neutrophil count, the hemoglobin level was 12 gr/dL and the platelet count was 221×10^9 /l. Serum ferritin was normal and a moderate increase of LDH levels was noted. Molecular cytogenetic studies documented the absence of 17p-/*TP53* mutations. A computed tomography (CT) scan revealed multiple adenopathies 3–5 cm in size. Ibrutinib was prescribed at a daily dose of 420 mg qd. After 7 days febrile neutropenia occurred. Due to persistent fever and fatigue Ibrutinib was hold on day 16, and four days later the patient was admitted to the hospital with fever (39,0 °C), splenomegaly and upper airway infection, in the absence of pneumonia on a CT scan. Despite broad-spectrum antimicrobials the clinical condition rapidly worsened and, on day 24 he became critically ill with disseminated intravascular coagulation (DIC), associated with low fibrinogen level (77 mg/dL), pancytopenia (neutrophils 500×10^9/l, hemoglobin 8.2 gr/dL and platelets 23000×10^9/l), an impressive rise of serum ferritin up to > 100,000 ng/mL and an increase of LDH serum value (1193 U/L) and an increase of serum triglycerides (385 mg/dL). Given the presence of 5 out of 8 diagnostic criteria (fever > 38.5 °C, splenomegaly, cytopenias, raised ferritin and triglyceride levels) [2], a diagnosis of HLH syndrome was made. Due to high bleeding risk bone marrow and lymph-node biopsy were not performed. Epstein Barr Virus (EBV) reactivation was documented with a viral load of 7200 copies/mL. Cytomegalovirus (CMV) DNA was absent and herpes simplex viruses (HSV) serology was negative. Dexamethasone (16 mg/bid) in combina-

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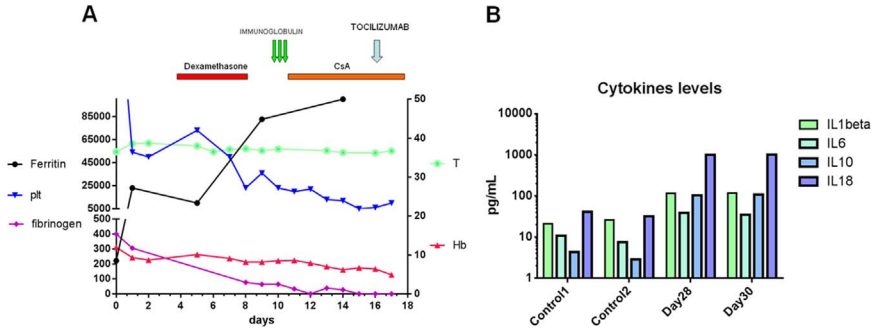

Fig. 1. Clinical and laboratory parameters in a patient with CLL developing HLH. Ferritin, serum ferritin in ng/mL; Plt, platelet count, x10^9/L; fibrinogen, plasma fibrinogen mg/dL; Hb, hemoglobin in gr/dL; and T, temperature in Celsius grade (°C) (A). IL18, IL1beta, IL10, and IL6 serum levels were significantly elevated at two different time points compared with the serum from two healthy donors (Control1, CTRL1; and control2, CTRL2)(B).

tion with Cyclosporine A (100 mg bid) and intravenous immunoglobulin (0.4 g/kg/d day 1–3) were started, but no clinical improvement was observed. Because anticytokine treatment proved effective in the setting of HLH induced by Blinatumumab in ALL [3,4] or by chimeric antigen receptor-modified T cells (CART) [4], the patient was treated by the anti-interleukin(IL)–6 receptor Tocilizumab on day 30. However, irreversible multiorgan failure developed and the patient died on day 33 with fatal bleeding. The late availability of the EBV viral load result and the deteriorated clinical conditions did not allow us to administer rituximab.

This is the first report describing the occurrence of HLH in a patient with refractory CLL who had started Ibrutinib treatment. Hemophagocytic lymphohistiocytosis (HLH) is a rare and frequently fatal disorder characterized by an ineffective T-cell and NK response resulting in an exuberant cytokine production, activation of disseminated coagulation, multi-organ failure and death. Although, hemophagocytosis is the hallmark of HLH, this morphologic picture can be documented in a limited proportion of cases and, in the absence of defined genetic abnormalities, the diagnosis of HLH may be challenging [2]. Infections, autoimmunity, solid cancers or hematological malignancies, and drugs may represent important factors contributing to the development of this condition [2]. Recently, Teachey et al. described a case of a patient with acute lymphoblastic leukemia who had been treated with the CD19/CD3-bispecific T-cell receptor-engaging (BiTE) antibody Blinatumumab, developing a cytokine release syndrome resembling HLH that ameliorated with cytokine-directed therapy [3].

Although due to the presence of DIC precluding BM aspiration, we could not show the presence of hemophagocytosis in our patient, the diagnosis of HLH was well documented by the presence of 5 out of 8 diagnostic criteria usually adopted for the diagnosis of this rare condition [2]. Interestingly, the presence of serum ferritin level > 10,000 ng/mL was shown to have a 90% sensitivity and a 98% specificity for the diagnosis of HLH in the pediatric setting [5].

To confirm the diagnosis of HLH, we retrospectively analyzed the serum levels of interleukin (IL)-1b, IL-6, IL-10, IL-12, IL-18. As expected [2], our patient presented very high levels of IL-18. IL-10 and IL-6 were also higher compared with control sera from two healthy blood donors (Fig. 1B). Interestingly, in a small series of patients with HLH, including five cases associated with EBV infection, Takada et al. showed that IL-18 levels significantly correlated with disease activity and gradually decreased with clinical improvement [6]. Finally, our patient presented with significantly increased IL1-beta levels compared with healthy controls, as previously reported in patients with HLH [7] and the high IL10 levels may reflect an attempt to temper the pro-inflammatory condition and the cytokine storm that is associated with HLH.

Hematologic malignancies, especially T-cell malignancies, with or without coexisting suspected infections represent possible triggers of HLH [2] and a few cases with CLL progression possibly responsible for HLH were described [8,9]. Thus, we speculate that Ibrutinib may have contributed to HLH because of the strict temporal association between ibrutinib start and the onset HLH, which was possibly also favoured by the immunosuppression related with the recent treatment with CP. Interestingly, few cases of HLH induced by drugs are reported in literature [2,3]. Recently, it has been demonstrated that Ibrutinib irreversibly inhibits ITK contributing to degranulation impairment in NK cells, a functional defect which that is crucial in the pathogenesis of HLH [10]. Thus impaired NK degranulation, associated with EBV reactivation and CLL-related immunodeficiency, may have contributed to the development of HLH in our patient and the awareness of this possible association may favour early diagnosis and treatment.

Conflict of interest

none.

Authorship contributions

AC designed the study. MC, MC, GMR, FC and LF analyzed the results. SF and FDV performed ELISA for cytokines measurement. AR performed EBV DNA quantification. MC, MC and AC wrote the draft and the final version was critically reviewed and approved from all the authors.

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