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Influenza-Associated Hemophagocytic Syndrome in Adults: Case Report and Review

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Abstract

Hemophagocytic syndrome (HPS) is a rare, but increasingly reported disease characterized by severe dysfunction of cytotoxic T cells and NK cells, often associated with poor outcome. It has been related to multiple processes including a large variety of infections. Even though viral infections have been described as triggers of HPS, influenza associated hemophagocytic syndrome in adults has been rarely reported. Here, we present a case of an 85 year-old man with essential thrombocytemia who developed HPS triggered by influenza A H1N1 infection and a review of the literature with special emphasis on the importance of a prompt diagnosis and an early treatment to achieve a more favourable outcome. Hemophagocytic syndrome secondary to influenza virus infection is a rare condition with high mortality that should be suspected in patients with an aggressive disease course. Early diagnosis and initiation of antiviral treatment and in some cases immunomodulatory therapy are crucial for the prognosis.

Keywords: Influenza; Hemophagocytic syndrome; Hemophagocytic lymphohistiocytosis; Virus associated hemophagocytic syndrome

Introduction

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is a rare histiocytic disorder characterized by uncontrolled phagocytosis throughout the reticuloendothelial system caused by impaired activity of NK cells and cytotoxic T-cells that leads to proliferation and activation of histiocytes. HPS has been traditionally classified into primary (genetic) and secondary (reactive) forms; however, an underlying genetic mutation is found only in 40% of primary HPS, suggesting that the distinction between primary and secondary forms may be artificial. Secondary HPS has been related to infections, autoimmune disorders, and neoplasias, among other causes. More than one underlying cause has been described in some cases. Both primary and reactive forms may be triggered by an infection [1].

Diagnosis of HPS relies on various clinical, laboratory and histopathologic criteria proposed by the Histiocyte Society (HS) (Table 1) [2]. Even though HLH-04 criteria has its shortcomings, as it is often too restrictive, and in some cases untimely for diagnosis, to this day it remains the most accepted diagnostic tool in HPS. It is important to mention that attempts have been made to develop other HPS criteria, such as the HScore [3].

1. Pathological mutations of PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A, or XIAP OR **2. Five of the following criteria:**
Fever of 38.5ºC or more
Splenomegaly
Cytopenias affecting at least two of three cell lineages in peripheral blood (hemoglobin ≤ 9 g/dl, platelets <100000/mcl, neutrophils <1000/mcl)
Hypertriglyceridemia (≥ 265 mg/dl) and/or hypofibrinogenemia (≤ 150 mg/dl)
Hyperferritinemia (≥ 500 ng/ml)
Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
Low or absent NK cell activity
Increased sCD25 concentration

Table 1: Diagnostic guidelines for hemophagocytic syndrome (HLH-04).

A large number of infections have been linked to HPS including viral, bacterial, and parasitic pathogens. The first description of virus-associated hemophagocytic syndrome (VAHS) was made in 1979 by Risdall et al. in nineteen patients whose bone marrow smears showed histiocytic hyperplasia with prominent hemophagocytosis in association with active viral infection [4]. Since then, various viral infections have been associated with reactive HPS. Most cases have been described in association with Epstein-Barr virus (EBV). Other agents include herpes simplex viruses, cytomegalovirus (CMV), hepatitis viruses, human herpesvirus 8, human immunodeficiency virus (HIV), enterovirus, and parvovirus B19. VAHS induced by influenza has been rarely reported [1].

Case Presentation

An 85-year-old man with a previous history of essential thrombocythemia treated with hydroxyurea, with normal laboratory tests in last control, presented with fever (39°C), tachycardia and dyspnea. Laboratory results demonstrated pancytopenia (hemoglobin 12.5 g/dl, leukocyte count 3,000 cells/mcl with 700 total lymphocytes,

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platelet count 56,000 cells/mcl), increased C-reactive protein (31.65 mg/dl), increased LDH (2146 U/l; n<225), acute renal failure, and abnormal liver function tests (AST 59 U/l). The chest x-ray was normal. Empiric antibiotic treatment with meropenem was initiated and hydroxyurea was stopped. Hemophagocytic syndrome was suspected because of persistent fever and malaise and abnormal laboratory results including hyperferritinemia (ferritin 2487 ng/ml), hypertriglyceridemia (triglycerides 204 mg/dl) and high levels of sCD25 (1706 U/ml; n<215). The patient had normal triglycerides and fibrinogen levels one month before disease presentation and slightly elevated ferritin (600 ng/ml) 4 months before hospital admission. Bone-marrow aspiration demonstrated normocellular marrow with 28% hemophagocytosis in which red blood cells, platelets, and neutrophils were captured. Blood protein electrophoresis was normal and autoimmune antibody test results were all negative. Blood and bone marrow cultures were negative for bacterial or fungal infection. Tuberculin skin test, cryptococcal serum antigen and serology tests for EBV, CMV, respiratory syncytial virus, hepatitis B virus, hepatitis C virus and HIV were also negative. On the contrary, nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) was positive for influenza A (H1N1). Antibiotic treatment was stopped and antiviral therapy with oseltamivir (75 mg orally twice daily) and corticosteroids (dexamethasone 10 mg/m^2, with a total dose of 17 mg/day) were initiated observing a prompt clinical improvement. Oseltamivir was stopped after seven days and dexamethasone was tapered to zero over 25 days. Laboratory tests became normal in 2 weeks.

Material and Methods

Given the scarcity of published data of HPS secondary to influenza A virus, we systematically reviewed all further adult patients with influenza A associated HPS and made a descriptive analysis of the results, including data from our case report. For this purpose we follow the next search strategy and selection criteria. Data for this review were identified by searches of PubMed and references from relevant articles. Search terms were "Influenza and hemophagocytic syndrome", "Influenza and haemophagocytic syndrome", "Influenza hemophagocytosis", "Influenza haemophagocytosis", "Influenza histiocytic hemophagocytosis", "Influenza histiocytic haemophagocytosis", "Influenza hemophagocytic lymphohistiocytosis" and "Influenza haemophagocytic lymphohistiocytosis". We only included adult patients (>17 years) with established diagnosis of hemophagocytic syndrome and concomitant influenza A infection. Only English language papers were reviewed. This search revealed 15 other cases of adults with influenza A associated HPS [5-13] and a prospective observational study carried out in 25 critically ill patients with VAHS secondary to influenza H1N1 which was not included in the analysis because of incomplete individual patient data [14].

Results

Of the 16 cases for which data were available, 10 were men and the median age was 44 years (interquartile range 23-85). Only 5 patients had underlying comorbid conditions associated with a severe course of illness; 2 were under immunosuppressive therapy, one had diabetes mellitus and two had hematologic malignancy. Six patients had comorbid infections during their course of illness; the most common observed pathogens were *Staphylococcus aureus* (3 patients) and vancomycin-resistant enterococci (3 patients). Only 1 patient had influenza A H3N2 infection and the rest were secondary to influenza A H1N1. Fever was present in all cases. Dyspnea (43%), cough (25%), and diarrhea (25%) were other common presenting symptoms. Two patients presented with hemoptysis.

Pancytopenia was present in 4 cases. Seven patients experienced moderate (20,000-50,000 cells/mcl) to severe (<20,000 cells/mcl) thrombocytopenia. Of the 8 patients for which ferritin levels were available, the median serum concentration was 3489 ng/ml (interquartile range 199-11060). Only 3 patients had available sCD25 levels, with 1360, 1706 and 3780 U/l, respectively. Only 2 patients had available information from the bone marrow aspirate, which demonstrated 4% and 28% of hemophagocytosis. Clinical and laboratory findings in patients with VAHS secondary to influenza A infection are shown in Table 2.

Of 9 cases for which data was available, 6 patients received immunomodulatory treatment and 7 patients received antivirals, with only 4 cases receiving both therapies. Immunomodulatory therapy consisted in high dose steroids in all cases with one case receiving concomitant etoposide, one case receiving concomitant rituximab and one case receiving concomitant intravenous immunoglobulin. Antiviral treatment consisted in oseltamivir in 5 cases, amantandine in one case, and peramivir in one case. The mortality was 68%, with only 5 out of 16 patients recovering from the disease. Of the 9 patients who received some form of therapy, 5 survived. None of the patients who did not receive any therapy survived. In 7 cases, the diagnoses of hemophagocytic syndrome and influenza A infection were made at autopsy.

In the only prospective observational study that has been done in patients with VAHS secondary to influenza A H1N1 infection [14], 9 out of 25 critically ill patients with influenza infection presented hemophagocytic syndrome. The median age of these 9 patients was 53 years (39 to 56), 7 were male, and 5 patients (56%) had an underlying comorbid condition associated with a severe course of illness. Regarding laboratory data, median peak serum ferritin level was 7576 mcg/l (4708 to 68070) and median peak serum sCD25 level was 8188 kU/l (5120 to 10650). All of them received antiviral therapy (oseltamivir or zanamivir) with a median duration of treatment (oseltamivir) of 10 days (5 to 12). Mortality rate of patients with HPS was 89% compared to 25% in patients without HPS. This high mortality rate could be explained by the fact that 72% of the patients presented with one or more risk factors for a severe course of illness. This study highlights the unfavourable prognosis of patients with HPS secondary to influenza H1N1 infection in relation to those patients with the infection but no HPS. These patients were not included in our table given the absence of individual clinical and laboratory data.

Discussion

Seasonal (H3N2), avian (H5N1), and swine (non-pandemic) (H1N1) influenza have all been associated with fatal cases of HPS in immunocompromised and in immunocompetent hosts [5-13]. It is a rare disease whose exact incidence is not known. On the one hand, the link between influenza A infection and HPS is relatively new, making it a difficult diagnosis due to the low index of suspicion and explaining why many cases have been identified postmortem [15]. On the other hand, hematological abnormalities (cytopenias) are frequently associated with influenza A infection (especially lymphopenia and trombocytopenia) [16,17] although they tend to be mild in most patients and are generally not associated with a poor prognosis. Therefore, diagnosis of HPS is easily missed if there is no clinical suspicion that takes the treating physician to order specific disease markers as proposed by HLA-04 [2]. As presented in Table 2, levels of ferritin, triglycerides and sCD25 were ordered in only 50%, 68%, and 18% of the patients, respectively. Bone marrow aspirate was made rarely.

Reference	Age	Sex	Comorbidities/ co-morbid infections	Influenza virus	Treatment		Presenting signs and symptoms	Cytopenias	L Yes/No (/mcl)	A Yes/No (Hb g/dl)	T Yes/No (x104/ mcl)	AST (IU/l)	Ferritin (ng/ml)	TG (mg/ dl)	sCD 25 (U/l)	HP in BM Yes/No (%)	Outcome
					for HPS	for Influenza											
1. Ando M, et al. [4]	40	F	History of lingual carcinoma	H3N2	CCS, IG	No	Fever, cough	P	Yes (200)	Yes (9.8)	Yes (2.3)	61	ND	ND	3780	Yes (4)	Recovery
2. Kimura K, et al. [5]	37	F	None	H1N1	No	Amantadine	Dyspnea, fever, cough	L, A	Yes (1500)	Yes (9.6)	ND	ND	ND	ND	ND	ND	Died
3. Schulert GS, et al. [6]	28	M	None	H1N1	ND	ND	Fever, hemoptisis, HS	A	No	No	Yes (10.6)	276	ND	308	ND	Yes*	Died
4. Schulert GS, et al. [6]	57	M	*Acinetobacter baumannii* (blood, sputum, BAL)	H1N1	ND	ND	Fever, cough, diarrhea, H	N, T	Yes	No	Yes (7.1)	53	ND	ND	ND	Yes*	Died
5. Schulert GS, et al. [6]	51	M	None	H1N1	ND	ND	Malaise, fever, dyspnea, HS	T	No	No	Yes (9.2)	15479	ND	789	ND	Yes*	Died
6. Schulert GS, et al. [6]	60	F	*Stenotrophomonas* and *Aspergillus* (BAL), MRSA and VRE (blood)	H1N1	ND	ND	Fever, confusion, H	A, T	No	Yes	Yes (2.5)	397	1214	368	ND	Yes*	Died
7. Schulert GS, et al. [6]	37	F	MSSA (blood), *C.albicans,* Pseudomonas, *C. freundii,* HSV (BAL), *C. albic*ans and VRE (urine)	H1N1	ND	ND	Fever, dyspnea, hemoptysis	A, T	No	Yes	Yes (1.8)	401	ND	453	ND	Yes*#	Died
8. Schulert GS, et al. [6]	43	M	*Clostridium difficile* (feces)	H1N1	ND	ND	Malaise, fever, cough, HS	A, T	No	Yes	Yes (9.9)	ND	ND	237	ND	Yes*	Died
9. Schulert GS, et al. [6]	23	M	MSSA (blood), VRE (rectal swab)	H1N1	ND	ND	Fever, diarrhea, lethargy, H	N, T	Yes	No	Yes (2.7)	1086	ND	ND	ND	Yes*	Died
10. Willekens C, et al. [7]	42	F	None	H1N1	CCS, Rituximab	No	Fever, diarrea, H	L, T	Yes (720)	ND	Yes (2.2)	ND	11060	1190	ND	Yes	Died
11. Katsumi A, et al. [8]	55	M	Unrelated BMT	H1N1	CCS	Oseltamivir	Fever, lethargy	P	Yes (3700)	Yes (9.3)	Yes (2.9)	140	3222	101	1360	Yes	Recovery
12. Asai N, et al. [9]	39	F	Rheumatic	H1N1	CCS	Peramivir	Fever	P	Yes (2100)	Yes (10.6)	Yes (10.1)	69	199	100	ND	Yes	Recovery
13. Ur Rehman J, et al. [10]	29	M	Type 1 DM	H1N1	No	Oseltamivir	Fever, dyspnea	P	Yes (1680)	Yes (6.7)	Yes (5.0)	ND	1966	230	ND	Yes	Died
14. Lai S, et al. [11]	50	M	CLL/ *Enterococcus* species, *K. pneumoniae* and *S. epidermidis,* (blood)	H1N1	No	Oseltamivir	Fever, dyspnea, diarrea, S	A, T	No	Yes (6.9)	Yes (6.2)	ND	1761	ND	ND	Yes*	Died
15. Henter JI, et al [12]	31	M	None	H1N1	CCS, Etoposide	Oseltamivir	Fever, dyspnea, S	L, T	Yes	ND	Yes	400	6016	716	ND ^	Yes	Recovery
16. Present case	85	M	ET	H1N1	CCS	Oseltamivir	Fever, dyspnea	P	Yes (3000)	Yes (12.5)	Yes (5.6)	59	2487	204	1706	Yes (28)	Recovery

Table 2: Clinical and laboratory findings in patients with VAHS secondary to influenza A infection. F=Female; M= Male; DM=Diabetes Mellitus, BAL=Bronchoalveolar Lavage, MRSA=Methicillin-resistant *Staphylococcus aureus*; VRE=Vancomycin-resistant *Enterococci*, HSV=Herpes Simplex Virus; *C. albicans=Candida albicans*; *C. freundii=Citrobacter freundii*; MSSA=Methicillin-susceptible *Staphylococcus aureus*; CLL=Chronic Lymphocytic Leucemia; ET=Essential Thrombocythemia; BMT=Bone Marrow Transplantation; *K. pneumoniae=Klebsiella pneumonia*; *S. epidemidis=Staphylococcus epidermidis*, PCR=Polymerase Chain Reaction, HPS=Hemophagocytic Syndrome; CCS=Corticosteroids; IG=Immunoglobulin; ND=No Data; H=Hepatomegaly; S=Splenomegaly; HS=Hepatosplenomegaly; P=Pancytopenia; L=Leukopenia; A=Anemia; N=Neutropenia, T=Thrombocytopenia; AST=Aspartate Transferase; HP=Hemophagocytosis; BM=Bone Marrow; TG=Triglycerides. In all cases diagnosis was made with polymerase chain reaction except in case 1 and 2 in which diagnoses were made by antibody titer in sera and culture of tracheal secretions, respectively.

*Diagnosis was made postmortem. #Hemophagocytosis was found in lymph nodes (not in bone marrow). ^ sCD25 was elevated but levels were not specified.

Clinical signs of HPS include high fever (>38.5°C), lymphadenopathy, hepatosplenomegaly, and non-specific cutaneous involvement. Other common symptoms include cough, dyspnea, diarrhoea, nausea, vomiting, abdominal pain and heterogeneous neurologic manifestations. Multiple organ involvement is frequent and it can be attributed to the underlying disease, infectious triggers, or complications related to hemophagocytosis itself. As gathered in Table 2, the most common presenting symptoms in our review were fever, lower respiratory symptoms, and diarrhoea.

Common laboratory abnormalities in HPS result from prominent liver dysfunction, cytopenias and elevation of ferritin levels, hypertriglyceridemia, hyperbilirubinemia, and low fibrinogen levels. Two main diagnostic parameters are an increased plasma concentration of sCD25 and impaired NK cell activity. Hyperferritinemia, increased beta2-microglobulin levels and high levels of sCD25 have been associated with poor prognosis [18]. In the present study we observed mostly moderate cytopenias and highly variable levels of ferritin and triglyceride as the most important laboratory abnormalities. We believe that an aggressive disease presentation associated with the presence of moderate to severe cytopenias should raise the diagnostic suspicion of an underlying HPS.

Pathophysiologic mechanisms of HPS remain poorly understood. Defects in the mechanism of granule (perforin/granzyme) mediated cytotoxicity seem to be the main factor that predisposes an individual to HPS. This impaired cytotoxic activity causes NK cells and cytotoxic T cells dysfunction that leads to persistent activation of lymphocytes and histiocytes [19]. The uncontrolled immune response causes hypercytokinemia with elevated levels of diverse proinflammatory (IFN-γ, TNF-α, IL- 1, IL-6, IL-8, IL-18) and inhibitory cytokines (IL-4, IL-10) with consequent destruction of hematopoietic cells by macrophages present in bone marrow, lymph nodes and spleen. This so-called cytokine storm could pathogenically contribute to tissue damage and progressive systemic organ failure. Improper intracellular trafficking and impaired apoptosis have also been implicated [1,20,21]. The strikingly inflammatory state promoted by hypercytokinemia could explain the beneficial role of high dose steroids that we observed. None of the patients who received no therapy survived, whilst 55% of the ones that received immunomodulatory treatment (steroids in all cases) recovered. Unfortunately, treatment was never started in many cases because of delayed diagnosis. In the study by Beutel et al. [14], the median time from the onset of symptoms to the diagnosis of VAHS was 23 days (interquartile range 15-29). This could explain, at least in part, the poor prognosis of HPS secondary to influenza A infection.

To our knowledge, no controlled clinical trials of VAHS therapy have been performed. For patients with HPS secondary to pathogens other than EBV, supportive care and treatment of the underlying infection is recommended. EBV associated HPS has a poor prognosis if untreated; therefore, it is recommended to promptly start treatment with a combination of chemotherapy (etoposide), and immunotherapy (dexamethasone) [1,2,13]. We believe that patients with HPS secondary to influenza A infection could benefit from treatment with moderate to high doses of steroids (e.g. dexamethasone 10 mg/m^2) with the aim of regulating the characteristic inflammatory imbalance of the disease.

Mortality caused by influenza H1N1 infection is between 0.77% and 5.3% [22,23]. In the case of avian influenza and influenza H1N1 associated hemophagocytic syndrome, the mortality is around 50%-89% [1,14,21]. Because of the high mortality observed in HPS secondary to influenza A infection, we believe it is crucial to make an early diagnosis and start antiviral and immunomodulatory treatment as soon as possible. In the 16 cases we describe, none of the patients who did not receive specific therapy survived. The main factor for not starting treatment in most cases was delayed diagnosis. In our patient the outcome was excellent, with full recovery observed 2 weeks after diagnosis. The fact that the patient was on hydroxyurea for quite a while with good control of his disease, made us discard both factors as potential triggers of HPS. We believe that early diagnosis and treatment with concomitant oseltamivir and dexamethasone had vital influence on the observed favourable outcome.

Conclusion

VAHS secondary to influenza A infection is a rare entity with high mortality that should be suspected in patients who present with an aggressive disease or multiorgan failure and compatible laboratory data. Early diagnosis and treatment with antivirals and in some cases immunomodulatory therapy could greatly influence the prognosis.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Consent for Publication of Individual Patient Data

As there is no identifiable patient data, the Ethics Committee of Clinical Research from the Hospital 12 de Octubre considers that an informed consent for publication is not necessary.

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