Acquired Hemophagocytic Lymphohistiocytosis in a critically ill patient with invasive pulmonary Aspergillosis and Turicella Otitidis bacteraemia: A Case Report

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ABSTRACT

Acquired Hemophagocytic Lymphohistiocytosis in a critically ill patient with invasive pulmonary Aspergillosis and Turicella Otitidis bacteraemia: A Case Report.

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Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening syndrome of excessive immune activation that mostly occurs as primary (hereditary) disease in children. Acquired HLH is associated with infections, cancer of rheumatological conditions. Both are rare in adults. Turicella otitidis is a bacterium, that is associated with ear infections and there is only one case report of bacteraemia. The present report describes a case of acquired HLH with invasive pulmonary Aspergillosis and Turicella otitidis bacteraemia in an adult patient; and also reviews the relative literature. In conclusion though rare, acquired HLH is a devastating condition that clinicians should have in mind when managing patients with multiple infection or underlying immunosuppression.

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a severe systemic inflammatory syndrome that can be fatal. Neonates and infants up to 18 months of age are most frequently affected by the primary form of this disease; it can be presented in children and adults of all ages. In adults, there may be a slight male predisposition. Secondary HLH can occur as sporadic disorder following an infection. HLH is often associated with viral infections, such as Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV) and less commonly with bacteria (Gram negative), parasites (eg. Malaria) and fungi[1]. Turicella otitidis, a bacterium described twenty years ago, has been associated mostly with ear infections[2]. The present report describes a case of acquired HLH and Turicella

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otitidis bacteraemia in an adult patient and reviews the literature about the subject.

CASE REPORT

A 68-year-old female (BMI: 31 kgr/m²) presented to hospital for prolonged (14 days) fever (>38ºC) of unknow origin, shortness of breath and malaise. Her medical history included type II diabetes mellitus and hypothyroidism under medication with insulin glargine 18 UI s. q q d and levothyroxine 137 μgr p.os. q.d. respectively. No allergies or previous surgeries were documented. Clinical examination findings were mild hypotension (arterial pressure 110/40 mmHg) heart rate (HR) 80 bpm, pulse oxygen pletysmography (SpO_2) 92%, hepatomegaly and the presence of dermatoinoma at the left shin. Laboratory findings revealed peripheral blood cytopenia, high serum ferritin and c-reacted protein level (CRP), hepatic dysfunction, coagulation abnormalities and hypertriglyceridemia (Table 1).

Table 1. Laboratory findings.

	Hb	**WBC**	**Neu**	**PLT**	**Chol**	**Tryg**	**SGOT**	**SGPT**	**γ-GT**
units	gr/dl	k/μl	%	k/μl	mg/dl	mg/dl	IU/l	IU/l	IU/l
ED	8.8	5.02	70	97	127	471	78	99	122
Int Med	10.1	4.56	72	64	138	502	80	37	112
ICUad	10.2	6.22	74	60	141	564	29	21	91
ICU	10.4	8.62	72	50	121	475	51	20	119
	LDH	**Bil tot**	**CPR**	**PCT**	**Ferritin**	**Prot tot**	**Alb**	**Bil tot**	
units	IU/l	mg/dl	md/dl	md/dl	ng/dl	gr/dl	gr/dl	mg/dl	
ED	1168	0.7	10.6	0.02	4062	5.8	2.4	0.7	
Int Med	1695	0.9	12.4	0.09		5	2	0.9	
ICUad	2635	1.1	13	1.05	5000	4.5	2.4	1.1	
ICU	2953	1.1	11.8	1.6	23863	4.4	2.2	1.1	
	aPTT	**INR**	**Fib**	**D-dimers**	**aPTT**	**ESR**			
units	sec		mg/dl		sec	sec			
ED	28.1	1.22	435.8		28.1	119			
Int Med	30.5	1.2	724.88		30.5				
ICU ad	39	1.55	394	0.81	39				
ICU	42.6	1.8	210	1.18	42.6				

ED: emergency department, Int Med: Internal Medicine clinic, ICU ad: Intensive Care Unit admission, ICU: Intensive Care Unit, WBC: white blood cells, Neu: neutrophils, PLT: platelets, Chol: cholesterol, Tryg: triglycerides, SGOT: serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, γ-GT: Gamma-glutamyl transferase, LDH: lactate dehydrogenase, Prot tot: total protein, Alb: albumin, Bil tot: total bilirubin, Fib: fibrinogen, ESR: erythrocyte sedimentation rate.

The patient was admitted to internal medicine department where a bone marrow examination was performed. The latter revealed histiocytosis (11%); thus, a diagnosis of Hemophagocytic Lymphohistiocytosis was set. Along with that, Escherihia coli and Turicella otitidis were isolated from urine and blood cultures, respectively. Antibiotic therapy with piperacillin-tazobactam 4,5 gri.v.t.i.d and imipenem 1gr i.v. t.i.d was initiated; yet, 72 hours later the patient transported to Intensive Care Unit (ICU)due to acute respiratory failure and hemodynamic instability. On admission her Acute Physiology, Age, Chronic Health Evaluation IV score (APACHE score) was 94. Bronchial secretions culture taken after patients' intubation revealed Aspergillus flavus. Later the same day, antibiotic regiment was changed to meropenem 2gr iv t.i.d., vancomycin 1gr iv b.i.d., moxifloxacin 400 mgivq.d. and itraconazole 200mg i.v.b.i.d; due to a septic episode that also needed high dose of norepinephrine (up to 1.1μg/kg/h civ) to control arterial pressure. Corticosteroids (hydrocortisone 50mg q 6h i.v) were also administered. However, the clinical status of the patient continued to deteriorate, and the woman died the day after.

DISCUSSION

Though first described in 1939, HLH is considered a rare condition. It's not only in the past decade that this devastating condition-almost universally fatal without treatment- has gained reputation. However, since primary HLH is a hereditary condition with incidence between 1-225/300.000 live births, most of our knowledge comes from pediatric cases[1,3]. Acquired (secondary) HLH is related to immunodeficiency or an underlying malignant (non-Hodgkin leukoma, acute leukaemia), infectious (mainly viral), or autoimmune disorders. When HLH arises in association with rheumatologic diseases (Still systemic juvenile idiopathic arthritis, systemic lupus erythematosus, it is termed macrophage activation syndrome (MAS)[1,4].

The clinical and laboratory manifestation of HLH is produced by an overactive but ineffective immune system and is diagnosed by a constellation of nonspecific signs, symptoms, and laboratory abnormalities (Table 2)[5,6].

Due to evidence absence about optimal choice of therapeutic interventions, treatment decisions are currently be made on a case-by-case basis[6]. Mortality of acquired HLH in adults is high (up to 50-70%), though data come from limited case series[7].

In our case, we believe that the syndrome was trigged by the concomitant presence of different pathogens (Escherichia coli, Turicellaotitidis, Aspergillus flavus), which eventually lead to overactivation of immune system. Turicellaotitidis is a Gram-positive bacillus belonging to *Coryneform* bacteria, first described in 1993[2]. It is highly pleomorphic, non-sporulating, nonfermentative, catalase-positive, oxidase-negative, nonhemolytic and is

considered part of the normal flora of the external ear canal. Though resistant toaztreonam, cotrimoxazole, nitrofurantoin, fosfomycin, and a high resistant to macrolides and clindamycin, it is highly susceptible to beta-lactams (penicillins, cephalopsorins, carbapenems) as well as to chloramphenicol, linezolid, vancomycin, teicoplanin[8]. Most of the literature regards ear infections of children and there is only one report about of Turicellaotitidis bacteraemia in adult patient, a 75-year-old institutionalized adult manwith multiple hospital admissions [9]. Our case is the second report of bacteraemia with this pathogen.

Table 2. Diagnostic criteria for primary HLH (A) and acquired HLH (B).

A. The diagnosis of HLH requires a molecular diagnosis consistent with HLH or 5 of 8 of the following criteria:	**B. HScore**	**B. Deplhi study**
1. Fever	Immunodepression	Predisposing underlying condition
2. Splenomegaly	High temperature	Fever
3. Cytopenia affecting 2 lines	Organomegally	Organomegaly
a. Haemoglobin <9 g/dl	Cytopenia	Cytopenia
b. Platelets <100 k/μl	Hyperferritinemia	Hemophagocytosis
c. Neutrophils <1.0 x10^9/l	Hemophagocytosis	Elevated LDH
4.Hypertriglyceridemia and/or hypofibrinogenemia	Elevated SGOT/SGPT	
a. Tryglycerides> 265 mg/dl	Hypofibrinogemia	
b. Fibrinogen	Hypertriglyceridemia	
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes		
6. Low or absent NK cell activit		
7. Ferittin> 500 mg/l		
8. CD25, (sIL2R)>2400 U/mL		

Aspergillus flavus produces several mycotoxins, primarily aflatoxin B1 and B2, which cause acute liver damage, cirrhosis, and is known for their immunosuppressive and carcinogenic properties[10]. In the present case we hypothesize that chronic immunosuppression (diabetes melitus) facilitated invasive pulmonary aspergillosis that deteriorated more with ICU hospitalization. Thus, we believe that asymptomatic colonisation of the respiratory tract was present before her admittance[11,12].

On the contrary, we do not assess Escherichia coli as colonisation[13]. In fact, we hypothesize that urinary tract infection was the first to occur,

followed by symptomatic aspergillosis, acquired HLH and Turicellaotitidis bacteraemia.

CONCLUSION

Though rare, acquired HLH is a devastating condition that clinicians should have in mind when managing patients with multiple infection or underlying immunosuppression. High level of suspicion and early diagnosis is essential; even though not always enough to change the course of the disease.

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Author Disclosures:

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