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**CASE REPORT**

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## **Hemophagocytic Syndrome Associated with Herpes Virus 8 and Multicentric Castleman Diseases in a HIV-Negative Patient**

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### **ABSTRACT**

The Hemophagocytic syndrome (HS) is a very rare and aggressive disorder characterized by strong immunological activation of the mononuclear phagocyte system sometimes triggered by viral infections such as Epstein-Barr Virus. Castleman disease is a heterogeneous group of lymphoproliferative disorders associated in some cases with the human immunodeficiency virus (HIV) and human Herpes Virus 8 (HHV-8). The association of HHV-8, Multicentric Castleman Disease (MCD) and Hemophagocytic Syndrome is extremely rare. There are very few reported cases in literature, mostly in HIV positive elderly patients with fatal prognosis. We report a case of Hemophagocytic syndrome, HHV-8 and MCD on an HIV negative young adult. *J Microbiol Infect Dis 2017; 7(4):202-206*

**Keywords:** Hemophagocytic syndrome, Multicentric Castleman Disease, Herpes virus 8, HIV

### **INTRODUCTION**

Herpes virus 8 (HHV-8) discovered in 1990 by Chang and col. is the first known human member of the genus Rhadinovirus. In 1994 was reported for the first time the association of HHV-8 infection with the development of Kaposi sarcoma and in 1995 HHV-8 was also related to the development of multicentric Castleman disease (MCD) and primary effusion lymphoma [1].

The prevalence of HHV-8 infection varies from approximately 50% in most of Africa where is endemic, and even greater in sub-Saharan Africa countries, to 1-2% in Spain and northern Europe, however, it is relatively high (10-20%) in southern Italy and other Mediterranean areas [2].

In low prevalence countries HHV-8 transmission occurs mainly via sexual exposure, with high rates of coinfection with Human Immunodeficiency Virus (HIV).

The Hemophagocytic Syndrome (HS) is very rare, aggressive and life-threatening syndrome characterized by an excessive immune activation with hemophagocytosis, pancytopenia, and increase levels of cytokines and serum ferritin and clinical symptoms of extreme inflammation. It can be classified as primary or secondary to several infections, predominantly Epstein-Barr Virus (EBV), and also autoimmune diseases and neoplastic malignancies. Diagnosis is quite complex, based mainly on the clinical, laboratory and histopathological characteristics.

The association of HHV-8 with HS and MCD is extremely rare, there are very few cases reported in literature referring to elderly and immunocompromised patients, such as HIV-positive [3]. In this paper, we present a case of HS associated with MCD and HHV-8 in an HIV-negative and immunocompetent young patient.

### **CASE**

A 21-year old male patient from Mali, resident in Spain for the last 43 months, comes to our emergency department due to persistent fever, poor general condition, abdominal pain and diarrheal episodes for the

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past 4 days. Patient had history of HBeAg-positive chronic hepatitis B. Systemic examination showed generalized lymphadenopathy and hepatosplenomegaly.

Initial laboratory test revealed important pancytopenia (Table 1): white blood cells (WBC) 2270/uL (normal range 4500-11500/uL) with 42% neutrophils and 55% lymphocytes, hemoglobin 6g/dL (12-16 g/dL) and platelets 45000/uL (130000-450000/uL). Peripheral blood smears showed moderate red blood cells (RBC) anisocytosis and frequent lymphocytes with activated appearance. Considering the clinical setting, the patient was admitted to Hospital for further studies and treatment.

Chest and upper abdomen computed tomography scan (CT) revealed splenomegaly and multiple axillary, mediastinal, peripancreatic, hepatic and retroperitoneal lymph nodes, taking biopsy samples for anatomopathological studies.

Serology and parasitological testing including HIV, EBV, cytomegalovirus, hepatitis C virus (HCV), Hepatitis D, Toxoplasmosis, *Treponema pallidum*, hydatidosis, filariasis, *Leishmania*, *Schistosoma*, *Strongyloides*, *Plasmodium* and urinary parasites were negative except HBV serology with positive Hepatitis B surface antigen (HBsAg) and HBV DNA (deoxyribonucleic acid) detected by polymerase chain reaction (PCR) with quantification >17.000.000 IU/mL.

During the first days after admission the patient received several transfusions of red blood cells due to severe pancytopenia and after one week continued with high fever (40° C) presenting repeated vomiting episodes with analytical and ultrasound data suggestive of acute pyogenic cholecystitis and probable perforation requiring urgent surgical intervention finding after bilateral subcostal incision, a giant splenomegaly of at least 35 cm of major axis. Considering these findings and the hypersplenism component, a therapeutic splenectomy was performed to correct the pancytopenia of the patient.

Pathologic studies of axillary lymph nodes and spleen biopsy revealed histological alterations concordant with plasma cell variant of Castleman's Disease. Microscopic examination of the lymph nodes showed extensive infiltration of mature plasma cells within medullar and interfollicular tissues. The spleen biopsy showed an important mature polyplastic plasmacytosis, atrophic white pulp with fibrosis phenomena and a small number of hemosiderin laden macrophages.

Based on these results, an immunohistochemical study was performed on the paraffin-embedded biopsy tissue for HHV-8 showing latency-associated nuclear antigen (LANA-1) in part of the immune-stained cellularity. HHV-8 DNA was also detected in spleen and lymph nodes by PCR analysis.

These findings lead to the diagnostic impression of multicenter Castleman's disease corresponding to the plasma cell variant associated with HHV-8 initiating treatment with rituximab, along with methylprednisolone and tenofovir.

Considering the clinical setting, the patient was admitted to the Intensive Care Unit (ICU). For the following 10 days persisted the hepatosplenomegaly along with several episodes of hematemesis which required a new transfusion of red blood cells and platelets.

Laboratory testing showed hypertriglyceridemia (662mg/dL), Lactate dehydrogenase (LDH) 407 IU/L, Total Bilirubin 4.02 mg/dL, Direct Bilirubin 2.4 mg/dL, ferritin 7747 ng/ml, anemia (hemoglobin 8.2 g/dL), thrombopenia (platelets 51,000/uL) and red blood cell dysplasia with plasmacytosis and histiocytosis of reactive appearance in bone marrow cytological study.

All these findings strongly suggested the diagnosis of Hemophagocytic Syndrome, initiating corticoid treatment with dexamethasone with a good clinical response in the following days.

After 28 days in the ICU the patient remained stable with favourable evolution and remission of fever and pancytopenia but suddenly started with a massive upper gastrointestinal bleeding with extreme anemia (hemoglobin 4.5g/dL) along with severe coagulopathy, thrombocytopenia and hypovolemic shock progressing to multiorgan failure and requiring renal replacement therapy with continuous venous-venous hemodialysis and numerous transfusions of blood products, mainly platelets and red blood cells.

Two weeks later the patient died due to progressive worsening of thrombocytopenia despite polytransfusions, as well as severe hemodynamic failure and acute oligoanuric renal failure.

Table 2. Evolution of laboratory test results.

Parameter	Normal Range	Day 1	Day 7 (Splenuctomy)	Day 10 at ICU (HS diagnosed / corticoid therapy)	Day 17 at ICU	Day 35 Multiorganuc failure
Hemoglobin (g/dL)	12-16	6	5.6	8.2	9.1	4.5
WBC ( $10^3$ /UI)	4.5-11.5	2.27	2.62	7.28	9.35	5.51
Neutrophils (%)	40-74	42	53	55	60	54
Lymphocytes (%)	19-48	55	26	18	22	28
Platelets ( $10^3$ /uL)	130-450	45	35	51	50	13
Triglycerids (mg/dL)	50-200	191	189	662	219	213
LDH (IU/L)	0-247	367	495	407	330	252
Ferritin (ng/mL)	20-300	1486	2074	7747	4536	5203
Total Bilirubin (mg/dL)	0.3-1.2	1.68	8.38	5.72	4.02	8.35
Direct Bilirubin (mg/dL)	0-0.2	0.54	5.15	4.37	2.4	5.41
PCR (mg/dL)	0.01-0.5	5.71	15.49	16.79	15.17	18.21
HBV DNA (UI/mL)	<10	>17000000		>17000000		

## DISCUSSION

Castleman's disease, first described in 1956 by Benjamin Castleman, is an atypical lymphoproliferative disorder of unknown etiology characterized by non-neoplastic lymphoid nodule hyperplasia.

Clinically has two possible presentations, one variant unicentric (localized), as first described by Castleman, and a multicentric variant with involvement of several sites, which was first described by Gaba et al in 1972.

Histologically it has three well differentiated main types that were described by Flendring and Schilling in 1969 [4]:

The hyaline-vascular type characterized by lymphoid follicular proliferation at different levels of maturity, often forming a layered pattern. It is present in almost 90% of the cases, normally associated with the localized clinical form which is mostly asymptomatic and manifest as a single mass located in the mediastinum. It affects mainly to children and young adults and usually has good prognosis and good response to surgical treatment.

The plasma cells variant characterized by sheets of mature plasma cells within the interfollicular tissues surrounding larger germinal centers and significantly less vascularity and a third mixed form described by Keller in 1972, these variants are less common and are usually associated with the multicentric form, which presents with generalized lymphadenopathy and systemic symptoms such as fever, asthenia,

weight loss, anemia, hypergammaglobulinemia and increased rate of globular sedimentation. The prognosis of this form is less favourable [5].

The etiology of MCD is still poorly understood. Recent studies have suggested the role of viral infection of HHV-8 by demonstrating that HHV-8 is able to produce viral proteins similar to Interleukin-6 (IL-6) and Interleukin-10 (IL-10) which are considered to be the triggering factor of the disease and responsible for the systemic manifestations presented. It has been reported mainly in HIV-positive patients in whom higher levels of interleukins have been observed in exacerbations of the disease, coinciding with a worsening of immunity and increased viral levels of HIV and HHV-8 [6].

The hemophagocytic syndrome is a disorder of the mononuclear phagocytic system characterized by pathological immune activation with symptoms and signs of excessive inflammation producing fever, hepatosplenomegaly and lymphadenopathy.

It is an aggressive life-threatening disease, very rare and difficult to identify. The diagnosis is based on the clinical characteristics, laboratory tests and the histopathological study of bone marrow, spleen or liver, fulfilling either 5 of the 8 diagnostic criteria used in the HS-2004 trial listed below [7]:

1. Fever  $\geq 38.5^\circ\text{C}$  (for 7 days at least)
2. Splenomegaly

3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)

Hemoglobin <9 g/dL

Platelets <100 × 10<sup>3</sup>/uL

Neutrophils <1 × 10<sup>3</sup>/uL

4. Hypertriglyceridemia (265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)

5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver

6. Low or absent Natural Killer cell activity

7. Ferritin >500 ng/mL (>3000 ng/mL it's been suggested as more indicative of HS) [8]

8. sCD25 (soluble IL2 receptor alpha) >2500 pg/mL

Or with a positive molecular analysis for the known mutations of HS: PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A, or XIAP.

There is a primary form of HS associated to gene mutation and one secondary that can be triggered by infections or other immunological activating events, most common in EBV infections, occurring both at the beginning and during the evolution of the infectious disease.

The secondary form of HS associated with HHV-8 infection and MCD is extremely rare, it occurs mainly in HIV positive patients. On immunocompetent patients the first case was published in 2006 by Li et al [9] and there are very few more cases reported in literature, most of them in elderly patients with fatal prognosis.

This represents one of the few cases known of HS, HHV-8 and MCD on young immunocompetent, HIV negative adult and with absence of HHV-8 associated neoplasia. Our patient had no history of immune deficiency prior to admission to our hospital and it is unlikely that the short time spent on methylprednisolone, rituximab and Tenofovir for treatment of MCD could result in severe immunosuppression.

We believe that, as it has been suggested by other authors [1], HS may have developed as a complication of MCD associated with the infection of HHV-8.

The role of chronic HBV infection in the development of HS does not seem to be very relevant, we have found only one case in

literature reporting HS secondary to isolated HBV infection, however, the association of HHV-8 with coexistent chronic active HBV may have also contributed to the development of HS.

HHV-8 has a low prevalence in our environment but is relatively high in certain geographic areas such as Africa and certain Mediterranean countries therefore the occurrence of HHV-8 associated to HS, although is an extremely rare situation, should be considered in countries with immigration from these areas even in HIV negative patients.

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