

Case Study

# Multicentric Castleman Disease with Monoclonal Incomplete IgH Restriction: A Rare Coexistence

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Castleman disease is a rare lymphoproliferative disorder that may have a unicentric or multicentric clinical presentation. Herein we present the case of a 49-year-old female with a 3-year history of progressively worsening lymphadenopathy associated with fevers, chills and night sweats. Laboratory studies showed anemia and mildly elevated sedimentation rate. A computed tomogram scan of the chest, abdomen and pelvis showed multiple enlarged bilateral axillary, supraclavicular, subpectoral, submental, retroperitoneal, and para-aortic lymph nodes. A right axillary lymph node biopsy was performed and found to display histopathologic features compatible with the plasma cell type of Castleman disease. The patient was found to be human immunodeficiency virus (HIV)-positive, with a viral load of 104,000/mL and a CD4 cell count of 84 cells/mm<sup>3</sup>. Molecular studies on the lymph node specimen revealed an incomplete monoclonal DH-JH rearrangement in the IgH gene. The patient was initially treated with antiretroviral therapy with a combination of elvitegravir, cobicistat, emtricitabine and tenofovir that improved her fatigue and malaise. As treatment for Castleman disease, she was administered a combination of rituximab and etoposide, which led to a reduction in lymphadenopathy. To the best of the authors' knowledge, this is the first reported case of multicentric Castleman disease with monoclonal incomplete IgH gene rearrangement in an HIV-positive patient. [*J Clin Exp Hematop* 55(2) : 103-108, 2015]

**Keywords:** Castleman disease, multicentric, human immunodeficiency virus, immunotherapy

## INTRODUCTION

Castleman disease (CD) is a rare lymphoproliferative disorder with a unicentric or multicentric clinical presentation. Multicentric Castleman disease (MCD) is often associated with human herpesvirus 8 (HHV-8) and predominates in human immunodeficiency virus (HIV)-positive individuals. In the limited number of studies done to analyze the clonality status of plasma cells and B-cells in CD, only a handful of

cases have been found to be monoclonal. Herein we present a case of MCD positive for monoclonal IgH gene rearrangement in an HIV-positive individual.

## CASE REPORT

A 49-year-old African-American female presents with progressively worsening occipital and cervical lymphadenopathy for the past 3 years. The patient also reported fevers, night sweats, chills, malaise, and a non-productive cough. Laboratory studies showed anemia with a hemoglobin of 11.3 g/dL (reference range 12-16 g/dL) and mildly elevated sedimentation rate at 29 mm/hr (reference range 0-25 mm/hr). White blood cell count was low at 2,500/ $\mu$ L (reference range 4,000-12,000/ $\mu$ L) with a platelet count of 188,000/ $\mu$ L (reference range 140,000-440,000/ $\mu$ L). Total protein and albumin were 8.2 g/dL (reference range 6-8.4 g/dL) and 3.4 g/dL (reference range 3.5-5 g/dL) respectively. Ferritin was low at 18 ng/mL (reference range 8-250 ng/mL). Serum fibrinogen level was 260 mg/dL (reference range 200-400 mg/dL) and alkaline phosphatase level was 59 U/L (reference range 33-138 U/L). Other laboratory studies showed normal lactate dehydrogenase and C-reactive protein. A computed tomogram scan of the chest, abdomen and pelvis showed multiple

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Received: May 20, 2015

Revised : July 10, 2015

Accepted: July 19, 2015

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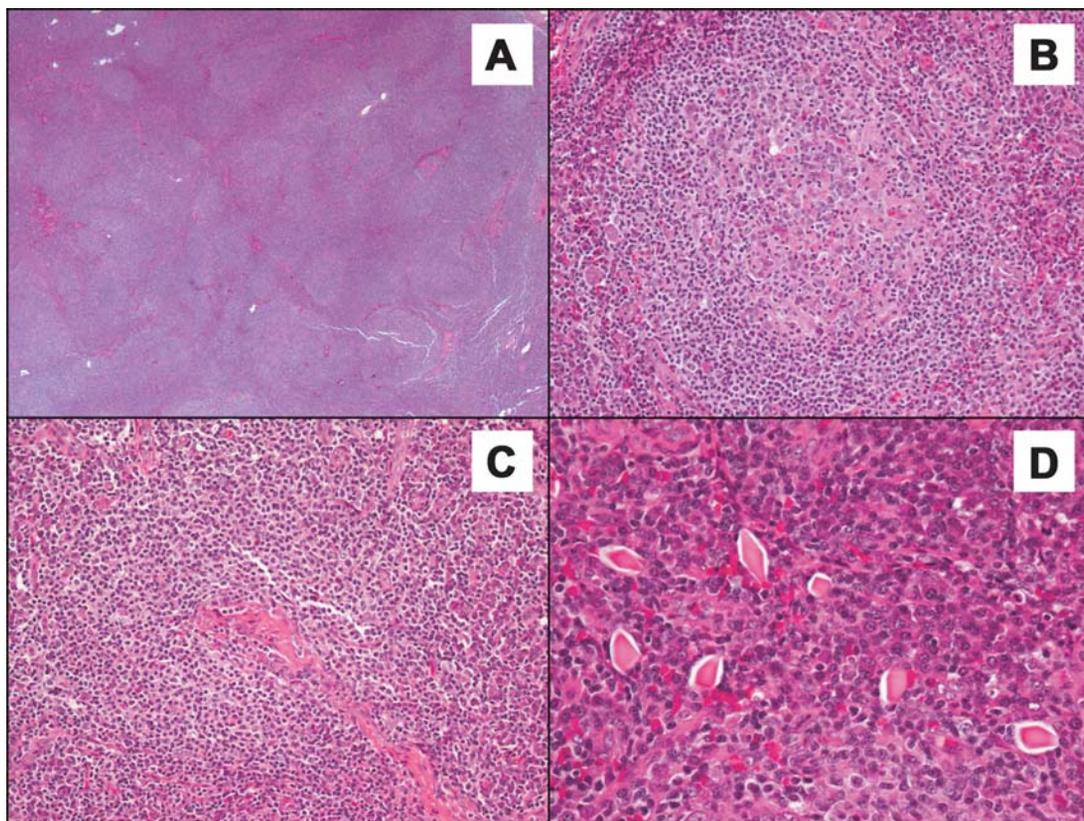
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enlarged bilateral axillary, supraclavicular, subpectoral, submental, retroperitoneal, and para-aortic lymph nodes. A right axillary lymph node biopsy was performed and histopathologic evaluation revealed findings compatible with CD, plasma cell (PC) type. The serum interleukin-6 level was subsequently tested and shown to be elevated at 8 pg/mL (reference value  $\leq 6$  pg/mL). The lymph node architecture showed scattered lymphoid follicles of variable size, with variable hyperplasia and frequent blurring of the boundary between the mantle zones and the interfollicular areas (Fig. 1A, 1B & 1C). A minor subset of follicles showed deposition of hyaline material and/or radially penetrating vessels (Fig. 1C). The interfollicular areas were occupied by large sheets of mature plasma cells and prominent vascular proliferation. A few Russell bodies and rhomboidal crystalline structures with the same tinctorial quality as Russell bodies were observed (Fig. 1D). The lymph node sinuses were patent.

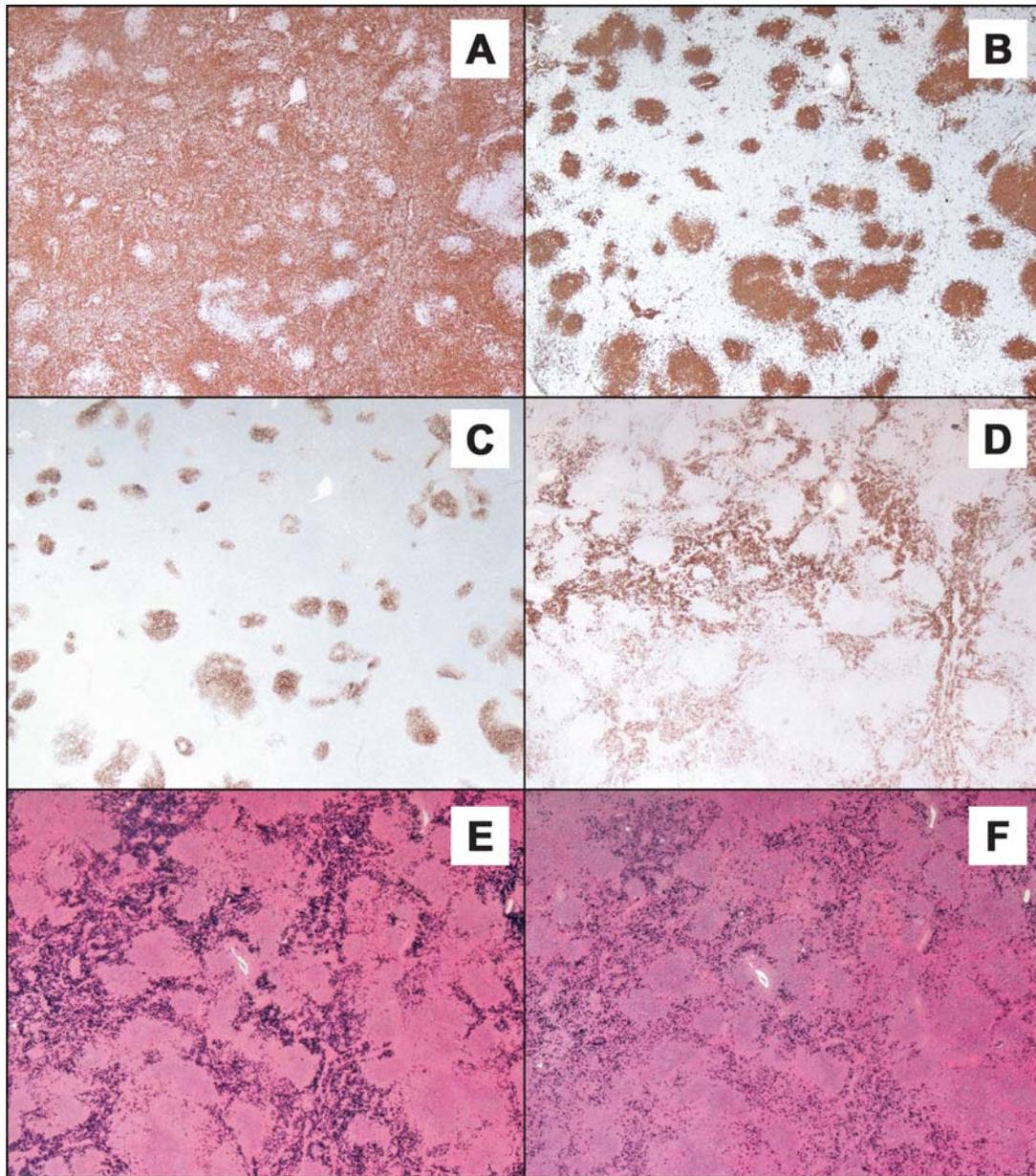
By immunohistochemistry for CD20, PAX5 and CD3, the lymphoid follicles were shown to be predominantly composed of B-cells and a minor proportion of T-cells (Fig. 2B). The germinal centers were positive for BCL6 and CD10, and

negative for BCL2. Immunostains for CD21 (Fig. 2C) and CD23 highlighted the follicular dendritic cell meshworks, which were small and round to moderately enlarged and irregularly shaped, but without significant disruption. Abundant T-cells were highlighted in the interfollicular areas with immunohistochemistry for CD3 (Fig. 2A), CD2, CD4, CD5, CD7, CD8 and CD43. No immunophenotypic abnormalities were observed on the T-cells. However, similarly to what was observed by flow cytometry, the CD8-positive T-cells were shown to predominate over the CD4-positive T-cells. The plasma cells were highlighted with an immunostain for CD138 (Fig. 2D), and chromogenic *in situ* hybridization for  $\kappa/\lambda$  revealed a polyclonal immunoglobulin light chain pattern (Fig. 2E & 2F). Epstein-Barr virus-encoded small RNA was positive on only rare scattered small cells, whereas immunohistochemistry for HHV-8 was negative. Occasional CD30-positive immunoblasts were identified. However, an immunostain for CD15 was negative on the latter and highlighted occasional neutrophils.

A polyclonal pattern of surface immunoglobulin light chains and an inverted CD4: CD8 ratio were identified on the



**Fig. 1.** Microscopic findings. (1A) Follicular hyperplasia (H&E,  $\times 2$ ) with (1B) hyaline material deposition in the germinal center (H&E,  $\times 20$ ), and (1C) occasional blurring of the boundary between the mantle zones and the interfollicular areas and rare hyalinized radially penetrating vessels (H&E,  $\times 20$ ). (1D) The interfollicular areas contained abundant plasma cells with occasional rhomboidal crystalline structures (H&E,  $\times 40$ ).

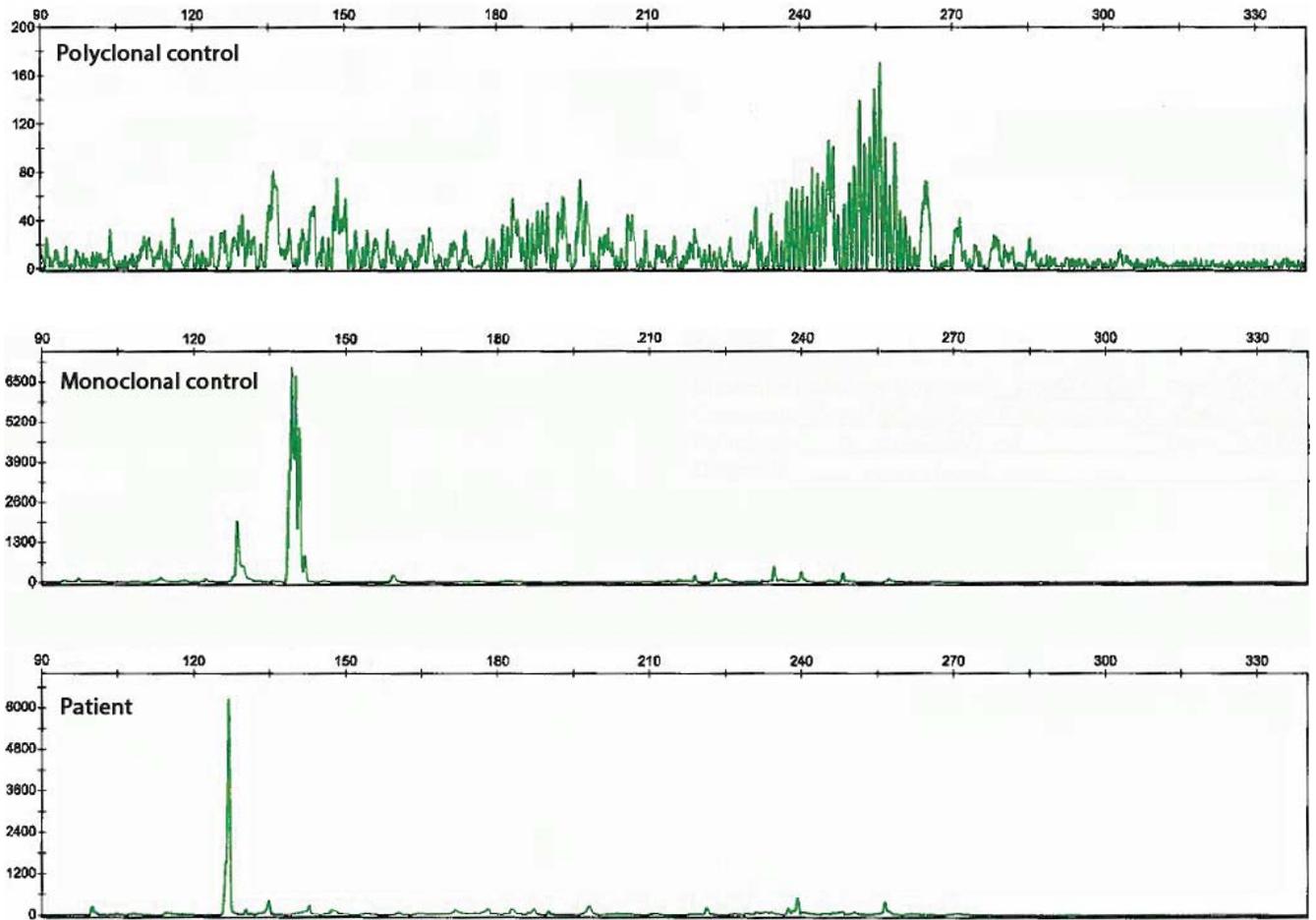


**Fig. 2.** Immunohistochemical evaluation. (2A) The T-cells were the predominant type of lymphocytes in the interfollicular areas (CD3,  $\times 2$ ). (2B) The follicles contained predominantly B-cells (CD20,  $\times 2$ ). (2C) The follicular dendritic cell meshworks were small and round to moderately enlarged and irregular (CD21,  $\times 2$ ). (2D) An abundant number of plasma cells were observed in the interfollicular areas (CD138,  $\times 2$ ). (2E & 2F) The plasma cells showed a polyclonal pattern by  $\kappa$  (2E) and  $\lambda$  (2F) immunoglobulin light chain expression (*in situ* hybridization,  $\times 2$ ).

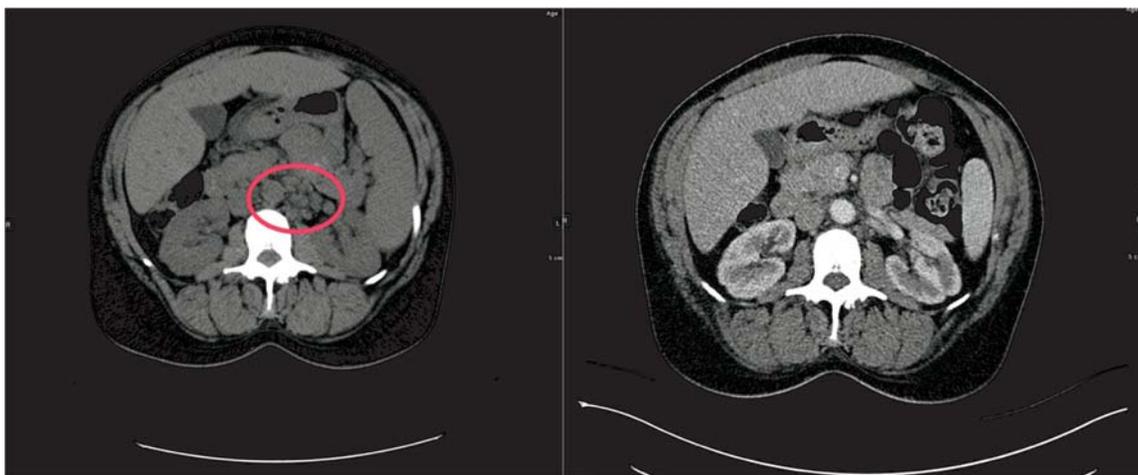
B- and T-cells, respectively, by flow cytometric evaluation. However, *IgH* gene rearrangement studies by multiplexed polymerase chain reaction were positive for a monoclonal incomplete *DH-JH* rearrangement (Fig. 3), with polyclonal rearrangements using primers for frameworks I, II and III.

A screening HIV-1/HIV-2 test was performed and found to be positive, with the confirmatory Western blot resulting

significantly positive as well. At this time, her HIV viral load was found to be 104,000/mL with a CD4 cell count of 84 cells/mm<sup>3</sup>. A bone marrow biopsy was performed which did not show any involvement by a monoclonal B-cell or plasma cell process. The patient was initially treated with antiretroviral therapy with a combination of elvitegravir, cobicistat, emtricitabine and tenofovir that improved her fatigue and



**Fig. 3.** Evaluation for *IgH* gene rearrangements by polymerase chain reaction and capillary electrophoresis done on the lymph node biopsy revealed a monoclonal pattern in the reaction with DH-JH primers, with adequate polyclonal and monoclonal controls (X axis: size of the amplified DNA fragments in base pairs; Y axis: fluorescence intensity units)



**Fig. 4.** Computed tomogram scans of the abdomen before (*left*) and after (*right*) therapy. Note the retroperitoneal and para-aortic lymph nodes in the image on the left (encircled by red line) that are not evident in the figure on the right.

malaise. As treatment for CD, the patient was administered a combination of rituximab and etoposide and showed clinical improvement. Her CD4 count 4 months after therapy was 200/mm<sup>3</sup> with an undetectable HIV viral load. The lymph nodes decreased in size and chemotherapy was discontinued (Fig. 4).

## DISCUSSION

CD (also known as angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder first discovered in 1956<sup>1</sup> that may clinically present in a unicentric or multicentric manner. At the time of diagnosis, most patients with unicentric CD are asymptomatic and are often treated with surgical resection. MCD affects more than one lymph node area and tends to be aggressive. MCD is commonly associated with systemic symptoms including fever, chills, and night sweats, along with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormality (POEMS) syndrome.<sup>2,3</sup> A new variant of MCD has recently been identified in Japan known as Castleman-Kojima disease, which includes a constellation of signs including thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly (also known as TAFRO syndrome).<sup>4,5</sup> MCD is also often associated with HHV-8 infections and predominates in HIV-positive individuals.<sup>6</sup> Overexpression and high serum level of interleukin-6 is seen in almost all cases of MCD but the underlying pathophysiology of the process is unknown.<sup>7</sup> Recently, a new subclassification system for MCD has been proposed - HHV-8-associated MCD and HHV-8-negative MCD or idiopathic MCD (iMCD). It has been hypothesized that the pathophysiology of iMCD involves an intense cytokine release mediated by one of three processes- systemic inflammatory response via autoantibodies or inflammatory gene mutations, paraneoplastic syndrome mechanism via ectopic cytokine secretion, and/or a non-HHV-8 virus.<sup>8</sup> CD is not a malignant condition; however, MCD has been associated with an increased risk of developing certain malignancies, most notably large B-cell lymphomas and follicular dendritic cell sarcomas. Kaposi sarcoma is also commonly diagnosed concurrently or sequentially with MCD because the 2 entities share a common viral pathogenesis.<sup>3</sup>

Imaging studies like combined positron emission tomography and computed tomogram show multiple areas of lymphadenopathy. Laboratory studies may show anemia, thrombocytosis, hypoalbuminemia, polyclonal hypergammaglobulinemia and elevated inflammatory markers. Diagnosis is confirmed by excisional biopsy of a lymph node.

Based on the histopathologic findings, CD may be classified into the hyaline-vascular type, PC type, or a mixed type. The hyaline-vascular type displays lymphoid follicular hyperplasia with poorly formed germinal centers that are infiltrated

by hyaline material and radially penetrating vessels. Germinal centers are concentrically arranged ("onion peel") by a mantle zone of small lymphocytes.<sup>6</sup> The PC type displays hyperplastic follicles of varying sizes with mildly increased interfollicular vascularity and focally patent medullary sinuses and abundant interfollicular plasma cells.<sup>6</sup> Unicentric CD is most often associated with the hyaline-vascular type (> 80% of cases), whereas MCD is most often associated with the plasma cell or mixed type.<sup>9</sup>

In the limited number of studies performed to analyze the clonality of B-cells and plasma cells in CD, very few cases have been found to be monoclonal. Most of these studies were of the PC type.<sup>10-15</sup> In a 1995 study by Soulier, *et al.* clonal *IgH* rearrangements were detected in 4 out of 34 CD patients using polymerase chain reaction and Southern blot analysis, and all of these cases were diagnosed in HIV-negative patients. Two of the latter cases were associated with non-Hodgkin B-cell lymphoma, one case with Hodgkin's lymphoma, and one case without malignancy. This study concluded that in the large majority of CD cases, the lymphocytes and plasma cells are polyclonal.<sup>10</sup> A study performed by Hall, *et al.* found that 2 out of 5 CD cases of the PC type were polyclonal, and 2 cases were  $\lambda$  light chain restricted.<sup>11</sup> To our knowledge, ours is the first case of Castleman disease, PC type, found to have a monoclonal incomplete *IgH* gene rearrangement, in the setting of HIV infection.

All HIV-positive patients should be treated with antiretroviral therapy (ART) following diagnosis.<sup>16</sup> Although CD4 counts and the use of ART do not influence the incidence of MCD, ART is important in the prevention of other consequential diseases of HIV infection. Additional treatment of MCD depends on the presence of organ failure and performance status of the patient. Patients without organ failure and HIV/HHV-8 positivity can be treated by immunotherapy alone, using siltuximab, tocilizumab or rituximab. Rituximab, an anti-CD20 monoclonal antibody, has been shown to be effective as monotherapy in MCD. In a prospective trial that enrolled 24 patients with chemo-dependent HIV-associated MCD, 17 patients sustained a 1-year complete remission following rituximab therapy (71% event free survival).<sup>17</sup> In a more recent study, out of 21 untreated HIV-associated MCD patients, 20 achieved remission of symptoms (95%), and 14 achieved a radiologic response (67%).<sup>18</sup> In the presence of organ failure and poor performance status secondary to disease itself, combining immunotherapy with chemotherapy in the form of etoposide is recommended. In addition, antiviral therapy in the form of ganciclovir is indicated for HHV-8 positivity.<sup>19</sup>

The prognosis in MCD is variable, ranging from an indolent clinical course to a rapidly progressive disease culminating in death if untreated. The identification of a monoclonal *IgH* gene rearrangement or a monoclonal light chain pattern may indicate a concurrent neoplastic process. It is therefore,

imperative to have a high degree of suspicion for appropriate management of such patients. This case calls for more research to study the association between monoclonal gene rearrangements and neoplastic process in HIV positive individuals with MCD.

### ACKNOWLEDGEMENTS

This case was presented previously at the 38<sup>th</sup> Annual Meeting of Society of General Internal Medicine, Toronto, ON, Canada. (April 22-25, 2015)

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