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Multicentric Castleman's Disease

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Abstract

Castleman's disease (CD) is a lymphoproliferative disorder, manifesting clinically as unicentric or multicentric disease and pathologically as hyaline vascular, plasma cell or mixed variants.

Multicentric Castleman's disease (MCD) is the most common form of CD encountered at Chris Hani Baragwanath Academic Hospital (CHBAH). From being a rare disease, MCD has increased in the last five years, primarily as a result of the association of human immunodeficiency virus (HIV), being highly prevalent in our patient population. The dominant clinical manifestations of the disease include constitutional symptoms, fever, anaemia, lymphadenopathy and hepatosplenomegaly.

We present a series of 35 adult patients with MCD, who were seen over a 25-year period at CHBAH, and highlight the similarities and differences compared with other published series.

Based on our local experience, we observed that the prognosis of HIV-associated MCD has improved with optimization and control of HIV replication (use of combination antiretroviral therapy), prophylaxis and treatment of opportunistic infections, as well as etoposide and rituximab based chemotherapy.

In the setting of HIV, MCD should no longer be regarded as a rare disease with a fatal outcome.

Keywords: Multicentric Castleman's disease, Human immunodeficiency virus infection, Human herpes virus-8, South Africa, immunosuppression

1. Introduction

Castleman's disease (CD), also known as angiofollicular or giant lymph node hyperplasia, is a rare B-cell lymphoproliferative disorder, first described by Benjamin Castleman in a series

of patients in 1956 [1]. It is a heterogeneous disorder, manifesting clinically as a unicentric (solitary; localised) or multicentric disease and pathologically as hyaline vascular, plasma cell or mixed variants [2–6].

The multicentric variety is aetiologically linked to human herpes virus-8 (HHV-8) [7]. It is strongly associated with immunosuppression and is now being encountered with increasing frequency in patients with HIV (human immunodeficiency virus) infection [8].

This review will focus on CD, with particular reference to Multicentric Castleman's disease (MCD), and it will include a description of the disease as seen at Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa over a 25-year period (1990 to 2014). The renewed interest in MCD stems from its association with HIV, particularly in areas such as sub-Saharan Africa where HIV has reached pandemic proportions, with South Africa being home to approximately 6.4 million people living with HIV/AIDS (acquired immunodeficiency syndrome) [9].

2. Epidemiology

Castleman's disease (CD), from being rare, is now more commonly encountered. In the last three decades since the discovery of HIV, the incidence of MCD has progressively increased over time. The median age at presentation of MCD is 40 (21–67) years, with a male predominance of 90%, based on a systematic review of published cases in the literature up to 2007 [10]. A younger age at presentation is noted in HIV-seropositive individuals with MCD compared to HIV-seronegative MCD [11,12].

3. Pathology

Two distinct variants have been described in CD: the hyaline vascular and plasma cell variant. Where features of both these varieties occur, it is referred to as the mixed type or variant [2,5].

The hyaline vascular variant is characterised by follicles which show prominent vascular proliferation and hyalinization of the central portion. There is concentric layering of the lymphocytes at the periphery of the follicles (mantle zone) – referred to as 'target follicles' and imparting a classical 'onion-skin' appearance (see Figure 1). Another feature of this variety is the presence of prominent sclerotic blood vessels which penetrate radially into the germinal centres and transfix it, resulting in a 'lollypop' follicle appearance (see Figure 2). The interfollicular stroma is also prominent, with numerous hyperplastic vessels, plasma cells, eosinophils, and immunoblasts. The hyaline vascular variety is most commonly associated with UCD [2,6].

The plasma cell variant is characterised by a diffuse interfollicular plasma cell proliferation. Intermingled with the plasma cells are immunoblasts, lymphocytes, and histiocytes. Features of the hyaline vascular variant are typically inconspicuous or absent. This variety is most commonly associated with MCD [2,5,6]. The histopathological characteristic of MCD is the

presence of large, abnormal plasmablasts located within the mantle zones of involved lymph nodes [13,14].

The mixed variant or type of CD shares morphological features between the hyaline vascular variant and plasma cell variant. It is classically encountered in MCD and is typically seen in HIV-associated MCD [4,5].

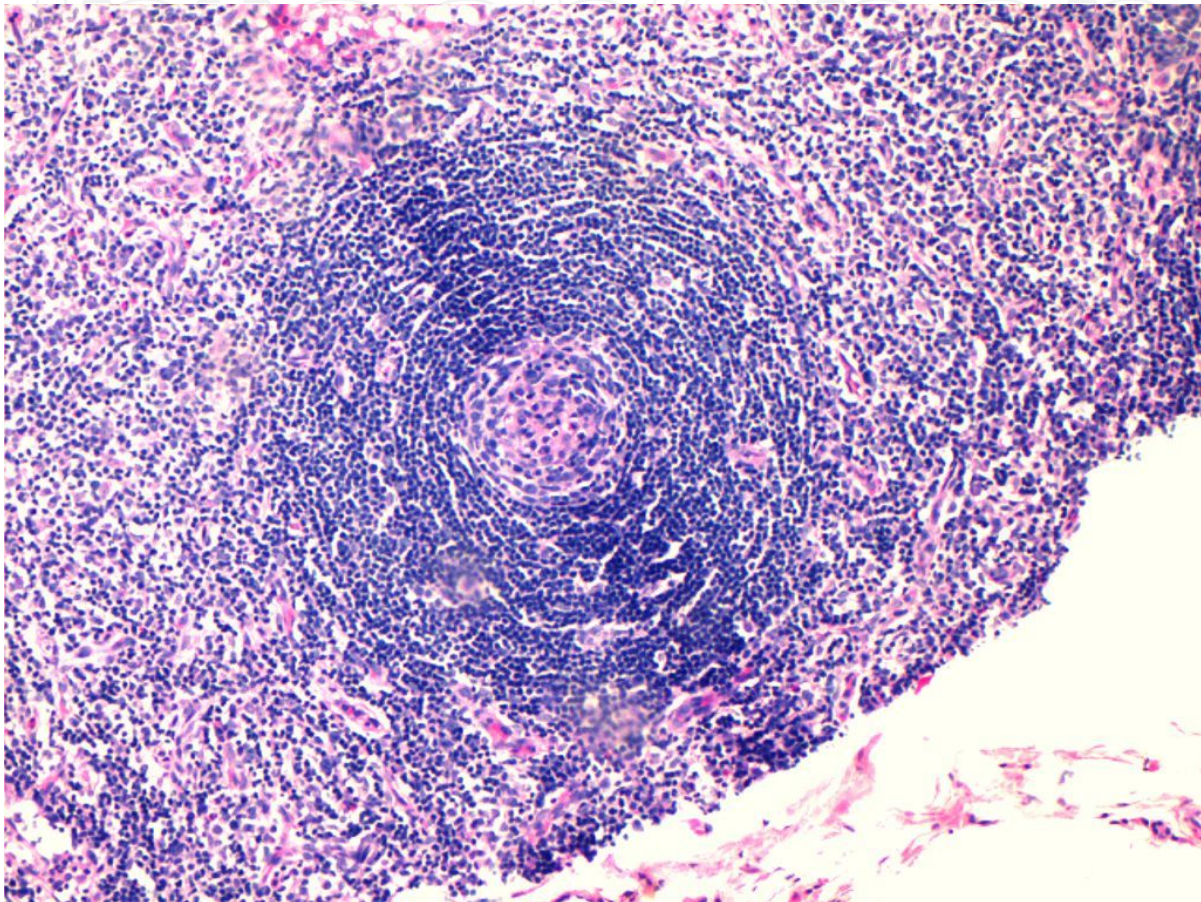


Figure 1. Haematoxylin and Eosin stained section of lymph node (100× magnification) showing the concentric layering of lymphocytes in the mantle zone of the lymphoid follicle – 'onion-ring' appearance

The pathogenesis of CD involves an interplay between viruses, namely HHV-8 and HIV, cytokines such as IL-6 (interleukin-6) and IL-10, and growth factors such as VEGF (vascular endothelial growth factor) [15,16].

Multicentric Castleman's disease (MCD) is aetiologically linked to HHV-8 [7]. Human Herpesvirus 8 is a gamma herpes virus and the causative organism in KS [17]. Soulier et al, 1995 [7], showed that HHV-8 sequences were detected in lymph nodes in 14/14 (100%) cases of HIV-associated MCD, compared to 7/17 (41%) cases with HIV-negative MCD. Other studies have demonstrated an almost universal association of HHV-8 with HIV-associated MCD [11,18].

Interleukin-6 levels are increased in CD. A raised CRP, a surrogate marker for IL-6, anaemia, hypergammaglobulinemia, plasmacytosis, splenomegaly, and lymphadenopathy are all

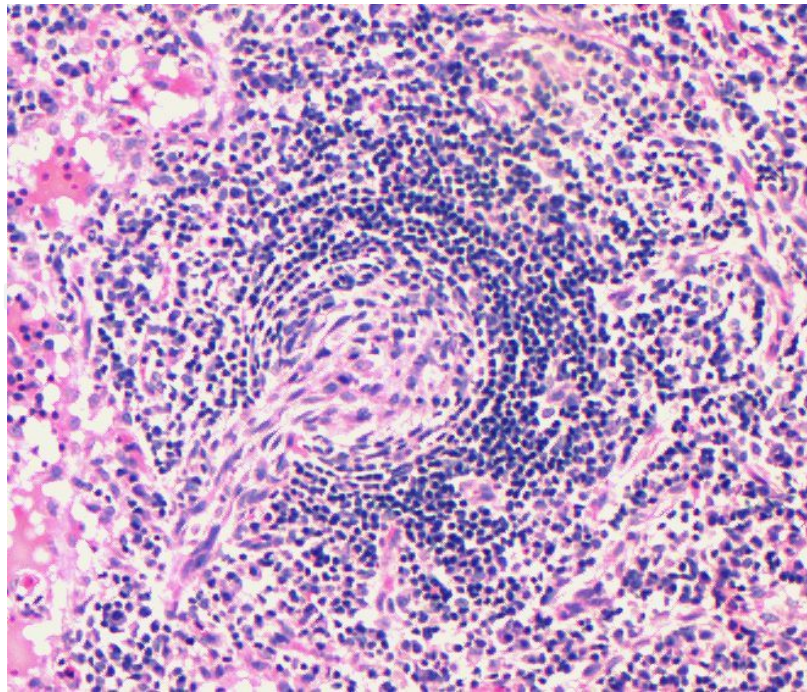


Figure 2. Haematoxylin and Eosin stained section of lymph node (200× magnification) showing the radially penetrating blood vessels transfixing the germinal centre – ‘lollipop’ appearance

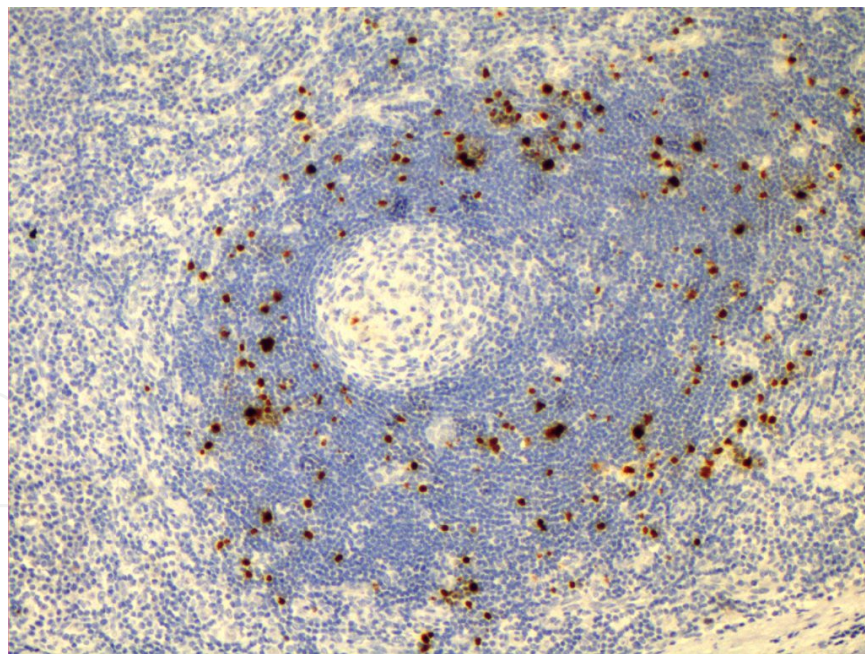


Figure 3. Human Herpesvirus-8 immunohistochemical stain showing mantle zone concentricity and distinct HHV-8 positive nuclear staining of lymphoid cells in the mantle zone (100× magnification)

associated with elevated levels of IL-6 [15,16]. Increased VEGF expression is also noted in CD and is likely to be responsible for the increased angiogenesis component of the disease [19].

The diagnosis of CD is based on a combination of compatible clinical features together with distinct histopathological features characteristic of the disease. Importantly, other benign and malignant disorders with overlapping clinical and histological features should be excluded. Recently, diagnostic criteria have been proposed for patients with MCD, particularly in association with HIV [20,21]. These include the French ANRS (Agence Nationale de Recherchesurle SIDA) criteria and the National Cancer Institute (NCI) criteria [20,21]. The diagnostic criteria devised by these two groups complement the histopathological findings and are particularly useful in those with idiopathic MCD. However, in HIV and HHV-8 associated MCD, the histopathological diagnosis has been made much easier due to the presence of DNA tests to detect HHV-8 in the blood and HHV-8 immunostaining of the tissue. Thus, Bower et al, 2014 [22], suggest that in these individuals a triad of 'B' symptoms, elevated plasma HHV-8 levels and histopathological findings should suffice in making the diagnosis of MCD.

4. Clinical features and management

Two distinct clinical variants of Castleman's disease are recognised: MCD and UCD. Unicentric Castleman's disease (UCD) refers to localized disease, presenting at a single site, such as the chest (most commonly the mediastinum), neck, abdomen, or other sites. Typically patients are asymptomatic and come to clinical attention when an enlarged lymph node is noted on physical examination or at imaging studies [1,2, 23].

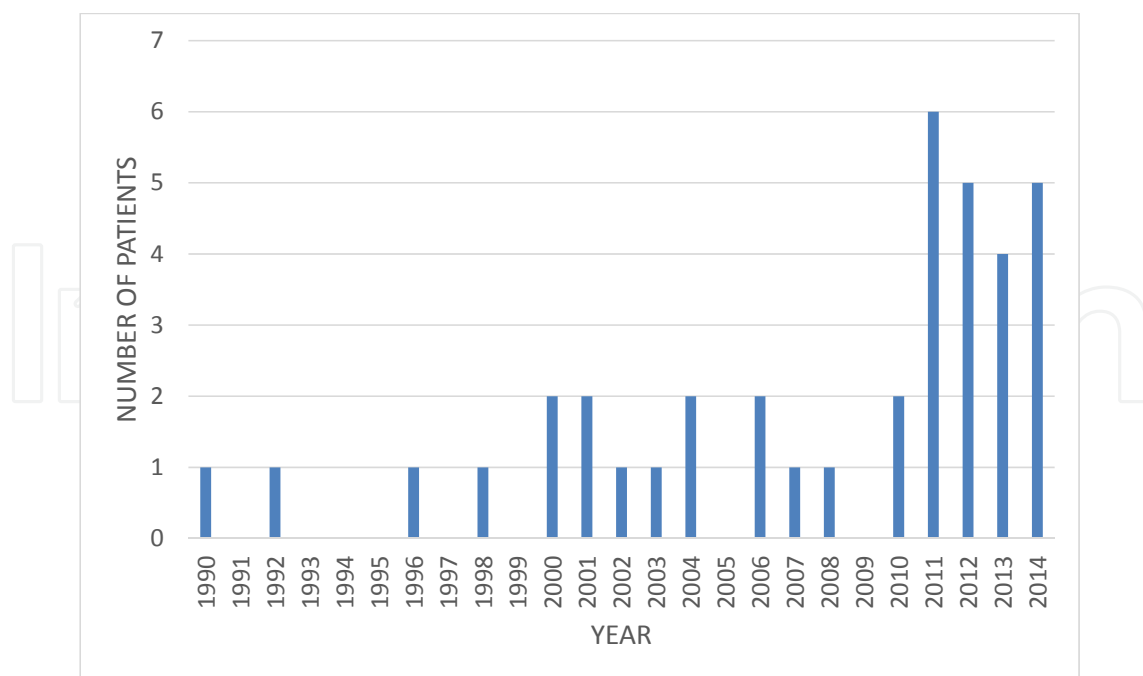


Figure 4. Bar graph which depicts the number of patients seen with Castleman's disease at Chris Hani Baragwanath Academic Hospital from 1990 to 2014

Multicentric Castleman's disease (MCD) refers to a systemic disease with constitutional symptoms (fever, night sweats, weight loss), generalized lymphadenopathy and hepatosplenomegaly. It is usually associated pathologically with the plasma cell or mixed variant. Unlike UCD, MCD is strongly associated with HIV, immunosuppression and HHV-8 [11,23,24]. Laboratory studies usually reveal the presence of anaemia, a raised ESR, elevated CRP, thrombocytopenia, hypoalbuminemia and polyclonal hypergammaglobulinemia [3, 4,11,15].

At Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, Johannesburg, a total of 38 patients were seen with CD over a 25-year period. Three of the patients (7.9%) were diagnosed with UCD and 35 (92.1%) with MCD. Of all the patients with CD, 22/38 (57.9%) were seen in the last 5 years compared to 42.1% in the first 20 years. The increase in the number of patients with CD in the last 5 years is primarily as the result of the ongoing HIV pandemic in South Africa and the contribution from HIV. Ninety five percent (21/22) of the patients seen in the last five years and 100% of those with MCD were HIV seropositive.

Age	Gender	Site of lymph-adenopathy	Localised or systemic disease	Anaemia (A) or thrombocytopenia (T)	Treatment	HIV	Response	Outcome	
1	18	M	Mediastinum	Localised	No A or T	Surgical resection	Negative	Complete response	Alive
2	64	F	Inguino-femoral	Localised	No A or T	Surgical resection	Negative	Complete response	Alive
3	59	F	Axilla	Localised	No A or T	Surgical resection	Negative	Complete response	Alive

Table 1. Clinical characteristics of Unicentric Castleman's disease

With regard to UCD, there were 2 females and 1 male, with a female to male ratio of 2:1. The mean age at presentation was 47 years. All the patients were diagnosed post biopsy/resection of localised nodal disease. None of the patients were HIV seropositive. No further treatment was required in these patients after the initial surgical resection. All the patients are alive and are well on observation (see Table 1).

A summary of the clinical characteristics of the patients with MCD is depicted in Table 2.

Characteristic	Result/Finding
Number of patients	35
Median age; Mean age; Range	Median = 36 years; Mean = 37years; Range = 18–64 years
Gender; ratio	Males = 19, Females = 16; M:F ratio – 1.2:1
Multicentric disease	35/35 = 100%

Characteristic	Result/Finding
Fever	16/35 = 46%
'B' symptoms	23/35 = 66%
Lymphadenopathy	35/35 = 100%
Hepatomegaly	18/35 = 51%
Splenomegaly	20/35 = 57%
Anaemia (Hb<12 g/dl)	32/35 = 91%; Mean Hb = 7.8g/dl; Range = 2.8 – 13.5 g/dl
Thrombocytopenia (Platelets <100 × 10 ⁹ /l)	9/35 = 26%; Mean platelet count = 211 × 10 ⁹ /l; Range = 22 – 602 × 10 ⁹ /l
HIV status (positive or negative)	30/35 = 86% positive; 5/35 = 14% negative
CD4 count × 10 ⁶ /l – mean and range; <350 × 10 ⁶ /l; <200 × 10 ⁶ /l	Mean CD4 count = 257 × 10 ⁶ /l; Range = 12 – 829 × 10 ⁶ /l; <350 × 10 ⁶ /l = 79%; <200 × 10 ⁶ /l = 46%
Morphology: i) Hyaline vascular (HV); ii) Plasma cell (PC); Mixed (M)	HV only = 1/35 (3%); PC only = 1/35 (3%); Mixed = 34/35 (94%)
HHV-8 immunostain on biopsy	Early part of the current series – not done. In the patients from 2010–2014, performed in 19/21 patients with MCD. The result was positive in 19/19 patients = 100%
Associations	Tuberculosis 15/35 = 43%; Kaposi's sarcoma 8/35 = 23%; Autoimmune haemolytic anaemia 6/35 = 17%; Pure red cell aplasia 2/35 = 6% and 1/35 = 3% with each of the following – primary effusion lymphoma, microlymphoma, adenocarcinoma, bullous pemphigoid, immune thrombocytopenia, hepatitis B, hepatitis C, hypoglycaemia and nephrotic syndrome
Response to treatment (evaluable patients – CR = complete response; PR = partial response)	17/35 evaluable patients; CR 9/17 = 53%; PR = 47%
Outcome: Alive; Died (mean survival, range); Lost to follow up (LTFU)	Alive 14/35 = 40%; Died = 34% (mean survival = 13 months, range 0.25 – 64 months); LTFU = 26%

Table 2. Summary of the clinical characteristics of Multicentric Castleman's disease

5. Associations

Castleman's disease may be seen in association with other diseases including POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein/gammopathy, and skin changes/sclerotic bone lesions), paraneoplastic pemphigus, Kaposi's sarcoma, Hodgkin lymphoma, Non Hodgkin lymphoma (in particular, primary effusion lymphoma (PEL), and diffuse large B-cell lymphoma -DLBCL) [2,11, 22, 25,26,27].

6. Management

Treatment modalities for CD include supportive care and specific modalities of treatment.

In the unicentric form of the disease, surgical resection of the localised site of the disease is usually curative. However, follow up is recommended as patients may rarely relapse or develop complications (such as an increased risk of lymphoma development) [23,26,28].

For MCD, a variety of specific treatment options are available, in addition to supportive care (such as analgesia, allopurinol, transfusion of blood and blood products where indicated). Specific treatment modalities include antiviral (anti-herpesvirus) and antiretroviral drugs where a viral association is documented, corticosteroids, monoclonal antibodies, immunomodulatory agents (such as thalidomide), splenectomy, and radiotherapy [29].

Chemotherapy has evolved from single-agent (e.g. chlorambucil) to combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone – CHOP), to the addition of rituximab and etoposide [3,11,20,29,30,31]. Bower, 2010 [29], in his excellent review on 'How I treat HIV-associated multicentric Castleman disease', uses a combination of weekly IVI rituximab (375 mg/m²) with IVI etoposide (100 mg/m²) for 4 weeks for aggressive HIV-associated MCD, with an overall 2 year survival of 85% and rituximab monotherapy (375 mg/m² weekly for 4 weeks) for low-risk HIV-associated MCD, with an overall 2 year survival of 100% [29].

For HIV-negative, HHV-8 negative MCD, other therapeutic options have been explored. This includes monoclonal antibodies directed against IL-6 (siltuximab) or the IL-6 receptor (tocilizumab) [27].

Multicentric Castleman's disease (MCD) is increasingly being recognised as a relapsing and remitting disease and in the HIV-seropositive setting is not necessarily suppressed or diminished by combination antiretroviral therapy [29]. As such, the role of both rituximab and antiherpesvirus agents such as valganciclovir have been explored as maintenance therapies [20,29,32,33]. However, the role of maintenance therapy in this disease remains controversial and requires further evaluation.

7. Discussion

Human immunodeficiency virus infection (HIV) is endemic in South Africa and is associated with an increased risk of infection and malignancy, primarily as a consequence of immunodeficiency [9]. The major impact of HIV on the haematological malignancies in South Africa has been in regards to an increased prevalence of Non-Hodgkin lymphoma and, more recently, Hodgkin lymphoma [34,35].

In South Africa, CD is rare. However, there has been a noticeable increase in MCD in the last five years, with more than doubling of the number of patients in the last five years, compared

to the previous twenty years (see Figure 4). This is attributable to the ongoing burden of HIV, as the majority of patients in this series with MCD are HIV seropositive (86%).

There were 35 adult patients diagnosed with MCD over a 25-year period at CHBAH, a large, tertiary, public sector, University of the Witwatersrand linked hospital, located in Soweto, Johannesburg. The median age at presentation was 36 years (18–64 years), with a male to female ratio of 1.2:1. The age is similar to that described in the literature. However, in our series, there is no marked male predominance, as the major risk factor in our patients for acquisition of HIV is heterosexual contact as compared to intravenous drug use or homosexuality.

The clinical presentation of MCD is similar to that described in the literature (see Table 2). Fever, 'B' symptoms, lymphadenopathy, hepatosplenomegaly, and anaemia are commonly encountered. Pathologically, the mixed variant is seen in 94% of the patients. The mean CD4 count in the HIV seropositive patients (86%) was $257 \times 10^6/l$, with 46% of the patients having a CD4 count of $< 200 \times 10^6/l$. Fifty three percent of the patients had newly diagnosed HIV (at the time of the diagnosis of MCD) and 47% were known to be seropositive (86% of the positive patients were on combination antiretroviral therapy). Concomitant Kaposi's sarcoma was diagnosed in 23% of patients. The HHV-8 immunostain performed on 19/21 patients with MCD in the last five years was positive in 100% of the patients (see Figure 3). Other associations are detailed in Table 2, most of these are related to coexistent HIV or HHV-8. Of note is the high prevalence of concomitant tuberculosis (43%).

A variety of treatments were used over the past twenty years, ranging from symptomatic/supportive treatment to corticosteroids, single agent chemotherapy, combination chemotherapy (such as CHOP and more recently the addition of etoposide to CHOP → CHOEP), rituximab together with CHOP or CHOEP, radiotherapy, and splenectomy. Of the evaluable patients, 53% achieved a complete response to treatment and 47% manifested a partial response to treatment. As our patients have more aggressive and advanced disease, the etoposide and rituximab combinations are now being favoured. All the HIV seropositive patients receive concomitant combination antiretroviral therapy.

Long term follow up is necessary to exclude relapse and complications of the disease, such as the development of large cell lymphoma, which has a 15-fold increased incidence in patients with HIV-associated MCD [36].

8. Conclusion

Multicentric Castleman's disease is the most common form of CD encountered in our patients at CHBAH. From being a rare disease, MCD has increased over the past few years, primarily as a result of the association of HIV, being highly seroprevalent in our patient population. The dominant clinical manifestation of MCD is lymphadenopathy. Therefore, the cause of significant lymphadenopathy should always be defined, particularly in the setting of HIV. Most of the patients were initially suspected of having a lymphoma, while others with HIV and Kaposi's sarcoma or autoimmune haemolytic anaemia had a lymph node biopsy to define the

possible cause of the lymphadenopathy in association with the KS or AIHA. The prognosis of HIV-associated MCD has improved with optimization and control of HIV replication (use of combination antiretroviral therapy), prophylaxis, and treatment of opportunistic infections, as well as etoposide and rituximab based chemotherapy. In the setting of HIV, MCD should no longer be regarded as a rare disease with a fatal outcome.

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