HIV-associated multicentric Castleman's disease

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Abstract

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder. It is found with higher frequency in patients with HIV infection, with systemic symptoms and poor prognosis. We present the case of a 32-year old man with HIV disease, Kaposi's sarcoma, lymphadenopathy, fever and hemolytic anemia. A diagnosis of Castleman's disease is confirmed through biopsy and treatment is often based only on published case reports. Systemic treatments for MCD have included chemotherapy, anti-herpes virus, highly active antiretroviral therapy and, more recently, monoclonal antibodies against both IL6 and CD20.

Introduction

The first description of Castleman's disease originally occurred at the Massachusetts General Hospital in 1954 by Benjamin Castleman, a pathologist at this institution.[1] Over two years, Castleman described 13 cases of localized, asymptomatic mediastinal masses with lymph node hyperplasia resembling a thymoma.[2] The disease has been histologically classified as vascular hyaline, that is follicular hyperplasia and unicentric (unifocal or localized) capillary hyalinization, usually seen in young adults, with mediastinum (60-75%), cervical (20%) and abdominal (10%) masses. It is also usually asymptomatic.[3] The second description, is called a plasma cell variant of Castleman's disease and is without hyalinization and plasma cell nests surrounded by a germinal center in the interfollicular space. It is associated with systemic manifestations and commonly associated to immunological abnormalities, having a worse prognosis than the HIV localized form.[4-6]

A third subtype is known as plasmablastic multicentric Castleman's disease (MCD). The mantle zone of lymph nodes involved contains abnormal and large plasma cells, with prominent nucleoli and abundant cytoplasm, called plasma blasts. It is a more aggressive disease, being multifocal and was first described in association with POEMS (polyneuropathy, organomegaly, monoclonal endocrinopathy, gammopathy and skin changes). It is very frequently found in HIV-positive individuals.[7] Despite the higher incidence in patients with HIV infection, epidemiological studies showed no correlation with CD4 count or highly active antiretroviral therapy (HAART).[7] The coexistence of Kaposi's sarcoma and HIV MCD was seen in 72% of cases in a systematic review.[8] Both diseases can be present in the same lymph node.[9] The KSHV viruses (Kaposi's sarcoma associated to herpes virus) is also known as human herpes virus 8 (HHV-8) and is present in all HIV MCD cases.[10] Patients with MCD often develop secondary tumors, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease and plamocitoma.[11,12] The histological findings in Castleman's disease are often non-specific and need to be supported by a well considered differential diagnosis. The pathologist and the clinician also need to work closely together.

Case Report

A 32-year old patient (I.C.M.) was hospitalized on 2007-07-07 with cervical lymphnodemegaly up to 2.0 cm. Kaposi's sarcoma was demonstrated by means of cervical biopsy. AIDS was confirmed and HAART was started. On 2007-07-07, exploratory data analysis also showed Kaposi's sarcoma in the oral cavity, esophagus and stomach and the start of some skin lesions. The patient was treated with liposomal doxorubicin (40 mg/m^2) every 21 days for 6 cycles, with complete response. One year after the treatment, a recurrence of the lesions was found in the oral cavity and skin, and there was cervical lymph node enlargement of up to 1.5 cm, armpit and mediastinum. At the time, the patient was using efavirenz, tenofovir and biovir (HIV-PCR with 40 copies/mL). Liposomal doxorubicin was reported up to March 2009 for 5 cycles (without exceeding the maximum cumulative dose of doxorubicin) and a complete response was again obtained. In February 2010, he progressed to cervical lymph node of up to 1.5 cm in the armpit, mediastinum and retroperitoneal up to 2.0 cm, with more homogeneous splenomegaly. He also presented sweating and mild fever in the evening, without weight loss. Serology for cytomegalovirus [Immunoglobulin (Ig) M negative, IgG positive] and for mononucleosis and toxoplasmosis (IgG and IgM negative) was performed. HIV PCR was less than 40 copies/mL, CD4 was 30.5% (VR 35-62%) and 716 mm^3 (VR 398-1535 mm^3), CD8 was 50.7% (VR 17-43%) and 1190 mm^3 (VR 255-1720mm^3) and C-reactive protein 40 mg/L. Cervical lymph node biopsy was performed and anatomopathological immunohistochemistry showed additional reactive lymphoid hyperplasia. A new biopsy was requested but initially the patient did not accept and missed several visits until being hospitalized with autoimmune hemolytic anemia in June, 2010. A stable condition was achieved. He was discharged with prednisone 20 mg/day. Initially, the patient did not accept other cervical biopsy for esthetic reasons (scar). He accepted a second biopsy, this time by laparoscopy of the retroperitoneal lymph node and on the same day (2010-09-07) a sample of the cervical lymph node was also taken. The anatomopathological test revealed Castleman disease' (multicentric), associated with HHV-8 in both lymph nodes. Hyalinization of germinal centers was observed, with intense plasmocytosis and paracortical lymphoid plasmablastic aspect. Immunohistoche-mistry showed HHV-8 positivity in scattered cells and polyclonal plasmacytosis. Before starting treatment, he was already presenting, besides the lymph nodes (cervical, armpit, retroperitoneal and inguinal), anemia, ascites, and pleural effusion in both lung bases. We could not perform HHV8 viral load PCR. Chemotherapy with COP (cyclophosphamide, vincristine plus prednisone) was started and rituximab plus prophylaxis for pneumocystis carinii and herpes. He has improperly used antiretroviral drugs since May 2010, (lopinavir/ritonavir, tenofovir and lamivudine) and has now been instructed as to the correct use of the medication. After the first cycle of chemotherapy, a resolution of the hemolytic anemia was observed, with the solution of all fever and sweating episodes. When the second cycle of chemotherapy was administered, the patient presented nausea and malaise, and the chemotherapy was delayed for four days. When the patient returned, he presented hypotension, jaundice and dark urine. We suspected the occurrence of drug-induced hepatitis, mainly due to antiretroviral drugs (AST 100, ALT 389, GGT 389, LDH 613, FA 141). He was hospitalized again on 11/29/2010 and the abdominal computed tomography (CT) scan was repeated, with no evidence of biliary compression. Liver biopsy was performed on 2010-12-17 and this was compatible with a drug inflammatory process. Lopinavir/ritonavir were substituted by efavirenz, maintaining tenofovir and lamivudine, with clinical improvement. Therefore, the treatment was completed with 8 cycles of COP-rituximab and CT scan showed

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Key words: Castleman's disease, HIV, human herpes virus-8, Kaposi's sarcoma, rituximab.

Funding: grants to publish from Roche Pharmaceuticals.

Conflict of interests: the authors report no potential conflict of interests.

Received for publication: 15 October 2012.
Revision received: 20 April 2012.
Accepted for publication: 11 June 2012.

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Rare Tumors 2012; 4:e40
doi:10.4081/rt.2012.e40

complete response. A reactivation of the Kaposi's sarcoma on the skin was also observed during the treatment, but no new drugs were introduced in order to avoid the occurrence of additional hepatic burden due to the former drug-induced hepatitis. The patient completed the 8 cycles in March, 2011 and, by maintaining the antiretroviral treatment, the spontaneous regression of the skin lesions has been observed. The patient currently maintains normal levels of CD8 and CD4 and the viral load is undetectable. Besides image tests, every three months with complete blood count, renal and hepatic function tests, we are waiting to receive the HHV8 (PCR) viral burden dosing as soon it is made available by the laboratories.

Table 1. Disease activity criteria (HIV Multicentric Castleman's Disease).

1	Fever
2	At least 3 of following symptoms: Peripheral lymphadenopathy Splenomegaly Edema Pleural effusion Ascites Cough Nasal obstruction Xerostomy Rash Central neurological symptoms Jaundice Autoimmune hemolytic anemia
3	Increased C-reactive protein (>20 mg/L) in the absence of another etiology

Discussion

The Castleman's disease pathogenesis is related to an exacerbated response of the immune system. It is believed that the lymphoproliferation mechanism in MCD is mediated by interleukin 6, a cytokine involved in acute phase inflammatory reaction. Interleukin 6 can be derived from the host or from the KSHV virus. Systemic symptoms of HIV MCD are attributed to high plasma levels of interleukin 6, and, therefore, we tried to block this pathway.[13]

The diagnosis of HIV MCD is based on clinical and pathological findings; the patient presents fever, increased C-reactive protein to more than 20 mg/L (in the absence of any other cause) and at least 3 of 12 additional clinical features (Table 1).[14] Interestingly, the criteria mentioned below by the French group does not include the prevalence of these symptoms in their patients.

It is difficult to distinguish HIV-related lymphadenopathy from those related to Castleman's disease.[12] This patient presented fever, increased C-reactive protein, peripheral lymphadenopathy, jaundice and severe autoimmune hemolytic anemia. Three biopsies were performed to complete the diagnosis. In the first biopsy, only Kaposi's sarcoma in lymph nodes were reported. The second biopsy presented reactive lymphoid hyperplasia and, finally, the third presented Calstleman's disease, with the patient already showing hemolytic anemia. Multicentric Castleman's disease associated with HIV is rare and there is no standard treatment available. There are no randomized trials due to the low incidence of the disease and the treatments are based on case reports and the small series published. Various approaches include treatment with antiretrovirals, antiherpesvirus, and chemotherapy with single agents or in combination with monoclonal antibodies. Several case reports show the benefit of rituximab monotherapy (375 mg/m^2) weekly for four weeks in patients with less aggressive disease.[14] For aggressive disease, treatment successes were obtained with rituximab (375 mg/m^2) with weekly etoposide (100 mg/m^2) i.v. for four weeks or with CHOP regime (cyclophosphamide, doxorubicin, vincristine, prednisone) without rituximab.[15-17] Bower suggests retaining chemotherapy associated to rituximab for patients with aggressive disease involving organs or severe hemolytic anemia.[15] It has also been suggested that the introduction of HAART improves outcomes because it can limit both the decrease in CD4 count assigned to chemotherapy and the reactivation of Kaposi's sarcoma related to immunotherapy. It is also usual to start prophylaxis for opportunistic infection. Another humanized monoclonal antibody (tocilizumab) which targets interleukin 6 and is used in the treatment of refractory rheumatoid arthritis, was used for patients with multicentric Castleman's disease who are HIV negative.[16] Experience is also very limited and there are no studies using this monoclonal antibody for HIV MCD. Experience is also restricted for cases of disease recurrence. According to Powles, one quarter of the patients with HIV MCD present relapse after three years of follow up and a second remission can be achieved in cases of additional treatment with rituximab.[17]

A recent study showed that in a multivariate analysis the detectable viral load of HHV8 (>50 copies/mL) during remission is predictive of disease onset (HR 2.9; 95% CI: 1.3-6.7). So far, it has been not established which is the best treatment (continuous or intermittent) to prevent disease recurrence and it has been suggested that maintenance therapy with rituximab may be considered for these patients. However, the potential benefit of rituximab maintenance, and also of valganciclovir, in patients with complete remission is still not clear.[18] As far as the response assessment is concerned, it is still uncertain whether the best criterion is clinical, radiological, biochemical or virological.[15] The study of Stebbing *et al*.[18] suggests that the viral load of HHV8 (PCR) can be used as a biomarker to monitor the disease.

Conclusions

Multicentric Castleman's disease is rare in HIV infected patients, and Kaposi's sarcoma and MCD may be present in the same lymph node, often requiring more than one biopsy for a conclusive diagnosis. MCD should be considered in the differential diagnosis of fever of unknown origin and generalized lymphadenopathy. Clinical studies are needed to determine the real benefit of maintenance therapy in patients in disease remission.

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