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(CASE REPORT)

HHV-8-associated multicentric Castleman disease with hemophagocytic syndrome in an HIV-infected patient: A case report

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Abstract

Multicentric Castleman's disease is a rare condition in HIV-infected patients that poses several difficulties in terms of diagnosis and treatment. The association of Multicentric Castleman's disease with the hemophagocytic syndrome is even less common and worsens the prognosis. Here we report a case of an HIV-infected patient with low-grade fever and pulmonary involvement with polyadenopathies diagnosed as multicentric Castleman's disease associated with the hemophagocytic syndrome, successfully treated with the combination of rituximab and etoposide.

Keywords: HIV; Multicentric Castleman disease; HHV8; Hemophagocytic syndrome; Pulmonary involvement

1. Introduction

Castleman disease (CD), was first described in 1954 by Benjamin Castleman. It represents a heterogeneous group of lymphoproliferative disorders, that share some characteristic histopathological features but have various etiologies, presentations, and treatments. [1,2]

Human herpes virus-8-associated multicentric Castleman disease (HHV8-MCD) is a rare entity belonging to this group of disorders. It affects multiple lymph nodes regions and mostly occurs in immunocompromised patients including human immunodeficiency virus (HIV) infected patients as a result of HHV8 uncontrolled infection. [1,3]

Besides being rare, the clinical presentation of this disease is non-specific, making the diagnosis difficult with a rich and complex differential diagnosis. We report the case of a 58-year-old HIV-infected patient who presented with chronic fever, lymphadenopathies, pulmonary involvement, and pancytopenia.

2. Case presentation

We report the case of a 58-year-old Moroccan man diagnosed positive for HIV two years before his admission. His HIV infection was discovered at the AIDS stage with Kaposi's lesions on both lower limbs. The initial HIV-1 RNA viral load was 861200 copies/ml and the CD4 count was 90/mm^3. He received bleomycin and antiretroviral therapy based on

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efavirenz/emtricitabine/tenofovir. The patient was followed for 6 months with remission of his Kaposi's disease but then stopped the follow-up and the antiretroviral therapy eighteen months before his admission.

In this episode, the patient reported a chronic dry cough evolving for more than three months accompanied by low-grade fever, night sweats, anorexia, profound asthenia, and weight loss. The physical examination revealed a poor general condition, hepatosplenomegaly. We also found generalized, firm, and mobile adenopathies measuring from 1.5 to 3 cm. Laboratory tests found pancytopenia, lymphocytosis, and an inflammatory syndrome (Table 1).

Table 1 The results of the main laboratory tests at admission and their evolution after four cycles of treatment and after four months of treatment

TESTS	Admission	After treatment	Follow up after four months	reference values
Hemoglobin (g/dl)	7.3	9.3	12.3	13-18 g/dl
Platelets (10^3/µl)	56	209	182	150-450
White Blood Cell (10^3/µl)	7.9	3.8	7.1	4-11
Neutrophils (10^3/µl)	1.4	2.1	3.6	1.4-7.7
Lymphocytes (10^3/µl)	4.6	1.4	2.5	1-4.8
CD4 cell count (cells/mm^3)	297	-	900	500-1200
HIV- 1 viral load (copies/mL)	150000	-	undetectable	
c-reactive protein (mg/L)	51	6	<5	<5
Ferritin (ng/mL)	654	190	102	30-400
Fibrinogen (g/L)	1.8	-	-	2-4
Triglycerides (g/l)	4.5	1.5	1.4	<1.5
blood urea nitrogen (mg/dL)	46	52	42	15-44
Serum creatinine (mg/L)	7.04	11.1	11.3	6.8-13.6
ALT (U/L)	14	27	26	<60
AST (U/L)	24	19	30	<50
LDH (U/L)	174	-	177	135-225

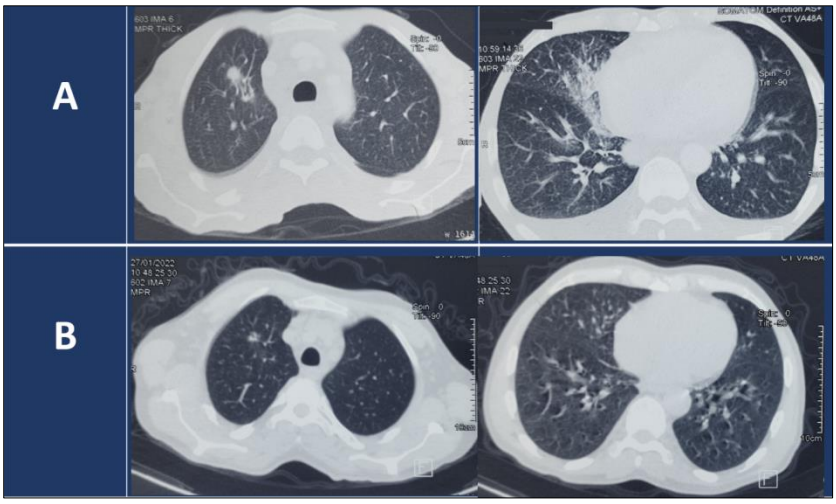

Figure 1 A patient's thoracic CT scan on admission. B patient's thoracic CT scan four months after treatment

The thoracic and abdominal computed tomography scan revealed multiple nodular lesions in the lung, including a right apical nodule measuring 12x10 mm. This nodule had irregular spiculated contours and a retractile appearance with the attraction of the adjacent branches which were thickened (Figure 1). The CT scan also revealed supra-diaphragmatic and sub-diaphragmatic adenopathies, hepatomegaly, splenomegaly, and both pleural and peritoneal effusion.

Histological examination of an axillary adenopathy biopsy showed effaced lymph node architecture. The few remaining lymphoid follicles contained regressed germinal centers. The interfollicular zones were the site of pronounced vascular proliferation with hyalinized thickened walls and abundant mature plasma cells. Immunohistochemistry with anti-HHV 8 antibody showed lymphoid cells infected with HHV8. which was compatible with HHV8-MCD (figure 2).

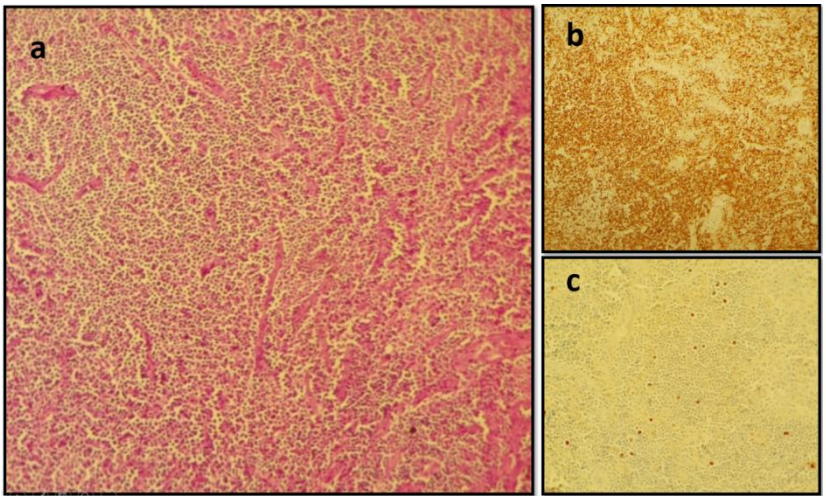

Figure 2 Lymph node histology a: microscopic image after staining with hematoxylin-eosin showing hyaline vascular hyperplasia with atrophic germinal centers b: Immunostaining with anti-CD138 antibody shows the presence of numerous polyclonal plasma cells c: nuclear staining for anti-HHV8 in some lymphoid cells

Analysis of the bone marrow aspirate revealed features of hemophagocytosis. The H-score calculated from the patient's clinical and biological elements was 277 and the probability of hemophagocytic syndrome was greater than 99%.

We treated the patient with dolutegravir, lamivudine, and tenofovir antiretroviral therapy and four weekly cycles of dual therapy with etoposide and rituximab.

The patient rapidly improved clinically and biologically with no adverse events. In the lung, in addition to the good clinical course, the radiological images of the follow-up CT scans performed in the fourth month after treatment showed a marked improvement (figure 1 and table 1). the patient had not relapsed during two years of follow-up.

3. Discussion

HHV8-MCD is rare in HIV-infected patients but its recognition has curiously increased in the combination antiretroviral therapy era without any clear explanation[3]. Its incidence measured in a cohort of over 10,000 HIV-infected patients is 4-3/10,000 patient-years[4].

Uncontrolled HHV8 infection seems to play a central pathogenetic role. The Infection of immunoblasts by HHV-8 and the production of viral interleukin-6 (IL-6) is responsible for a cascade of other cytokines including human IL-6 which drives the inflammation and the clinical presentation[3,5].

The clinical presentation of HIV-related MCD is nonspecific and characterized by fever, lymphadenopathy, hepatomegaly, splenomegaly, edema, and effusions[5]. This presentation can suggest several infectious, autoimmune, or even malignant diseases. In our case, the diagnosis of multifocal tuberculosis was the most reliable, especially with the pulmonary symptoms, the immunocompromised background, and the endemicity of tuberculosis in our country, especially in HIV-infected patients.

The thoracic computed tomography scan in our case revealed -in addition to adenopathies- multiple nodular lesions in the lung, including a right apical nodule with spiculated contours, a retractile appearance, and thickened adjacent

branches. This nodule has been considered suspicious of malignancy. However, a systematic review of MCD in HIV-positive patients documented respiratory system involvement in one-third of the patients and the main CT findings include poorly defined centrilobular nodules, thin-walled cysts, thickening of bronchovascular bundles, and interlobular septal thickening[5]. These features are partially consistent with our thoracic CT scan findings (figure 1) and support in addition to the improvement of pulmonary symptoms and CT scan results after the treatment of HHV8-MCD, that in our patient, the pulmonary involvement is related to MCD. This shows how difficult it can be to diagnose MCD, as it may mimic tuberculosis or even lymphoma and other solid neoplasms.

the association in our case of haemophagocytic syndrome makes this observation even more interesting and the patient prognosis even more uncertain. Indeed, the association of haemophagocytic syndrome and MCD is relatively uncommon, in a cohort including 44 HIV-MCD patients the haemophagocytic syndrome was present in 9% of cases[4].

Available therapy includes steroids, single-agent, and combination chemotherapy, antiviral strategies, and monoclonal antibody therapies targeting CD20 or IL6. [1] But only rituximab-based therapy has proven to be effective either in association or alone with more than 90% of remission[3]. We treated our patient with four cycles of the combination of rituximab and etoposide, the clinical presentation and laboratory tests improved rapidly, and the follow-up chest CT scan at four months of treatment showed almost complete improvement of the lesions (figure 1 and table 1).

4. Conclusion

The clinical presentation of HHV8-MCD is non-specific with a multitude of differential diagnoses. It may mimic opportunistic infections, lymphomas, or neoplasia, which are much more common in the context of HIV infection. The mortality associated with HHV8-MCD is greater than 30%. This high mortality prompts us to consider this diagnosis in any HIV-infected patient presenting with fever and polyadenopathy.

Compliance with ethical standards

Acknowledgments

I thank all the authors of this article.

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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