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Castleman Disease and Literature Review from Mankweng Hospital, Limpopo, South Africa

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Abstract

Castleman disease is a lymphoproliferative disorder and is easily confused with lymphoma or other lymphadenopathy. Castleman's disease is divided into unicentric Castleman disease, which involved a single enlarged lymph node or region of lymph nodes, and multicentric Castleman disease, which involved multiple lymph node stations. In this paper we highlight the presentation of Castleman's disease on a female patient to share our experience with literature review. **Case Presentation:** A 29 years old female patient was referred to our surgical outpatient clinic from the peripheral hospital with right & left painless neck cervical mass slowly growing which started 3 years ago along with a right breast lump and patient was RVD non-reactive. On physical examination she was severely wasted. She had 4cm by 3cm mass of the right supraclavicular region & another mass of 3cm x 1 cm mass on the left supraclavicular area. Her abdominal examination revealed hepatomegaly which is extended 8 cm below the subcostal margin. Histology report of cervical mass concluded Reactive lymph nodes with features of hyaline vascular Castleman disease and Breast mass revealed fibroadenoma. Immunohistochemistry of cervical node biopsy for HHV8 is negative. Blood result of inflammatory markers: C - reactive protein was 459 mg/L. **Conclusions:** Owing to the rarity of this condition, Castleman Disease Collaborative Network (CDCN) guideline is important for assessment & treatment plan.

Keywords: Castleman disease; Lymphadenopathy.

1. Introduction

Castleman disease (CD) is a lymphoproliferative disorder and is easily confused with lymphoma or other lymphadenopathy [1]. Its clinical characteristics do not provide specific information. The symptoms like weight loss, malaise, nausea, lymph node spleen, and hepatic enlargement which are ambiguous and may be caused by any other lymph node disorder [1]. It is crucial to accurately diagnose the exact type of CD and differentiate it from other diseases by clinical history and laboratory diagnostic measures with additional imaging techniques for prompt treatment and management procedures. A precise diagnosis can be made in a proper clinical setting when the signs and histological features can provide enough evidence for this disease [1].

There is very little knowledge available about the etiology of this disorder, but it has been postulated that impaired immunoregulation causes abundant proliferation of B lymphocytes and plasma cells in lymphoid organs. These conditions can result from chronic low-grade inflammation, lymphoid-hamartomatous hyperplasia, viral infections, abnormal modulation of cytokines, and angiogenesis [2]. Castleman's disease is divided into unicentric CD (UCD), which involved a single enlarged lymph node or region of lymph nodes, and multicentric CD (MCD), which involved multiple lymph node stations [3, 4].

UCD is more common than MCD [5]. There is an association observed between human immunodeficiency virus (HIV) and MCD. [6-8] Multicentric CD (MCD), is divided into idiopathic MCD (iMCD), human herpes virus-8 (HHV8)-associated MCD (HHV8-MCD) and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD (POEMS-MCD). [9, 10] Human herpesvirus 8 (HHV8) causes multicentric Castleman's disease in immunosuppressed patients. The cause of HHV8-negative multicentric Castleman's disease is termed idiopathic multicentric Castleman's disease(iMCD) [8].

Castleman's Disease is generally benign and is characterized by non-neoplastic lymph node hypertrophy, associated with infection by human herpesvirus-8 in people with the human immunodeficiency virus/acquired immunodeficiency syndrome. Although the unicentric Castleman's Disease presents as benign, the multifocal form can manifest severe systemic symptoms [11].

In this paper we highlight the presentation of Castleman's disease on 29 old female patient to share our experience with literature review.

2. Presentation of the Case

A 29 years old female patient was referred to our surgical outpatient clinic from the peripheral hospital with right & left painless neck cervical mass slowly growing which started 3 years ago along with a right breast lump. On further enquire there was significant history of massive weight loss of more than 40kg (from 84 kg to 46kg). Her HIV status was negative. Clinically, she was not pale or jaundiced. On physical examination she was severely wasted. She had 4cm by 3cm mass of the right supraclavicular region & another mass of 3cm x 1 cm mass on the left supraclavicular area. On chest examination she had a breast lump of 2cm x 2cm on the upper inner of the right breast. Her abdominal examination revealed multiple striae with hepatomegaly which is extended 8 cm below the subcostal margin and spleen was not palpable. Ultrasound done and confirmed bilateral well circumscribed hypochogenic soft tissue lesions in keeping with cervical lymphadenopathy. The largest on the right supraclavicular region measuring 4,85 x 3 cm and there was a mass defect on the right internal jugular vein. The left lymph node measured 3 cm x 1,6 cm, there were multiple matted nodes inferiorly with retro clavicular extension. The left internal jugular vein had hyper-echogenic contents and good Doppler flow. Abdominal ultrasound showed 27 cm hepatomegaly with no dilated intrahepatic ducts. The gallbladder was not distended. Both kidneys were enlarged with left measuring 14 x 7,7 cm and the right 14 x 6 cm in size. Incisional Biopsy was taken from neck mass and excision of breast lump was performed to exclude any malignancy. Blood result of inflammatory markers: C - reactive protein was 459 mg/L. Histology report of cervical mass concluded Reactive lymph nodes with features of hyaline vascular Castleman disease and Breast mass revealed fibroadenoma. Immunohistochemistry of cervical node biopsy for HHV8 is negative. She was then booked for CT Scan but postponed as she wasn't in a stable condition and subsequently passed on.

3. Discussion

The epidemiology of Castleman disease is poorly understood. Simpson stated that incidence of UCD is 16 per million patient-years and affects all age groups and incidence of iMCD is 5 per million patient-years. The incidence of HHV-8 is more common in HIV-positive men. [12] Male are slightly more affected with MCD than female, however for UCD there is no gender preference [3, 13]. Robinson D et al. found, 61% were males with the mean age of 53 years in the study conducted in the US from 2000 to 2009 [14]. UCD occurs in younger age group. The average age of diagnosis for UCD patients is usually fourth decade and for MCD patients in sixth decade, nevertheless patients of all ages can be diagnosed with any form of CD [3, 13]. However, our patient was young female of 29-year-old and had MCD.

Histopathologically, it can be classified as hyaline vascular type (HV-CD), plasma cell type, mixed type, and human herpesvirus (HHV)-8 associated Castleman disease [15-17]. Hyaline vascular type (HV) is most commonly seen in UCD, lymph nodes with HV histopathology are often characterized by capsular fibrosis with broad fibrous bands traversing through the lymph node [18, 19]. In plasmacytic (PC) type, lymph nodes are distinguished by the presence of sheets of PCs in the interfollicular zone and hyperplastic germinal centers. PC histopathology most commonly occurs in HHV8-MCD, iMCD, and POEMS-MCD, but rarely in UCD. [20, 21] In Mixed type, lymph nodes have both HV and PC features are considered to have mixed histopathology, which usually observed in UCD and iMCD. These lymph nodes demonstrate extensive regressed germinal centers as well as sheet-like plasmacytosis. [9] Histological sections of our patients show fragmented portions of lymphoid tissue which are partially encapsulated. The fibrous capsule is notably thickened. Attenuated follicles with small germinal centres and interfollicular sinus histiocytosis is seen. There are prominent hyalinized vessels, with foci of haemosiderin deposition and interstitial haemorrhage and concluded as reactive lymph nodes with features of hyaline vascular Castleman disease. Immunohistochemistry of cervical node biopsy for HHV8 is negative.

Angela Dispenzieri and David C. Fajgenbaum stated that patients should have complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), direct antiglobulin test (DAT), liver function tests, creatinine, serum protein electrophoresis with immunofixation, serology for HIV, urinalysis, and CT scanning of the chest, abdomen [9]. A single enlarged lymph node or region of lymph nodes on imaging suggests that a patient has UCD, whereas 2 or more regions of enlarged lymph nodes suggest that a patient has a form of MCD [9]. In the same study it is indicated that UCD occurs most commonly in the mediastinum, cervical regions [9]. Our patients had high C-Reactive protein 459 mg/L and serology for HIV is negative and occurred in cervical region. CT scan could not be done because of her condition was not stable when we saw the patients.

Few studies reflected that MCD patients exhibit constitutional symptoms, fluid accumulation, cytopenias, and liver and kidney dysfunction at the time of presentation [4, 13]. Clinically, unicentric Castleman disease manifest as a slow-growing and generally asymptomatic at the beginning, however it starts producing symptoms when it compressed the surrounding structures [22, 23]. Multicentric CD occurs at multiple sites and usually characterized by a proinflammatory response giving rise constitutional symptoms of fever, night sweats, malaise, and weight loss [1]. In extreme cases of iMCD, multiple organ failure with renal insufficiency can occur, often resulting in death [24]. Oksenhendler *et al* reported on the overall survival (OS) of CD patients at his institution in France over a 20-year period [25]. Our patient lost weight massively and started compression symptoms of internal jugular vein. Possibly, compression of this internal jugular vein cause early death within 3 year since notice of cervical mass.

The diagnosis of Castleman disease is difficult as it is very rare and does not have specific features that could be differentiated from other diseases causing lymphadenopathies [1, 26]. Therefore, it is suggested by Nimra Ehsan and Farah Zahra to consider other assessment criteria which include both major criteria, at least two of the minor criteria and one laboratory abnormality [1].

Major Criteria: 1)**.** Histopathologic screening of lymph nodes is done to assess a single node involvement (suggestive of UCD) or a multi lymph node involvement (suggesting MCD) after excluding other infectious, malignant, and autoimmune disorders that exhibit their characteristic features in the lymph nodes. In addition, their characteristic lymph node features are also noted and 2). The lymph node size must be enlarged.

Minor Criteria:

Clinical: 1). B symptoms: fever, weight loss, night sweats, fatigue. 2). Splenomegaly or Hepatomegaly. 3). Fluid accumulation (oedema, anasarca, pleural effusion)

Laboratory: 1)**.** Elevated CRP or ESR. 2). Anemia, 3). Thrombocytopenia or thrombocytosis. 4) Hypoalbuminemia. 5). Renal dysfunction or proteinuria. 6) Polyclonal hypergammaglobulinemia.

The patient should also have serology tests for HIV and HHV-8 and search for HHV-8 DNA in peripheral blood by polymerase chain reactive (PCR) to discover associations with CD. Before formulating a treatment plan, physicians should perform a thorough clinical staging to detect other sites of involvement. An evaluation including serum protein electrophoresis, bone marrow examination, CT scan of the chest, abdomen, and pelvis, radiographic skeletal survey [1].

For the treatment of unicentric Castleman disease lesion, complete surgical resection of the tumor is the best treatment as it is localized [1]. [For multicentric CD treatment, few options are available, including surgery, cytotoxic chemotherapy with or without corticosteroids, and autologous stem cell transplantation (ASCT) [27].

For HHV8-MCD, Rituximab-based therapy has shown effective and improved 5-year OS from 33% to 90% [28]. For those patients with concurrent POEMS syndrome**,** high-dose chemotherapy with autologous stem cell transplant (ASCT) is advocated [9].

An international expert consortium assembled by the Castleman Disease Collaborative Network (CDCN) which consists of international working group of 42 experts from 10 countries was convened to establish consensus recommendations based on review of treatment in published cases of UCD, the CDCN ACCELERATE registry, and expert opinion. CDCN stated that complete surgical resection is often curative and is therefore the preferred first-line therapy, if possible. The management of unresectable UCD may be observed in asymptomatic patients. The anti-interleukin-6 monoclonal antibody siltuximab should be considered for unresectable UCD patients with an inflammatory syndrome. Unresectable UCD that is symptomatic as a result of compression of vital neighbouring structures may be rendered amenable to resection by medical therapy (e.g. rituximab, steroids), radiotherapy, or embolization [10].

The outcomes and prognosis of CD depend on its cause and pathogenicity. However, prompt consultation with an interprofessional group of specialists is recommended to improve outcomes [1].

4. Conclusions

Owing to the rarity of this condition, Castleman Disease Collaborative Network (CDCN) guideline is important for assessment & treatment plan. Further studies are indicated to elucidate the clinical behaviour of the Castleman Disease.

Declaration

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Author Contributions

Equal contributions (concept, acquisition of data, analysis of data, drafting of the manuscript and critical revision for important intellectual content).

Informed Consent

A written informed consent was obtained from the patient to publish this case report.

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Conflicts of Interest

None.

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