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Case Report

A Case of Kaposi Sarcoma Herpesvirus Inflammatory Cytokine Syndrome Presenting as a Sepsis-Like Shock with Cytopenias

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Abstract

A 42 year-old HIV infected woman was admitted for a sepsis-like shock with cytopenias. Absence of obvious bacterial infection and intense KSHV replication motivated RITUXIMAB infusion with hypothesis of Multicentric Castleman Disease (MCD). Considering lack of histological evidence for MCD, the diagnosis of KSHV Inflammatory Cytokine Syndrome (KICS) was made.

Keywords: Human Immunodeficiency Virus; Castelman Disease; Kaposi Sarcoma Herpes Virus

Case Report

A forty-two year-old woman was admitted in the intensive care unit, for sepsis-like shock. She was of Ivorian origin, and was known to be dual-infected with HIV and inactive HBV carriers for twelve years. She was treated for left eyelid Kaposi's disease for five years. His care pathway was marked by several breaks in medical follow-up and she was suspected to be inobservant of antiretroviral therapy. At ICU admission, her blood pressure was 90/30mmHg, and she had fever at 39, 3°C. Physical examination showed axillary and inguinal polyadenopathy, moderate hepatosplenomegaly and lower limbs edema. Labs exam revealed profound anemia with 4.8 g/dL of hemoglobin, along with thrombocytopenia at 54 G/L. Anemia was non-regenerative with 18 G/L of reticulocytes, haptoglobin was at 2.45 g/L, and search for schistocytes was negative. Marked inflammatory syndrome was noted with C-reactive protein (CRP) at 195 mg/L and ferritin at 4500 ng/mL. Blood leukocytes reached 11.1 G/L. Serum creatinine was 61µmol/L. ASAT and ALAT were respectively at 79 and 11 UI/L. Arterial blood gas showed compensated metabolic acidosis with serum bicarbonate at 19 mmol/L and lactates at 3.2 mmol/L.

Because of suspected septic shock in an immunocompromised host, vasopressors and broad spectrum antibiotics, including PIPERACILLIN-TAZOBACTAM, AMIKACIN and SPIRAMYCIN, were started, after large microbiological sampling. A whole body CT scan showed a small unexplained peritoneal effusion, hepato-splenomegaly, and ground glass in the right upper lung lobe. The pulmonary lesions were compatible with pneumocystis pneumonia and motivated prescription of TRIMETHOPRIM-SULFAMETHOXAZOLE.

Considering the hypothesis of hematological malignancy, a bone marrow aspiration was performed and reported the presence of megacaryocytes, no signs of pathological infiltration neither hemophagocytosis. First microbiological results showed no bacterial infection, but viral replications: HIV-1 RNA at 5.8 log copies/mL confirming non-observance of antiretroviral therapy, reactivation of HBV at3.0 log copies/mL, Epstein Barr virus (EBV) 4.2 log copy/mL, Cytomegalovirus (CMV) 3.4 log copy/mL and Kaposi sarcoma herpesvirus (KSHV)at 6.74 log copies/mL. CD4 count was low at 108 cells/µL. Albuminemia was 20 g/L.GANCICLOVIR was started.

Four days after ICU admission, fine needle aspiration cytology of an axillar nod was performed for cytological analysis. In the following day, although cytopathology of lymph node was still unknown, it was decided to start a first infusion of RITUXIMAB because of associated multi-organ failure and strong suspicion of Multicentric Castleman Disease (MCD). Indeed, high viral load of Kaposi sarcoma herpesvirus, anasarca and tumoral syndrome were evocative. Antiretroviral therapy associating TENOFOVIR, DARUNAVIR and RITONAVIR, was resumed in order to control HIV-1 and HVB replications.

At day 6, she was intubated because of acute hypoxemic respiratory failure and non-hypercapnic coma. A new CT scan showed a severe worsening of pulmonary injury, with ground glass and crazy paving. Brain imaging showed old occipital and cerebellar ischemic injury. Trans-esophageal echocardiography excluded infective endocarditis. Lumbar puncture eliminated bacterial and cryptococcal meningitis, research for Toxoplasma gondii, Nocardia and herpesviridae were negative too. No respiratory pathogen was detectable on bronchoalveolar lavage, including an extensive research of Pneumocystis jirovecii by direct immunofluorescence and PCR.

At day 10, a lymph node biopsy was performed because cytology examination of the node ponction was not contributory. We started corticosteroids the same day.

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Table 1: Evolution of clinical and biological parameters during ICU stay.

Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
		ICU entrance	Bone marrow aspiration RBC transfusion		Node cytoponction	ART start	Intubation Rituximab n°1				Node biopsy Solumedrol	Solumedrol	Solumedrol		Bone marrow biopsy Etoposide	Extubation Rituximab n°2	Gastric biopsy			Rituximab n°3			
Temperature (°C)			39,5	39,4	38,9	38,1	38,2	37,9	37,2	38,4	37,2	36,7	36,5	36,9	37,3	36,3	36,4	35,6					
Hemoglobin (g/dL)		4,8	6	7,6	7,8	6,8	9,1	7,2	7,9	7,6	7,1	8,4	7,6	7,6	7,3	6,5	8	7,6	7,9	7,5	7,7	7,6	7,4
Platelets (G/L)		54	52	16	16	16	20	31	17	28	29	47	58	60	57	48	49	54	102	110	109	103	96
Bilirubin (µmol/L)				25	39		56	69	60	66	64		110	135	162	116	96	66		47	42		46
CRP (mg/L)		195	230						139						60								66
Lactate (mmol/L)		3,2	3,8	2,8	6,3	5,8	4,4	4,2	2	2	2,7	3	3,5	3,2	2,3	2,5	2,4	1,6					1,7
Viral load (log copy/ mL)	HIV		5.9																				
	HVB		3							2.3						1.9							
	EBV		4.2							3.7						< 1							
	CMV		3.5							< 1						< 1							
	KSHV		6.7													3.7							

At day 13, cytopathology exam revealed the presence of Kaposi sarcoma in the lymph node. After a multidisciplinary consultation with oncologist and hematologist, we concluded that disseminated Kaposi sarcoma did not explain the entire picture. Moreover, except for hyperbilirubinemia, clinical and biological parameters seemed to improve since the introduction of corticosteroids (Table 1), which are not active on Kaposi sarcoma.

As a consequence, at day 14, hypothesizing a typical MCD with negative histology, or at least a severe hemophagocytic lympho histiocytosis (HLH), the patient benefited from ETOPOSIDE.

She was extubated at day 15, just after the second injection of RITUXIMAB. Viral load of EBV and CMV were undetectable. Viral load of KSHV and HVB were respectively 3.72 log copies/mL and 1.9 log copies/mL.

At day 16, she benefited from endoscopic biopsy which provided histological proofs of gastric involvement of disseminated Kaposi sarcoma. Bronchial endoscopy did not show any abnormality.

She was transferred in infectious disease department at day 22. Liposomal doxorubicin was administered as treatment for the disseminated Kaposi sarcoma during hospitalization in infectious disease. Three months after resumption of antiretroviral therapy; the evolution was good with an undetectable HIV viral load, a CD4 rate of 165/mm^3 and regression of lymphadenopathies and Kaposi lesion of the eyelid. The patient was transferred to a rehabilitation service. Six months later she was still followed in infectious disease.

Discussion

We report here a case of sepsis-like shock, in which KSHV intense replication seems to play a key role. Diagnosis of disseminated Kaposi's sarcoma confirmed thanks to lymph nodes and gastric biopsies. However, despite of the lack of histopathological evidence, other diagnosis such as MCD, primary effusion lymphoma, and HLH can still be discussed.

First, despite of uncertainty, from a pragmatic point of view, timing of ETOPOSIDE may be discussed. Indeed, because of HIV and febrile cytopenias, initial picture was highly suggestive of HLH. Because of the absence of hemophagocytosis on bone marrow aspiration, this diagnosis was considered unlikely to justify aggressive treatment such as ETOPOSIDE. However, H-score, which is a validated score for probability assessment of HLH, was still at 227 when checking "no hemophagocytosis features on bone marrow aspirate", which indicate a probability of 97,5% to have a HLH [1]. High levels of ferritin associated with pancytopenia were clues for considering HLH.

With the information of a very high KSHV viral load, MCD became the first hypothesis. Indeed, fever, anasarca, peripheral lymphadenopathy, hepato-splenomegaly, cytopenia and hypoalbuminemia are classical features of HIV associated MCD attack [2]. This syndromic association motivated the first dose of RITUXIMAB, before knowledge of biopsy's result. Nevertheless, unexpectedly, the pathologist did not see follicular hyperplasia, hyalinization and involution of germinal centers, nor hyperplasia of the mantle zone shows concentric rings of lymphocytes. As a consequence, MCD cannot strictly be affirmed.

Although histologically proven, disseminated Kaposi sarcoma as a single diagnosis was not convincing. First, whether pulmonary involvement may be one feature of Kaposi sarcoma, neither the sepsis-like picture, nor cytopeniaare described in such sarcoma [3]. Second, we note a clinical and biological improvement after RITUXIMAB and corticosteroids that have never reported therapeutic effects on Kaposi sarcoma. Moreover, some worsening have even been reported [4,5]. So, response to treatment is here a strong argument to consider the hypothesis of an association of Kaposi sarcoma and an atypical MCD.

Other "MCD-like-syndrome" without histological proof has been previously reported. In a retrospective series, Uldrick et al. have described six HIV-infected patients with viral replication of KSHV and inflammatory symptoms. All were suspected to have a MCD, but have a negative histopathological examination. Those patients were characterized by a production of KSHV-encoded interleukine 6 (v-IL6) and human interleukine 6 (h-IL6) similar to MCD patients, and greater than HIV-infected patients seropositive for KSHV but

without MCD [6]. Considering that observation, Polizzotto et al. have proposed the "KSHV Inflammatory Cytokines Syndrome" (KICS), as a new entity. Then, they prospectively include patients corresponding with predefined criteria of "KICS" in a cohort study: 1) clinical or biological manifestations such as fever, edema, dyspnea, anemia, thrombocytopenia or hypoalbuminemia, 2) elevated CRP, 3) evidence of KSHV viral activity, and 4) no histologic evidence of KHSV - MCD. Ten HIV-infected patients were enrolled.In this series, mortality was high. Among the 6 patients who died, the median survival was 13,6 months. Anemia and hypoalbuminemia at diagnosis, both present in our case, were independently associated with mortality in the first year [7,8].

The case reported herein meets the KICS criteria. Similar to the reported cases, our patient has less than 200 CD4/μL, and no intercurrent infection was reported in our patient. Similar to the six patients who benefited from lymph node biopsy, features of Kaposi sarcoma were found in our case. She was critically ill, as 5 reported cases, and has needed invasive ventilation as in 3 reported cases.

Because MCD is a lympho-proliferative malignancy, histological proof is necessary to start chemotherapy. However, emerging data suggest that KICS could lead to severe complications and poor prognosis with a pathophysiology similar to MCD. It is possible that, in this setting, while histological evidence is not available, urgent chemotherapy may be necessary.

Sepsis-like shock in the setting of HIV needs first a large microbiological exploration and early administration of anti-infective therapy. When infection is not proven, multidisciplinary discussion is necessary because some diagnosis need urgent chemotherapy. First, there is an increased risk of HLH in the setting of HIV infection, and cytopenias might alert clinicians. Second, when there is replication of KSHV, MCD or KICS might cause severe activation of inflammatory response, requiring urgent treatment, as RITUXIMAB seems to have transformed our patient.

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