

Case Series

Recurrent and Hodgkin's lymphoma-associated multicentric Castleman's disease in head and neck region

Vinodh Kumar Selvaraj, Deleep Kumar Gudipudi*

Department of Radiation Oncology, Basavatarakam Indo-American Cancer Hospital and Research Institute, Road number 10, Banjara Hills, Hyderabad, India

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*Correspondence:

Dr. Deleep Kumar Gudipudi,

E-mail: deleep.gudipudi@gmail.com

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ABSTRACT

Background: Castleman's disease (CD) is a rare lymphoproliferative disorder. It can involve single (unicentric CD) or multiple (multicentric CD) lymph nodal regions. It occurs predominantly in mediastinum, and treatment options include surgery, radiotherapy, chemotherapy, and monoclonal antibodies.

Methods: Here, we describe two cases of CD which presented with stridor. The first case was a 38-year-old male, a recurrent multicentric CD in retropharyngeal and cervical lymph nodal regions, treated with radiotherapy and rituximab. The second case was a 25-year-old male, a multicentric CD in lower cervical lymph nodal region, treated with steroids and radiotherapy. He subsequently developed Hodgkin's lymphoma and was treated for the same with chemotherapy and involved-field radiation therapy (IFRT).

Results: Post-treatment, both the patients were asymptomatic and progression-free at 15 months and 42 months follow-up, respectively.

Conclusions: Combined modality of treatment with radiotherapy and chemotherapy or monoclonal antibodies offers good local control in multicentric CD.

Keywords: Angio-follicular lymph hyperplasia, Castleman's disease, Giant lymph node hyperplasia, Lymphoproliferative disorder, Rituximab

INTRODUCTION

Castleman's disease (CD), also known as Angio-follicular lymph hyperplasia (AFH) or giant lymph node hyperplasia, describes a rare group of non-malignant lymphoproliferative disorders characterized by enlargement of lymph nodes.¹ In 1956, Castleman et al first described this condition in a case of localized mediastinal lymph node hyperplasia resembling thymoma.² It presents most commonly in mediastinum; however extra-thoracic sites such as cervical, mesenteric or retroperitoneal regions can also be involved.^{1,3,4} CD involving retropharyngeal and cervical lymph nodal region causing stridor is a rare entity. Here we describe two such

cases of CD presenting with stridor and treatment modalities adopted.

CASE SERIES

A 38-year-old male, with no comorbidities, a known case of Castleman's disease previously treated with 2 cycles of cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (oncovin), and prednisone (CHOP) chemotherapy elsewhere 3 years back with grade III adverse events. Now he presented to our institute with breathlessness and stridor. There was no history of fever, night sweats, or weight loss. Family history was non-contributory. Physical examination revealed enlarged lymph nodes in right level II and III,

largest 1.5×1.5 cm at right level II. 18 F- Fluorodeoxy-Glucose (FDG) Positron emission tomography computed tomography (PET CT) scan showed enlarged conglomerated and discrete right retropharyngeal lymph nodes with extension to roof, right lateral wall and posterior wall of nasopharynx; and enlarged right level II, III and IV cervical lymph nodes (figure 1).

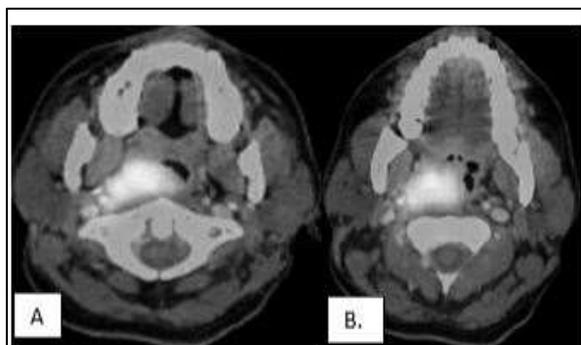


Figure 1: 18F-FDG PET CT axial images showing increased metabolic uptake A, in retropharyngeal lymph nodes B, in upper cervical lymph nodes.

Compared to previous PET-CT scan, there was significant increase in size and metabolic activity of right retropharyngeal lymph nodes and decrease of same in right level II to IV lymph nodes. Histopathological examination of right cervical lymph node biopsy showed lymph node with partially effaced architecture by lymphoid follicles with atretic germinal center and prominent mantle zone; interfollicular areas showed expansion with predominant plasma cell infiltration. These findings along with immunohistochemistry (IHC) markers staining were consistent with Castleman's disease. In view of breathlessness and stridor, he was treated with external beam radiotherapy of 46 Gy delivered in 23 fractions at 2 Gy per fraction to head and neck region using intensity modulated radiotherapy (IMRT) technique. During treatment, he developed grade II mucositis and improved with supportive care. After 3 months, he presented with pain in right side of neck. PET-CT scan showed increased tracer uptake in right retropharyngeal lymph node measuring 2.8×2.7 cm and few small right level II, III and IV nodes, largest measuring 0.9 cm (figure 2). In view of post-radiotherapy residue, he was planned for 4 cycles of weekly rituximab 375 mg/m². Patient received four cycles of rituximab and tolerated treatment without adverse events. At 15 month follow-up, he was still asymptomatic.

A 25-year-old male presented with cyanotic spells and stridor. On examination, small volume lymph nodes were palpable in neck. 18F-FDG PET-CT scan showed multiple metabolically active lymph nodes in level II, III and V on both sides of neck; and an anterior mediastinal mass of 4.5 cm at D2-D6 region with bilateral mediastinal lymph nodes causing compression of trachea. Histopathological examination of cervical lymph node biopsy proved to be Castleman disease, plasma cell type. He was initially treated with steroids and there was good response with

near-total complete remission (CR) of neck nodes clinically. After a month, he presented with swelling in neck, hence he was planned for external beam radiation of 50 Gy in 25 fractions at 2 Gy per fraction by Rapid-arc IMRT technique to head and neck region and thorax. Since the patient developed grade III esophagitis, radiotherapy was stopped at 46 Gy in 23 fractions. Seven months post-treatment, patient presented with enlarged left supraclavicular which developed along the lateral margin of previous radiation treatment field and axillary lymph nodes. Biopsy of which proved to be Hodgkin's lymphoma. Hence, he was treated with 4 cycles of adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) chemotherapy followed by involved-field radiotherapy (IFRT) to left supraclavicular region to a dose of 20 Gy in 10 fractions using 3-dimensional conformal radiotherapy. At 42 months follow-up, patient was clinically and radiologically free of disease.

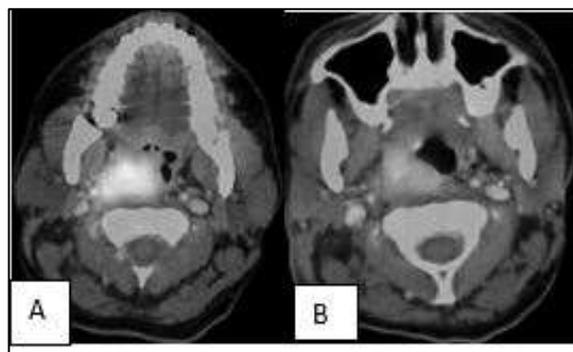


Figure 2: Post-radiotherapy 18F-FDG PET CT axial images showing decreased metabolic uptake A, in retropharyngeal lymph nodes B, in upper cervical lymph nodes.

DISCUSSION

Castleman's disease can be histologically subdivided into three types: hyaline vascular, plasma cell and mixed type. 1 Of these, hyaline vascular and mixed variants are usually benign while plasma cell variant is aggressive. Based on lymph nodal involvement, CD is classified broadly into unicentric (UCD) or multicentric (MCD). UCD is defined as involvement of either a single enlarged lymph node or single region of enlarged lymph nodes. It is the most common variant (90%) and occurs mostly in children and young adults.⁵ Most cases of UCD are asymptomatic and few cases have symptoms due to enlarged nodes. 90% of UCD are histological hyaline vascular type, hence have a favorable prognosis.^{5,6}

On the other hand, MCD is the least common variant (10%) involving multiple lymph nodal regions.⁵ Histologically, almost all MCD are plasma cell variant and have a worse prognosis.^{5,6} They typically present with fever, fatigue, excessive sweating, weight loss and skin rash.⁷ It can be either idiopathic (iMCD) or HHV-8 associated MCD.⁸ Based on clinical features, iMCD is

further subdivided into iMCD-Thrombocytopenia, anasarca, fever/elevated C-reactive protein (CRP), renal dysfunction/reticulin myelofibrosis, organomegaly (TAFRO) and iMCD-Not otherwise specified (NOS).⁹ Pathophysiology of Human herpes virus 8 (HHV-8) associated multicentric CD (MCD) is postulated to be excess production of interleukin-6 (IL-6) in germinal centers and at increased risk of developing Kaposi sarcoma.¹⁰ Early destruction of red blood cells leads to hemolytic anemia and elevated immune factors cause hypergammaglobulinemia. There can also be enlarged liver or spleen, peripheral neuropathy, edema, or effusion. Thus, MCD can be associated with amyloidosis, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, autoimmune disease, immune thrombocytopenic purpura (ITP) and Hodgkin's lymphoma.^{11,12}

The diagnosis of CD needs a thorough clinical examination, radiological evaluation with ultrasound, CT or magnetic resonance imaging (MRI) scan and expertise in histopathological examination of biopsy tissue or surgically resected specimen of enlarged lymph node(s). IHC markers help to rule out other associated malignancies like lymphoma. Castleman Disease Collaborative Network (CDCN) international evidence-based consensus diagnostic criteria for iMCD suggests presence of both major criteria (characteristic lymph node histopathology of CD and multicentric lymphadenopathy), at least 2 out of 11 minor criteria along with at least 1 laboratory abnormality, and exclusion of infectious, malignant and auto-immune disorders that can mimic iMCD.⁹

The primary treatment of UCD is surgical removal of the lymph node, which usually cures the patient.¹³ The role of radiotherapy is limited in UCD, however studies has shown that radiotherapy dose in range of 40-50 Gy confers good local control when surgery is not possible or desired.^{14,15} In contrast to UCD, monoclonal antibodies or chemotherapy is the cornerstone in the treatment of iMCD.^{16,17} Siltuximab, a chimeric monoclonal antibody against interleukin-6 (IL-6) is the only Food drug administration (FDA) approved drug for treatment of iMCD.¹⁸ Siltuximab-refractory patients are treated with chemotherapy or newer agents like rituximab, sirolimus, or anakinra.¹⁹ Rituximab, monoclonal anti-CD20 antibody is particularly useful in HHV-8-associated MCD. Additional symptomatic and supportive therapy with steroids, anti-virals and/or cytotoxic chemotherapeutic agents is also helpful to alleviate symptom and improve disease control.¹⁹ In our case series, although association of HHV-8 not tested, four cycles of Rituximab following 46 Gy of radiotherapy resulted in good disease control in the first case. While chemotherapy with IFRT resulted in prolonged progression-free survival in the second case.

There are no clear prognostic data for CD. In MCD, few cases have persistent disease for several months or years without progression, while few progresses rapidly. Based

on literature review, the 10-year survival rate for resectable UCD is 95% after complete resection while survival rates are poor for HIV or HHV-8-associated MCD.²⁰ However, studies have shown 5-year survival rates of 92% with the use of Rituximab.^{21,22} Based on our case series, we hereby report a prolonged disease-free survival with combination of radiotherapy and rituximab or chemotherapy in multicentric CD.

CONCLUSION

Castleman's disease constitutes a heterogenous group of lymphoproliferative disorders, ranging from limited disease to malignant association. Careful evaluation and sub-grouping are mandatory to decide on appropriate treatment modality such as surgery for UCD and chemotherapy for MCD. Addition of radiotherapy to monoclonal antibodies or chemotherapy results in good disease control, apart from playing a vital role as primary treatment in unresectable cases and for symptomatic relief from compression effects due to enlarged lymph nodes.

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