Author's response to reviews

Title: An unusual presentation of Castleman's Disease: A Case Report

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Re: ID - 5472905091561800
"An unusual presentation of Castleman's Disease: A case report"

Ifeoma Izuchukwu MD, MPH, Kamal Tourbaf MD and Martin Mahoney MD, PHD
BMC Infectious Diseases

Dear Editor,

Thank you for considering our paper for publication. We appreciate the helpful comments provided by the reviewers which have helped to strengthen this manuscript.

Below, we have summarized a point-by-point response to the reviewers' comments. We have submitted two manuscript files - one with all substantive edits identified and another as the final revised manuscript.

Thank you again for your interest. We look forward to your reply.

Sincerely,

Ifeoma Izuchukwu MD, MPH

Responses to reviewer comments:

Reviewer: Jonathan Day

1. What makes this article original is the fact that HHV-8 was not found. Might the authors be able to further clarify how they came to this conclusion and how hard they looked? Were the samples tested blood or lymph node biopsy, and what technique was used - PCR, or immunohistochemistry or something else?

Reply: Blood and lymph node biopsy using PCR and immunohistochemistry were negative. These laboratory assays have been described in the text

2. The authors have described in great detail the presentation and work up of the patient. They include many of the investigations they carried out that yielded negative results and the possible
differential diagnoses they excluded. While this approach is important clinically, for the purpose of the article there are other aspects of MCD, HIV and HHV-8 that might be useful to cover to strengthen the discussion:

i) More on HHV-8 and its normal association with both MCD, KS, & lymphoma's in HIV.

Reply: The following text has been included in the paper -- In some patients, multi-centric disease has been associated with both HIV infection and co-infection with human herpesvirus-8 (HHV-8). HHV-8 is also known as Kaposi sarcoma-associated virus, and it is postulated that HHV-8 produces interleukin 6 and is responsible for lymphoplasmacytic proliferation. Moreover, the presence of other human cytokines produced by HHV-8 could contribute to lymphoplasmacytosis and to endothelial proliferation. In one study, HHV-8 sequences were found in lymph nodes in all 14 cases of HIV (+) MCD and in 7 of 17 cases of HIV(-) MCD, as compared to 1 of 51 HIV(-) reactive lymph nodes and 3 of 17 HIV(+) reactive lymph nodes. Other studies have confirmed that HHV-8 appears to be universally found in HIV (+) MCD and in approximately 40 to 50 percent of HIV (-) MCD. Interestingly, our patient was negative for HHV-8 virus, which appears to be the first report of an HIV (+) patient with MCD who is negative for HHV-8 infection.

ii) More on IL-6 and its role in the pathogenesis and new treatment strategies aimed at blocking IL-6.

Reply: The following text has been included in the paper -- It has been suggested that expression of Castleman's Disease is partly due to IL-6 activity, and HHV-8 is known to encode a viral IL-6. One hypothesis for the origin of MCD is that HHV-8 expresses viral IL-6, which induces vascular endothelial growth factor (VEGF), which then induces human IL-6 production by endothelial cells. Use of neutralizing antibodies against IL-6 and monoclonal antibody blocking the IL-6 receptor rather than IL-6 have demonstrated clinical efficacy, resulting in symptom resolution. All seven patients, in one study, treated with monoclonal antibodies to IL-6 receptor had resolution of their clinical symptoms, followed by improvement in their lymphadenopathy. Once therapy was stopped, however, symptoms recurred.

iii) The role of IL-6, IL-10, CRP in monitoring MCD. Are there any implications for our understanding of this disease in the context of your findings?

Reply: While CRP is usually elevated in cases of MCD and decreases following active treatment, we were unable to find any literature supporting its use for monitoring purposes. Being an acute phase reactant, CRP can be elevated in a variety of other conditions. Symptomatic patients with Castleman's Disease found to have high HHV-8 viral loads have also been noted to have high serum levels of IL-6 and IL-10. However, there is no published literature advocating for use of IL-6 or IL-10 in monitoring MCD.

3. Figure 1. For final publication I think higher resolution images would be useful and also some mention in the legend of the level of the scan slice, +/- contrast etc. For example we are asked to refer to figure 1 (on page 4) to see retroperitoneal, pelvic and inguinal lymphadenopathy?

Reply: We will defer to editorial input regarding how to maximize image clarity and contrast.

4. Figure 2. The high-resolution image is totally illegible here and needs correcting prior to publication.

Reply: Again, we request editorial input regarding image clarity. It is possible that the reviewer was unable to view this image at the level of detail that we are able to view.
Reviewer: Douglas K. Frank

1. Paper seems to adhere to case report guidelines. However, Castleman's disease is relatively uncommon and I think that the authors need to spend a bit more time discussing disease background information for the sake of readers who are unfamiliar with this important pathologic entity.

Specifically, distinction needs to be made between the plasma cell and hyaline vascular types (pathologically and prognostically). Also, the significance of unifocal vs. multifocal disease needs to be made, particularly with respect to prognosis and associated lymphoma (both Hodgkins and non-Hodgkins). Although the article is not intended to be a review, I think that these points are important enough that they should be included in the authors' discussion.

Reply: The following text has been included in the paper -- There are two pathological types of Castleman's Disease - the hyaline vascular variant and plasma cell variant. The hyaline vascular variant exhibits prominent proliferation of small hyalinized follicles with marked interfollicular vascular proliferation, while the plasma cell variant exhibits hyperplastic germinal centers, sheets of plasma cells in the interfollicular region, and proliferation of blood vessels and persistent sinuses. It is postulated that 10 - 20 percent of all cases are of the plasma cell variant, with a small percentage being of mixed histologic appearance. Multicentric Castleman's Disease (MCD) or multifocal disease, is usually the plasma cell variant, and presents as a systemic disease with generalized peripheral lymphadenopathy, hepatosplenomegaly, frequent fevers, and night sweats.

The first case of MCD, which presented as generalized lymphadenopathy with systemic manifestations of fever, night sweats, weight loss and fatigue, was reported in 1978. It typically presents in patients ages 50 to 65 years but for those who are HIV (+), it occurs at younger ages, as in the patient described in this report. HIV seropositive individuals appear to be at an increased risk for MCD, and it can often arise concurrently with Kaposi sarcoma (KS). It has been reported that among HIV (+) patients with multicentric CD who are co-infected with HHV-8, as many as 70 percent develop KS at some time in their clinical course. MCD commonly results in a fatal course due to infectious complications, multi-organ failure, and development of malignancies such as lymphoma (Hodgkins and non-Hodgkins) or Kaposi sarcoma. In contrast, localized, Castleman's Disease, also referred to as unifocal or unicentric disease (UCD), is typically an isolated benign lymphoproliferative disorder of young adults, is usually not associated with HHV-8 infection, and is generally curable with surgical resection (with or without radiotherapy).