Hemophagocytic Lymphohistiocytosis and Inflammatory Bowel Disease: Case Report and Systematic Review

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Keywords

Lymphohistiocytosis, hemophagocytic · Inflammatory bowel diseases · Crohn's disease · Colitis, ulcerative · Thionucleosides

Abstract

Aim: To report a case of a female patient with hemophagocytic lymphohistiocytosis (HLH) and to systematically review the available cases of the association between HLH and inflammatory bowel disease (IBD). **Methods:** In accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, retrieval of studies was based on Medical Subject Headings and Health Sciences Descriptors, which were combined using Boolean operators. Searches were run on the electronic databases Scopus, Web of Science, MEDLINE (PubMed), Biblioteca Regional de Medicina, Latin American and Caribbean Health Sciences Literature, Cochrane Library for Systematic Reviews and Opengrey.eu. Languages were restricted to English, Spanish and Portuguese. There was no date of publication restrictions. The reference lists of the studies retrieved were searched manually. **Results:** The search strategy retrieved 223 references. In the final analysis, 28 references were included, with the report of 35 cases. The

most common clinical finding was fever, 57% of patients had a cytomegalovirus infection and 30 patients were on thiopurines previously to HLH diagnosis. Most patients were treated with steroids and antiviral therapy. All-cause mortality was 22%. **Conclusion:** These findings suggest that there might be a connection of HLH to IBD, opportunistic viral infections and the use of thiopurines. Due to the severity of such disease, the clinical suspicion is paramount to early diagnosis and therapy.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe systemic syndrome characterized by a rapidly progressive generalized inflammatory response associated with the release of pro-inflammatory cytokines and the

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Table 1. HLH 2004 diagnostic criteria [37]

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:	
1.	Molecular identification of an HLH-associated gene mutation (e.g., PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, BIRC4, LYST, ITK, SLC7A7, XMEN, HPS).
2.	At least 5 of the following 8:
–	1. Splenomegaly
–	2. Fever > or = 38.5°C
–	3. Peripheral blood cytopenia, with at least 2 of the following: hemoglobin <9 g/dL; platelets <100,000/microL; absolute neutrophil count <1,000/microL
–	4. Low or absent NK cell activity
–	5. Ferritin >500 ng/mL
–	6. Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
–	7. Elevated soluble CD25 (soluble IL-2 receptor alpha) 2 SDs above age-adjusted laboratory-specific norms
–	8. Hemophagocytosis in bone marrow, spleen, lymph node, or liver
HLH, hemophagocytic lymphohistiocytosis.	

activation of the immune system. It can be mistaken for sepsis due to similar clinical characteristics [1]. Thus, HLH is a differential diagnosis to be considered in cases of multiple system organ failure in the presence of hepatosplenomegaly and pancytopenia.

Terms are used to describe HLH and related syndromes. Primary HLH is caused by a gene mutation, which can be one of the familial HLH loci or in a gene responsible for one of several immunodeficiency syndromes. Primary HLH is also called familial HLH [2]. The term secondary HLH, also called sporadic or acquired HLH, is used to describe patients without a known familial mutation and who typically have a trigger for developing acute HLH [2]. Although viruses are the most common triggering factors for HLH, other triggering factors are bacteria, fungi, and parasites. Examples of viral triggering factors are herpesvirus (Epstein-Barr virus [EBV], Cytomegalovirus [CMV], VHH8, HSV), HIV, HTLV, hepatitis virus (A, B and C), measles, mumps, rubella, adenovirus, dengue, hantavirus, parvovirus B19, enterovirus and influenza [3]. Macrophage activation syndrome is a form of secondary HLH that occurs in patients with autoimmune diseases [4]. The most frequent are systemic juvenile idiopathic arthritis, followed by systemic lupus erythematosus, Kawasaki disease and juvenile dermatomyositis [5]. In addition to autoimmune triggers,

other factors like tumors especially lymphomas, transplants, drugs, pregnancy, vaccines, surgery and hemodialysis can lead to secondary HLH [3].

Since the disease is difficult to diagnose, criteria have been established for this purpose. The diagnostic criteria of HLH are shown in Table 1. Clinical and laboratory manifestations of HLH include fever, splenomegaly, cytopenias, hypertriglyceridemia, hyperferritinemia, hemophagocytosis, diminished NK cell activity, coagulopathy, liver dysfunction and also neurologic dysfunction. The syndrome usually is treated with immunosuppressants, allogeneic hematopoietic stem cell transplantation and etoposide [6].

It has been described in the literature several cases of association between HLH and inflammatory bowel disease (IBD). These cases occur mostly in patients with infections by opportunistic pathogens, while using immunosuppressive agents [7].

The aim of this paper is to report a case of a female woman with IBD diagnosed with HLH and to systematically review available cases of this association.

Case Report

Female patient, 37-year old, previously diagnosed with ulcerative colitis (UC) in 2015, Montreal type E1, using oral mesalamine in remission since the diagnosis. She was admitted to the emergency department due to recurrent fever (39–40 °C), chills, malaise, asthenia, nausea, weight loss and liquid diarrhea. On physical exam, she had abdominal pain in the right hypochondrium and genital lesions compatible with herpes.

A colonoscopy was performed due to the suspicion of UC exacerbation, which showed multiple punctiform and superficial ulcers, with flat borders, from caecum to rectum. The mucosa was normal between ulcers. This was suggestive of ischemic ulcers. Immunochimistry to herpes-virus and CMV were negative. The genital lesions were biopsied and immunochimistry came back positive for herpes infection. The patient began to receive intravenous acyclovir, with improvement of the genital lesions.

During her hospital stay, she presented with an acute acalculous cholecystitis, undergoing urgent video laparoscopic cholecystectomy. The pathological analysis of the gallbladder demonstrated inflammatory infiltrate consisted of neutrophils and eosinophils and epithelial erosion associated with edema and transmural acute inflammatory process (Fig. 1). She was started on piperacillin-tazobactam. Aminotransferase levels were measured on admittance, before and after cholecystectomy, and the results were, respectively, aspartate transaminase 94, 25, and 29 UI/L; alanina transaminase 110, 40, and 37 UI/L; gamma-glutamyl transpeptidase 475, 415, and 413 UI/L. After surgery, she began to present pancytopenia, hyperferritinemia, hypoalbuminemia, high-grade fever, hepatosplenomegaly, ascites and pleural and pericardial effusion. The main diagnostic hypotheses were CMV infection due to immunosuppression, systemic lupus erythematosus and HLH. The results of CMV serology and antinuclear antibody were negative. This raised the clinical value of the diagnosis of HLH. Hence,

Fig. 1. Gallbladder. **a** Epithelial erosion associated with edema and transmural acute inflammatory process (haematoxylin and eosin 40×). **b** Inflammatory infiltrate consisted of neutrophils and eosinophils, (haematoxylin and eosin 100×).

Fig. 2. Colon. **a** Thrombi in arterioles on colonic wall (haematoxylin and eosin 40×). **b** Macrophages associated with hemophagocytosis (haematoxylin and eosin 400×).

a bone marrow biopsy was promptly performed and high dose dexamethasone was started.

While the patient waited for results, she presented spontaneous pneumoperitoneum. An explorative laparotomy was performed and an acute perforation in the caecum was found, motivating a right colectomy with an ileostomy. She was admitted to intensive care unit after surgery and antimicrobial treatment was escalated to meropenem, polymyxin B, anidulafungin, and vancomycin. The patient died shortly afterwards due to a fungal sepsis – *Candida sp.* was isolated in her bloodstream. After her death, the histopathologic analysis of the bone marrow showed hypercellularity (80%) due to granulocytic hyperplasia and the anatomopathological study of the caecum showed retrocecal and mesenteric lymph nodes with macrophages associated with hemophagocytosis inside the sinusoids (Fig. 2), thrombi in arterioles on colonic wall causing ischemic infarction,

ulceration and neutrophilic exudate, confirming the suspected diagnosis of HLH. The key aspect to this case is that the HLH presented initially as an UC exacerbation and masked the real causing factor of the HLH, which was the herpes virus infection.

Materials and Methods

This study was carried out in accordance with the recommendations contained in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [8]. Our systematic review was registered with the International Prospective Register of Systematic Reviews, maintained by York University, on May 4, 2019 (registration No. CRD 42019125584 [www.crd.york.ac.uk/prospero/]).

Fig. 3. PRISMA-P flowchart of the systematic review. BIREME, Biblioteca Regional de Medicina; LILACS, Latin American and Caribbean Health Sciences Literature.

Data Sources

Studies were retrieved using the terms described on Appendix. Searches were run on the electronic databases Scopus, Web of Science, Medline (PubMed), Biblioteca Regional de Medicina, Latin American and Caribbean Health Sciences Literature, Cochrane Library for Systematic Reviews and Opengrey.eu. Languages were restricted to English, Spanish and Portuguese. There was no date of publication restrictions. The reference lists of the retrieved studies were submitted to manual search. Databases were searched in January 2019.

Inclusion Criteria and Outcomes

Inclusion criteria were clinical case report or case series studies involving HLH and IBD. Exclusion criteria were types of studies other than case reports or case series and articles that were not related to the topic. If there was more than one study published using the same case, the most recent study was selected for the analysis. Studies published only as abstracts were included, as long as the data available made data collection possible. The outcome measured was recovery or death.

Study Selection and Data Extraction

The search terms used for each database are described in the Appendix. An initial screening of titles and abstracts was the first stage to select potentially relevant papers. Studies that did not address the inclusion criteria were excluded. The second step was the analysis of the full-length papers. In this step, some studies were removed for lack of clinical information. Two independent reviewers (B.B., A.M.B.) extracted data using a standardized data extraction form after assessing and reaching consensus on eligible studies. The same reviewers separately assessed each study and extracted data about the characteristics of the subjects and the out-

comes measured. A third party (J.S.) was responsible for divergences in study selection and data extraction, clearing them when required.

Statistical Analysis

Data was summarized using descriptive analysis – frequency and means. This was calculated using Microsoft Excel.

Results

Systematic Review

Using the search strategy, 223 references were found and 112 references were excluded because they were duplicates. After analyzing titles and abstracts, 65 references were excluded and 46 full text papers were analyzed. In the final analysis, 28 references were considered, including 35 cases. A flowchart illustrating the search strategy is shown in Figure 3. Studies included were either a case report or a case series.

Cases from France, Spain, the United States, Australia and Canada were the most common (22.8, 14.2, 11.4, 8.5, and 8.5% respectively). A total of 35 patients were included, corresponding to 22 males (62.8%) and 13 females (37.1%). The age ranged from 11 to 77 year-old (mean age was 32 years). Of all patients, 26 (74.2%) were cases of Crohn's disease and 9 (25.7%) were cases of UC.

Table 2. Summary of systematically reviewed clinical cases

Reference	Country	Age, years	Gender	Clinical presentation	IBD	Co-morbidities	Immunosuppressive agent	Neoplasia	Criteria	Treatment	Outcome
Miechowiecki et al. [9], 2018	Austria	35	Male	High-grade fever, night sweats, skin rash, and abdominal pain	CD	CMV infection	AZA	None	5	Ganciclovir	Recovery
Viridis et al. [10], 2013	United Kingdom	19	Male	Fever, jaundice, and weakness	CD	EBV infection	6-MP	Diffuse large B cell lymphoma	5	Etoposide, Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Methotrexate, steroids	Recovery
N'Guyen et al. [11], 2009	France	25	Male	Asthenia, weight loss, nocturnal sweats, and sore throat	CD	EBV infection	AZA	X-linked lymphoproliferative disorder	4	Cytostatic polychemotherapy, acyclovir, steroids, and rituximab	Death
Vakkalagadda et al. [12], 2017	USA	59	Female	Fever, sore throat, shortness of breath	UC	CMV infection	MSM, AZA	None	5	Subcutaneous granulocyte colony-stimulating factor and ganciclovir	Recovery
Thompson et al. [13], 2017	Australia	24	Male	Fevers, sore throat, lethargy, cervical lymphadenopathy and hepatosplenomegaly	CD	EBV infection	6-MP, ADM	None	6	Rituximab, steroids and antibiotics	Recovery
Vikse et al. [14], 2016	Norway	30	Male	Night sweats, intermittent fever, nausea, vomiting, diarrhea and tachycardia	UC	Bipolar disorder, CMV infection	MSM, AZA	None	5	Antibiotics, Intravenous ganciclovir, followed by oral valganciclovir	Recovery
Pop et al. [15], 2015	Romania	63	Male	General malaise, loss of appetite, weight loss	CD	CMV infection	MSM	None	6	Antibiotics, steroids, ganciclovir, parenteral nutrition	Death
Ma et al. [16], 2015	Canada	77	Male	Fever, diarrhea, dyspnea	UC	CMV infection	IFX	None	6	Antibiotics, ganciclovir	Death
Hernández-Camba et al. [17], 2013	Spain	35	Male	Fever, malaise and hepatosplenomegaly	CD	CMV infection	AZA	none	5	Antibiotics, steroids, ganciclovir	Recovery
Mun et al. [7], 2013	South Korea	52	Female	Fever, abdominal pain, hematochezia, splenomegaly	UC	CMV infection	0	None	5	Steroids and ganciclovir	Recovery
Weinkove et al. [18], 2013	New Zealand	21	Male	Fever, pancytopenia	CD	CMV infection	AZA	None	5	Antibiotics, steroids, foscarnet followed by valganciclovir, infliximab, surgery – ileocaecal resection	Recovery
Fitzgerald et al. [19], 2013	United Kingdom	14	Female	Fever, headache, abdominal pain, rash, hepatosplenomegaly, bilateral cervical lymphadenopathy pharyngitis, glossitis and tonsillitis	CD	EBV infection	AZA	None	8	Rituximab	Recovery
van Langenberg et al. [20], 2011	Australia	32	Female	Fevers, lethargy, myalgia, headache, cough, dyspnea	UC	CMV infection	MSM, AZA	None	4	Steroids and intravenous ganciclovir	Recovery
van Langenberg [20], 2011	Australia	22	Male	Fatigue, malaise, tachycardia, fever, sore throat	CD	CMV infection	AZA	None	3	Antibiotics, ganciclovir	Recovery
Côté-Daigneault and Bernard [21], 2011	Canada	21	Male	Fever, cytopenia	CD	EBV infection	6-MP, IFX	Hepatosplenic lymphoma	4	Dexamethasone, etoposide and cyclosporin	Death
Presti et al. [22], 2011	Italy	32	Female	Fever	CD	Psoriasis, CMV infection	AZA, IFX	None	5	Antibiotics, steroids, ganciclovir followed by oral valganciclovir	Recovery
Salado et al. [23], 2011	Spain	24	Male	Fever and tachycardia	CD	EBV infection	Steroids, IFX	None	5	Dexamethasone, cyclosporine, and etoposide	Recovery
N'Guyen et al. [24], 2011	France	28	Female	Fever, cytopenia, hyperferritinemia and hypertriglyceridemia	CD	CMV infection	AZA, anti-TNF	None	5	Steroids and ganciclovir followed by valganciclovir	Recovery
N'Guyen et al. [24], 2011	France	33	Female	Fever, lymphadenopathy, cytopenia, hyperferritinemia, hypertriglyceridemia	CD	CMV infection	AZA, anti-TNF	None	5	Steroids and ganciclovir followed by valganciclovir	Recovery
N'Guyen et al. [24], 2011	France	30	Female	Fever, pericarditis, acute colitis	CD	CMV infection	AZA, anti-TNF	None	4	Steroids, intravenous immunoglobulin, foscarnet and ganciclovir followed by valganciclovir	Recovery
N'Guyen et al. [24], 2011	France	38	Female	Fever, pneumopathy, cytopenia, hyperferritinemia, hypertriglyceridemia	CD	CMV infection	AZA	None	5	Steroids, intravenous immunoglobulin, foscarnet and ganciclovir followed by valganciclovir	Death

Table 2 (continued)

Reference	Country	Age, years	Gender	Clinical presentation	IBD	Co-morbidities	Immunosuppressive agent	Neoplasia	Criteria	Treatment	Outcome
Duque et al. [25], 2011	Portugal	19	Male	Fever, headache, abdominal discomfort, jaundice, lymphadenopathies, hepatosplenomegaly, peripheral edema	UC	EBV infection	AZA	None	7	Antibiotics, steroids, intravenous immunoglobulin	Recovery
Uslu et al. [26], 2010	Turkey	11	Male	Fever, bloody diarrhea, vomiting, abdominal pain, weight loss, fatigue, malnutrition	CD	Familial Mediterranean fever	Steroids, MSM, AZA	None	6	Antibiotics, steroids, intravenous immunoglobulin, cyclosporine	Death
Serrate et al. [27], 2009	France	53	Female	Fever, pancytopenia, jaundice	CD	EBV infection	Steroids, MSM, AZA	None	5	Steroids, intravenous immunoglobulins, rituximab and etoposide	Recovery
Miquel et al. [28], 2009	France	63	Female	Fever, cough, abdominal pain, weight loss, hepatosplenomegaly	CD	CMV infection	AZA	None	6	Steroids, intravenous immunoglobulins, ganciclovir followed by valganciclovir	Recovery
Miquel et al. [28], 2009	France	23	Male	Asthenia, fever, cough, and hepatosplenomegaly	CD	CMV infection	Steroids, AZA, IFX	None	5	Ganciclovir followed by oral valganciclovir	Recovery
Francolla et al. [29], 2008	USA	18	Female	Fever, abdominal pain, mild jaundice, rash, tonsillitis	CD	EBV infection	Steroids, AZA, IFX	None	4	Steroids and acyclovir	Recovery
Siegel et al. [30], 2007	USA	29	Male	Fatigue, fever, diarrhea, nausea, rash	UC	EBV infection	6-MP	None	3	Antibiotics, intravenous immunoglobulin, steroids, acyclovir and etoposide	Death
Hindupur [31], 2005	USA	26	Male	Fever, myalgia, night sweats	CD	None	IFX	None	5	Dexamethasone and cyclosporine	Death
Babua et al. [32], 2004	Canada	12	Male	Fever, lethargy, poor appetite	CD	CMV infection	AZA	NA	5	Antibiotics, mesalamine, discontinuation of azathioprine	Recovery
Bosman et al. [33], 2009	The Netherlands	21	Female	Fever, anorexia, lymphadenopathy, jaundice, rash, myalgia	UC	EBV infection	AZA	NA	5	Cyclosporine and dexamethasone. After, rituximab and CHOP (cyclophosphamide, adriamycin, vincristine and prednisone)	Recovery
Sanchez et al. [34], 2015	Spain	24	Male	Fever, hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia	CD	EBV infection	IFX	NA	6	Steroids, intravenous immunoglobulin, ganciclovir, cyclosporine and etoposide	Recovery
Sanchez et al. [34], 2015	Spain	36	Male	Fever, hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia	CD	CMV infection	AZA	NA	7	Ganciclovir, steroids, cyclosporine and etoposide	Recovery
Sanchez et al. [34], 2015	Spain	43	Male	Fever, hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia	CD	CMV infection	AZA	NA	5	Ganciclovir, steroids, cyclosporine and etoposide	Recovery
Fathalla et al. [35], 2018	Tunisia	45	Male	Pruritus, liver failure	UC	NA	SFZ	None	NA	NA	NA

NA, not available; EBV, Epstein Bar Virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; CD, Crohn's Disease; UC, ulcerative colitis; MSM, mesalamine; SFZ, sulfasalazine; AZA, azathioprine; 6-MP, 6-mercaptopurine; IFX, infliximab; ADM, adalimumab.

The most common clinical presentation was fever, present in 91.4% of cases. Hepatosplenomegaly was present in 9 patients (25.7%) and just one had isolated splenomegaly.

Opportunistic viral infection was very common. CMV infection was present in 57.1% of patients, while EBV infection was present in 34.2% of patients. Three cases had an associated malignancy (8.5%).

Regarding medication in use, 12 patients were on anti-TNF (8 on infliximab and 1 on adalimumab); 30 patients were on thiopurines (24 on azathioprine and 4 on 6-mercaptopurine) and 8 patients were using aminosalicylates (6 on mesalamine and 2 on sulfasalazine).

The mean score of the criteria for diagnosing HLH was 5. Most patients were treated with steroids: 26 patients. Antiviral drugs were used in 23 patients (ganciclovir: 18, acyclovir: 3, and foscarnet: 3). Chemotherapy was used in 10 for treatment of HLH. In percentage, the chemotherapy drugs used were 80% etoposide, 20% Cyclophosphamide, 20% Hydroxydaunorubicin. One of the studies does not mention which medication was used.

Regarding outcome, 26 of the cases showed recovery (74.2%) and 8 patients died (22.8%). The systematic review findings are summarized on Table 2.

Discussion

HLH is a rare and life-threatening syndrome known for an excessive inflammatory reaction and tissue destruction [36]. While HLH is considered to be a disease that requires genetic predisposition, viral infections are recognized as its most important triggers, especially CMV and EBV [36]. It is frequently related to immunosuppressive therapy, such as those generally used for the treatment of IBD, post-transplantation patients and other conditions [36].

The main cells involved in HLH are the natural killers cells and macrophages [37]. The pathophysiology consists in an excessive immune activation and inflammation, caused by a failure of the NK cells to eliminate damaged cells as the macrophages, resulting in a lack of the normal down-regulation of macrophages and of lymphocytes activation [37]. The activated macrophages start to phagocyte blood cells, such as platelets, red blood cells, and white blood cells. This might lead to pancytopenia [37].

The hemophagocytosis undergoing inside the blood vessels may cause endothelial injury and thrombi, which leads to ischemia. Therefore, it is not uncommon that pa-

tients with HLH develop acute acalculous cholecystitis due to the stasis and concentration of bile salts inside the gallbladder [38]. After the AAC is established, the gallbladder becomes vulnerable to opportunistic infections, such as CMV, *Escherichia coli* and *Cryptosporidium* [39]. If not diagnosed and treated soon, it evolves to perforation and generalized peritonitis. The case report is an example of this complication [40].

HLH is primary an autosomal-recessive disorder of the immune system, and it has been reported with an incidence of 1.2 per 1 million population per year [40]. However, it is more common as a secondary condition [41]. It generally presents itself as a multiple organ disease [42]. The first signs can mimic common infections [41]. It can be frequently mistaken to an exacerbation of a previously diagnosed disease, such as IBD, and hence it can show similar symptoms, such as diarrhea and gastrointestinal bleeding, as presented in Table 1 [42]. However, IBD associated with HLH is rare [43]. There is no data about geographic differences in HLH presentations or outcomes in IBD patients in our region, as it is a predominant region of European immigrants.

Prolonged courses of thiopurines may decrease circulating lymphocytes due to their effect of apoptosis, which is important to HLH [43]. However, they also affect immunological defense, which leads to a predisposition to a viral infection, such as CMV, EBV or varicella zoster virus [43]. The most common clinical features are fever, hepatosplenomegaly, lymphadenopathy, neurologic symptoms (seizures, ataxia, mental status changes and headache) and skin rash [42]. It can also affect pulmonary system, heart and kidneys. These clinical features are described on several of the cases reports presented on Table 2, which confirm the information that they are the most usual clinical presentation of HLH.

The diagnosis is based upon the criteria used in HLH-2004 trial, detailed in Table 1 [41]. HLH has also been related to malignancy, especially lymphoid cancers, such as T-cell or natural killer-cell lymphomas, B-cell leukemia, Hodgkin Lymphoma, solid tumors and myeloid malignancies [44]. Some of the cases reported on Table 2 present malignancy during the course of HLH, and also infections, that seem to be a trigger in this case as well: it has been described that patients with lymphoma might demonstrate EBV infection in neoplastic tissue during thiopurine use [45].

Despite the strong association between HLH and EBV infection, EBV testing before therapy with thiopurines is not recommended. EBV is not a sole trigger and

will not eliminate the risk of HLH [46]. However, according to a large study performed with 1,483 patients over 17 years old, it is important to know the serological status of the patient to avoid a primary EBV infection during thiopurines use [45]. It is very important to also stress that CMV, herpes-virus and EBV infections might mimic IBD exacerbation [47], which can trigger HLH.

In the reported case, the herpetic infection was the actual trigger to activate the macrophages. This, although, is more associated to neonate patients. It is likely that HSV leads to unregulated production of T cells, histiocytes and macrophages due to a cytokine reaction [48]. Similar to HLH, HSV infections might increase the level of serum ferritin. Hyperferritinemia is one of the HLH criteria for diagnosis, but it may be seen in other inflammatory and infectious processes, such as viral infections [49].

Treatment is necessary to control the abnormal activation of NK cells [44]. An early diagnostic is very important to survival. Cessation of immunosuppressive therapy is mandatory [50]. In case of viral infection as a trigger, the antiviral treatment should be promptly initiated [44]. Specific treatment must be initiated as soon as possible. It is generally used an association of high-dose steroids (dexamethasone or methylprednisolone), cyclosporine A and etoposide, in an attempt to control inflammation [47]. If not treated quickly, it can lead to death shortly [44].

In conclusion, HLH is a life-threatening disease that can simulate an IBD exacerbation. It is generally triggered by a viral infection, which can also simulate an IBD exacerbation. It should be promptly suspected in patients with IBD on thiopurines, which develop hepatosplenomegaly and fever, leading to a diagnostic evaluation and immediate treatment.

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Statement of Ethics

A family member of the deceased patient has acquiesced to the reporting of the case. The systematic review has been registered with the International Prospective Register of Systematic Reviews, maintained by York University, on May 4, 2019 (registration no. CRD 42019125584 [www.crd.york.ac.uk/prospero/]).

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Author Contributions

All authors contributed to study concept and design, and drafting of the manuscript; all authors contributed to acquisition of data, analysis and interpretation of data. J.S. and B.B. contributed to statistical analysis. J.S. contributed to study supervision. All authors contributed to critical revision of the manuscript for important intellectual content.

Appendix

Search Strategy

PubMed:

“Lymphohistiocytosis, Hemophagocytic”(Mesh) AND (“Inflammatory Bowel Diseases”[Mesh] OR “Crohn Disease”[Mesh] OR “Colitis, Ulcerative”[Mesh])

Biblioteca Regional de Medicina:

“Hemophagocytic Lymphohistiocytosis” AND (“Inflammatory Bowel Disease” OR “Crohn’s Disease” OR “Ulcerative Colitis”)

Latin American and Caribbean Health Sciences Literature:

(“Linfohistiocitose Hemofagocítica” OR “Linfohistiocitose Hematofagocítica”) AND (“Doença Inflamatória Intestinal” OR “Doença de Crohn” OR “Retocolite Ulcerativa”)

Cochrane Library:

“Hemophagocytic Lymphohistiocytosis” AND (“Inflammatory Bowel Disease” OR “Crohn’s Disease” OR “Ulcerative Colitis”)

OpenGrey.eu:

“Hemophagocytic Lymphohistiocytosis” AND (“Inflammatory Bowel Disease” OR “Crohn’s Disease” OR “Ulcerative Colitis”)

Scopus:

(TITLE-ABS-KEY [“hemophagocytic lymphohistiocytosis”] AND TITLE-ABS-KEY [“inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis”])

Web of Science

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