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CASE REPORT

Multicentric Castleman Disease a Diagnostic Dilemma: A Case Series of Three Patients Seen at a Tertiary Health Facility in Zambia

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ABSTRACT

Background: Castleman disease (CD) is a heterogeneous group of lymphoproliferative disorders of uncertain cause presenting with lymphadenopathy. There are three generally described immunological disorders of CD that occur in individuals of all ages and share a similar microscopic lymph node appearance but different immunohistochemical profile. Oftentimes, diagnosis can be challenging where histology is not done, with most patients being presumptively treated as tuberculous (TB) adenitis.

Method & Results: We present three case reports of CD, one is of an Human Immunodeficiency Virus (HIV) naive patient, the other two are in HIV positive patients. All three patients presented with fever, recurrent anemia and generalized lymphadenopathy. Whole body Computed Tomography (CT) scans as well as excision biopsies (for histopathology and immunohistochemical staining for Human Herpes Virus-8 (HHV-8) were done on all three patients.

Case 1: Idiopathic Multicentric Castleman Disease in a 20 year old male patient who also developed TAFRO syndrome (Thrombocytopenia, Ascites, myeloFibrosis, Renal dysfunction and Organomegaly) in the course of the illness.

Case 2 & 3: HHV-8 associated Multicentric Castleman Disease in HIV positive 42 year and 27 year old female patients respectively. The 42 year old received chemotherapy for six months, and had symptomatic relief and remission, while the 27 year old was yet to commence chemotherapy.

Discussion: Most cases of CD go undiagnosed or mostly misdiagnosed for other common causes of lymphadenopathy in Zambia. These are the first case reports in our hospital, with notable backgrounds of physicians having suggested TB treatment from the referring facilities.

Conclusion: Both HHV-8 and none-HHV-8 associated CD may be very common in our population, and there is need for prompt biopsy, reporting and treatment of all patients presenting with lymphadenopathy in our hospitals.

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INTRODUCTION

Castleman Disease (CD) describes a group of three immunologic disorders that occur in individuals of all ages and share a similar microscopic lymph node appearance, with signs and symptoms related to the release of cytokines, particularly interleukin 6.[1] These entities were first described by Dr. Benjamin Castleman who first described the constellation of lymph node features observed in CD ("CD-like features") in the 1950s.[2] Approximately 6600-7700 patients are estimated to be diagnosed with CD every year in the United States.[3] Currently epidemiologic data on this heterogenous group of diseases does not exist in Zambia.

The 3 subtypes of CD that are often described are:

(i) UnicentricCD (UCD),
(ii) Human Herpes Virus-8 (HHV-8)–associated multicentricCastleman disease (HHV-8-associated MCD) and
(iii) HHV-8–negative/idiopathic multicentricCastleman disease (iMCD).

Clinically CD demonstrates significant overlap with Tuberculosis,[4]disseminated Kaposi Sarcoma[5] and lymphomas.[6] To further murken up the differential diagnosis CD can coexist with Tuberculosis, Kaposi Sarcoma and lymphomas[4–6], all three diseases being highly associated with HIV. Given that MCD appears to be increasing in the highly active antiretroviral therapy (HAART) era,[7] it seems reasonable to suggest that the diagnosis of CD be considered in our setting as we are an HIV endemic country ranked 8th in the world[8,9] in which the target of placing 90% of people living with HIV on combined anti-retroviral therapy has been attained.[10] There is a further unmet need for histopathology services across the country if such cases are not to be missed in all patient groups.

Case 1: iMCD

We report a case of iMCD/TAFRO in an HIV negative 20 year old black male who presented with generalized lymphadenopathy, fever, recurrent anemia, thrombocytopenia and acute renal insufficiency. He was being treated as sickle cell disease since the age of 16 years (based on a positive sickling test result, later it was discovered hypergammaglobulinaemia can cause a false positive sickling test result). C-Reactive Protein (CRP)> 300 mg/l (0-10) Urinalysis- Protein 30mg/dl(in the setting of Anasarca in a young adult this may be misdiagnosed as Nephrotic syndrome if other investigations are not carried out) , pH 6.0, Leucocytes 1+, Glucose -0, Microscopy –Normal, HIV- Negative, HHV-8 immunohistochemical staining-not done, HB electrophoresis- No evidence of Sickle Cell disease. Serum Interleukin -6 & anti-CD 20 were not done. Malaria Parasite Slide (MPS)- 200 parasites/high power field. (Plasmodium Falciparum), Full Blood Count (FBC) results showed anemia, thrombocytopenia, creatinine and urea were elevated. Chest and abdominal Computed Tomography (slide i) revealed multiple air filled cysts in the lungs, hepatosplenomegaly and multiple enlarged lymph nodes. An excisional biopsy of inguinal lymph node showed lollipop lesions (slide iii) and reactive follicular hyperplasia with onion skin architecture (slide ii) in keeping with Castleman's disease-mixed plasmacytoid and hyaline vascular variant. HHV-8 was negative. Bone marrow biopsy showed megaloblastoid changes and less than 5% plasma cells. Serum Protein Electrophoresis: Total protein 8.61g/dl (6.4-8.3), Serum Albumin 1.64 (3.57-5.42), Gamma globulin 5.14g/dl (0.71-1.54), alpha 1 globulin 0.61g/dl (0.19-0.40), alpha 2 globulin 0.55 g/dl (0.45-0.96), Beta2 globulin 0.22g/dl (0.30-0.59), Albumin-Globulin ratio 0.23g/dl (1.1-2.2). Polyneuropathy,Organomegaly, Endocrinopathy, Monoclonal Gammopathy and Skin abnormalities (POEMS) was excluded by absence Polyneuropathy and Monoclonal gammopathy.

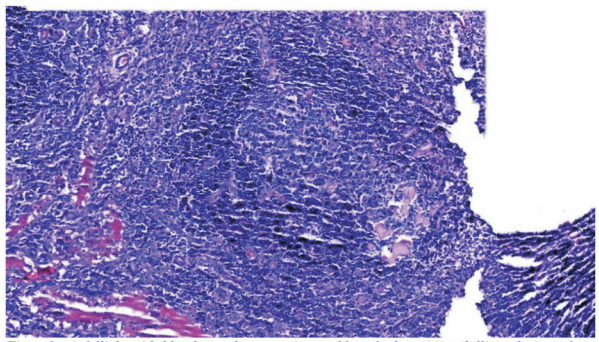

Figure1 . A follicle with blood vessel penetrating at 11 o clock position (lollipop lesion), from case 1.

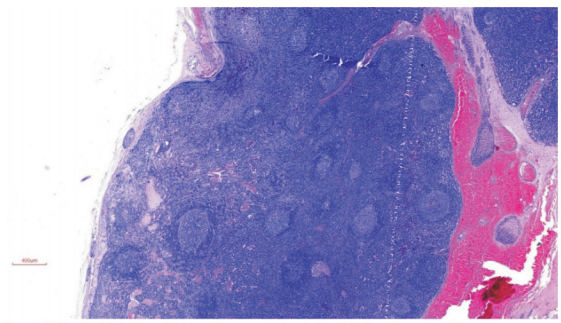

Figure2 Reactive follicles with some demonstrating onion skinning. from case 3

CASE 2: HHV-8-associated MCD

We report a case of a 42 year old male who presented with fever and non-projectile vomiting for one week. He had associated epigastric pain and loose stool. He had been on anti-retroviral drugs for 3 years and the last CD 4 count done in 2018 was 511cells/ul. Had history of enlarged lymph nodes, liver and spleen in 2018. In 2018, the excisional lymph node biopsy showed vasoformative spindle shaped lesions. HHV-8 Immunohistochemical chemical staining was not done at that time. He was presumptively treated for tuberculosis (TB) in 2019 based on chest x-ray. He had repeated blood transfusions due to recurrent anemia. Results of the tests done were as follows: Hemoglobin 4.3g/dl, Mean CorpuscularVolume (MCV) 100.3 fL, Platelets 552, White Blood Cell count (WBC) 12.0, Urea 6.8mmo/l, Creatinine 101umol/l, Alanine transaminase (ALT) 28.9 U/L, Aspartate transaminase (AST) 42.9U/L, Rapid plasma regain (RPR) –non reactive, Hepatitis Bsurface Antigen (HBsAg)-non reactive, Erythrocyte sedimentation rate (ESR)-53mm/h, Serum Adenosine deaminase (ADA) 2.8, sputum for gene Xpert- no Mycobacteria Tuberculosis (MTB) detected, stool microscopy, culture and sensitivity- normal, Chest x-ray showed heterogeneous opacities bilaterally in the lower zones with cavitations. Excisional lymph node biopsy: mild degree of reactive sinus histiocytosis, follicular pattern retained reactive hyperplastic follicles, HHV 8 positive staining lymphocytes and lymphoblasts encroaching on follicles. Patient received six cycles of Cyclophosphamide, Vincristine and Prednisolone which induced remission and improve quality of life.

CASE 3: HHV-8-associated MCD

We report a case of a 27 year old female presented with acute gastroenteritis with a long standing history of unexplained anemia. She had been on antiretroviral therapy for 1year and Tuberculosis (TB) drugs for two months. TB drugs were initiated on clinical grounds. Examination revealed fixed drug reaction rash, generalized matted lymph nodes. Results for the tests done were as follows: WBC 3.46, HB 4.0g/dl, MCV 102fL, Platelets 99, Albumin 42g/dl, Urea 2.8mmol/l, Creatinine 66umol/l, AST 10.5U/L, ALT 40U/L, gravindex-non reactive. Excisional lymph node biopsy showed spindle cells in capsule and subcapsular areas of the lymph nodes, HHV 8+ immunohistochemical staining within sinusoids and dendritic cells. She is yet to start treatment. Patient declined to give consent for bone marrow aspiration and biopsy.

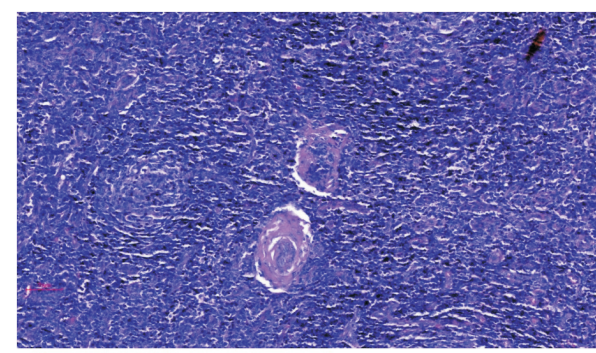

Figure 3. Hyalinized blood vessels. From case 3

DISCUSSION

Our three case reports do demonstrate what literature says about Castleman disease (CD), which describes a group of three immunological disorders that occur in individuals of all ages and share a similar microscopic lymph node appearance.

HHV-8 associated MCD is associated with the worst prognosis,[11] with death reported within 2 years of diagnosis[3], but survival could probably be improved with early diagnosis and treatment as demonstrated in our 42 year old patient.

MCD is characterized by cytokine storm, B-symptoms which mimic other diseases like Tuberculosis, disseminated Kaposi sarcoma and Lymphoma[4–7] and HIV infection. In the case series presented, the patients were initially asymptomatic, and presented with fever, anemia and generalized lymphadenopathy later on during the course of the disease. Excision lymph node biopsy is pivotal as the characteristic architecture is basically pathognomonic of CD. All the patients had MCD evidenced by generalized lymphadenopathy and histology showing Onion ring skin architecture and Lollipop lesions.

Diagnosis in the patient with iMCD was late as the patient was initially managed as Sickle Cell Disease based only on sickling test without hemoglobin electrophoresis test result.

These case reports demonstrate that it is important for all clinicians to consider the diagnosis of Castleman disease as a differential diagnosis in patients presenting with lymphadenopathy, anemia or unexplained fever. Given that examination of an excised lymph node is necessary to establish the diagnosis[7], referral for lymph node excisional biopsy is very important (punch biopsy may lead to misdiagnosis[5]

CONCLUSION

Both HHV-8 and none-HHV-8 associated CD may be very common in our Zambian population, and there is a need for prompt biopsy, reporting and treatment of all patients presenting with persistent lymphadenopathy in our hospitals. The clinical differential diagnosis for persistent lymphadenopathy in our setting should include TB lymphadenitis, disseminated KS, lymphoma and Castleman disease.

ETHICAL CONSIDERATION

No major ethical issues arose. Permission and authorization was obtained from the Kitwe Teaching Hospital Management to have the three case reports published, while an ethical waiver was sought from the National Health Research Authority (NHRA) Ethics Committee (Ref No: NHRA000032/ 01/06/2022).

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CONFLICT OF INTEREST

No conflict of interest to declare

REFERENCES

1. van Rhee F, C Munshi N. Castleman Disease. *HematolOncolClin North Am*. 2018;32(1):xiii-xiv.
2. Castleman B, Iverson L, Menendez P. Localized mediastinal lymph-node hyperplasia resembling thymoma. *acsjournals*. Published online July 1956:882-882.
3. Castleman Disease: Practice Essentials, Pathophysiology, Etiology. Accessed March 14, 2022. https://emedicine.medscape.com/article/2219018-overview
4. Anwar GR, Mehr MT, Tahir D, Humayun S, Farooq G. A Case of Castleman Disease: A Diagnostic Dilemma. *Cureus*. 2021;13(4). doi:10.7759/CUREUS.14372
5. Xiao H, Monika P, Cindy V. Multicentric Castleman's Disease with Disseminated Kaposi's Sarcoma: A Report of Prolonged Misdiagnosis. *International Journal of Blood*

Research and Disorders. 2020;7(1). doi:10.23937/2469-5696/1410051

6. Castleman Disease: Symptoms, Causes, Treatments and Tests. Accessed March 15, 2022. https://my.clevelandclinic.org/health/diseases/17920-castleman-disease
7. Reddy D, Mitsuyasu R. HIV-associated Multicentric Castleman Disease. doi:10.1097/CCO.0b013e328349c233
8. HIV/AIDS – people living with HIV/AIDS - The World Factbook. *www.cia.gov*. Accessed March 23, 2022. https://www.cia.gov/the-world-factbook/field/hiv-aids-people-living-with-hiv-aids/country-comparison
9. Global HIV & AIDS statistics — 2020 fact sheet. *www.unaids.org*. Accessed March 23, 2022. https://www.unaids.org/en/resources/fact-sheet
10. Centre for Infectious Disease Research in Zambia. Zambia Attains 90:90:90 UNAIDS HIV/AIDS Epidemic Control Targets. http://www.cidrz.org/2020/12/02.
11. Chan KL, Lade S, Prince HM, Harrison SJ. Update and new approaches in the treatment of Castleman disease. *Journal of Blood Medicine*. 2016;7:145. doi:10.2147/JBM.S60514