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CASE REPORT
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Management of a case of Castleman's disease coexisting with or occurring after transplanted Hodgkin's lymphoma

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ABSTRACT

Castleman's disease is a benign lymphoproliferative disorder. The coexistence of Hodgkin's lymphoma and multicentric Castleman's disease is a rare phenomenon. We discuss a case of a 48-year-old female patient who had been in the records of the Colentina Hematology Clinic since 2019, with the diagnosis of classic Hodgkin's Lymphoma, nodular sclerosis type I BNLI, stage IIXB. For this, she underwent 3 courses of ABVD and 2 courses of BEACOPP, without showing complete remission on PET/CT evaluation at the end of treatment. After that, we initiated rescue therapy and performed 4 IGEV courses, followed by autologous stem cell transplantation. For maintenance treatment, we opted for Brentuximab, but it was discontinued after the first administration due to the appearance of adverse reactions. Subsequently, we decided to perform radiotherapy with 20 fractions cumulating a total dose of 36 Gy. Shortly after the radiotherapy, symptoms reappeared which were suspected to be in the context of a relapse of the disease. For confirmatory diagnosis, we performed a new PET-CT which highlighted metabolically active ganglion images. Further, were carried out lymph node biopsy for histopathological and immunohistochemical examinations were carried out. The underlying disease was diagnosed as plasmacytic subtype, HHV8 negative, multicentric Castleman's disease. For treatment, we relied on administrations of Siltuximab treatment therapy that showed complete remission. Castleman's disease presents a unique diagnostic challenge, but a confirmatory diagnosis can be based on a biopsy examination, advisable after each relapse.

Keywords: lymphoid, hyperplasia, lymph node, histopathology, angio-follicular

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INTRODUCTION

Castleman's disease (CD) is a rare clinicopathological entity characterized by hyper-vascular lymphoid hyperplasia [1]. The disease was first described by Dr. Benjamin Castleman in 1954 when he observed solitary hyperplastic mediastinal lymph nodes with a regressive germinal center in a patient [2]. Lymph node hyperplasia is frequently reported in mediastinal regions and rarely observed in cervical regions. The underlying histological presentation of the disease includes hyperplasia of Angio-follicular nodes [3]. Although higher prevalence has been reported in adults, Castleman's disease does not manifest any sex or age-related predilection. The etiology of Castleman's disease remains unknown; however, a close association of CD is observed with Kaposi's sarcoma. Some studies implicate co-infection with human herpesvirus 8 and the production of interleukin-6 cytokines in the development of Castleman's disease [4].

Clinically, Castleman's disease has two forms including solitary (localized in one area) and multi-centric (multiple site involvement). The disease can penetrate any area where lymph nodes are present such as the mesentery, groin, lungs, tongue, and pelvis [5]. The localized form of the disease is asymptomatic, therefore, it is usually detected accidentally during routine examinations [6]. The multi-centric Castleman's disease (MCD) is manifested by pronounced symptoms which are attributed to the overproduction of interleukin-6 cytokines. The clinical presentation of MCD includes asthenia, fever, and polyadenopathy [7]. HIV-positive MCD usually exhibits a higher proportion of pulmonary symptoms, and can be differentiated from other types of HIV-associated systemic lymphoproliferative disorders [8].

The co-existence of Castleman's disease and Hodgkin's disease is a sparse phenomenon. Due to the rarity of symptoms, the diagnosis of CD presents a significant challenge for health experts [9]. Diagnostic investigation

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of CD should be based on diverse evaluation parameters. Blood tests in CD reveal elevated ESR, thrombocytopenia, anemia, and elevated polyclonal gamma globulins. The identification of an immunophenotypically varied population of B lymphocytes with polyclonal surface and cytoplasmic immunoglobulin markers can help in the differential diagnosis of Castleman disease and other lymphomas. However, histopathological examination is vital for confirmatory diagnosis of Castleman's disease [10]. We report a case of 48-year-old multicentric Castleman's disease after autologous stem cell transplantation for Hodgkin's disease.

CASE PRESENTATION

We present the case of a 48-year-old patient, diagnosed with multicentric Castleman's disease 6 months after autotransplantation of stem cells. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our institution; patient signed a standard consent form regarding the educational and scientific use of examination results. The patient had been in the records of the Hematology section of the Colentina Clinical Hospital since 2019, when she presented with dyspnea with orthopnea, wheezing, dry cough, and sweating. On presentation, diagnostic evaluations by the imaging techniques highlighted numerous lymph node images and a voluminous right upper mediastinal-pulmonary tumor formation (90/110/80 mm). We further performed a biopsy from the level of the mediastinal formation, which showed classical Hodgkin's Lymphoma, nodular sclerosis type I BNLI. Our initial analysis placed her in stage IIBX (bulky mediastinal disease), with an early unfavorable outcome. Unfavorable criteria included bulky disease, involvement of more than 3 lymph nodes, extranodal involvement, and ESR >/= 50 mm/h) (erythrocyte sedimentation rate).

After establishing the diagnosis of certainty, the patient underwent 3 ABVD (adryamycin, bleomicin, vinblastine, dacarbazine) courses, followed by interim PET-CT (Figure 1). The interim PET/CT revealed a partial response to the treatment (metabolically active right anterior mediastinal-pulmonary mass with over 50% reduction in size and metabolic activity), which is why she continued with 4 more courses of BEACOPP (Bleomycin, Etoposide Phospate, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, prednisone).

The PET-CT examination at the end of treatment highlighted the absence of a complete response, which is why 4 IGEV-type (Ifosfamide, Gemcitabine, Vinorelbine, prednisone) rescue treatments were performed, followed by stem cell autotransplantation in November 2020 (Figure 2).

In February 2021, the maintenance treatment with Brentuximab was initiated, however, it was interrupted after the first administration due to the appearance of severe adverse reactions (grade III neutropenia, moderate thrombocytopenia, altered general condition, dyspnea, nausea, vomiting). So, we decided to perform radiothera-

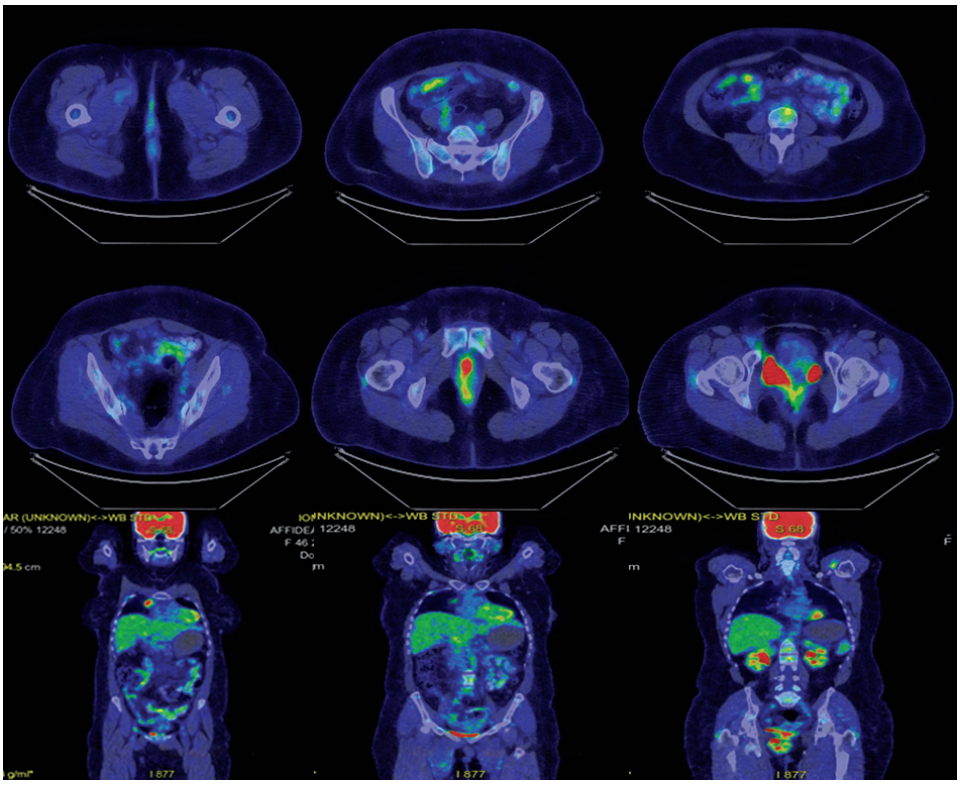

Fig. 1. Interim PET-CT: metabolically active right anterior mediastinal-pulmonary mass

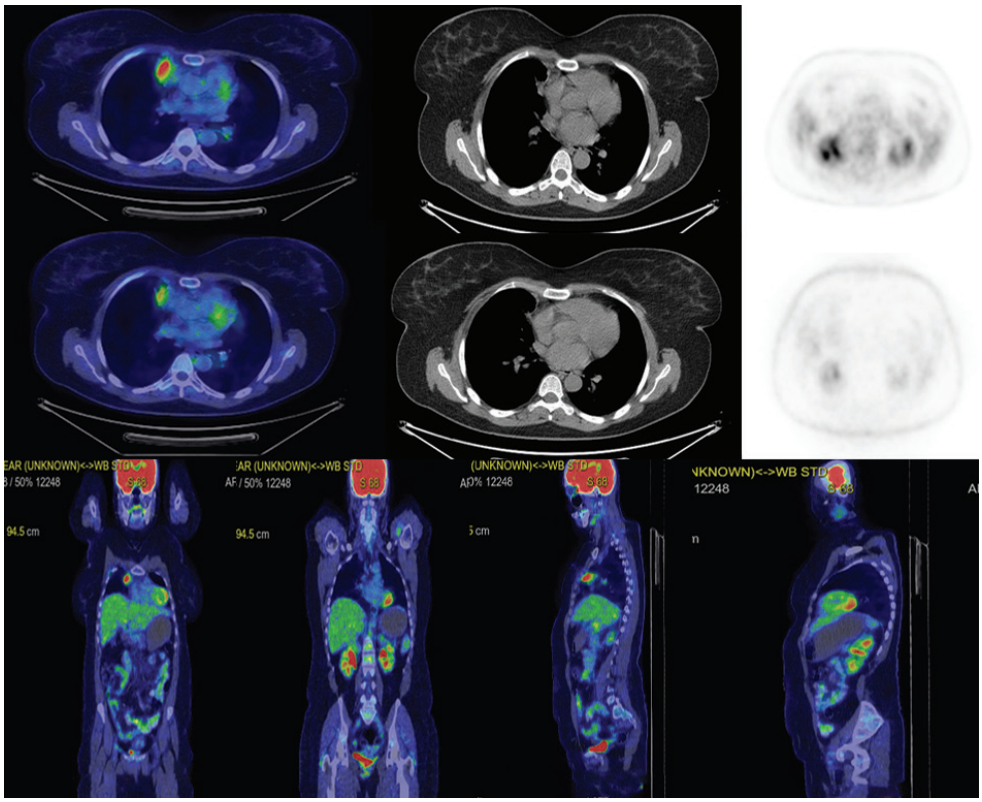

Fig. 2. PET-CT final treatment - partial response was observed after the 4 IGEV-type rescue treatments

py in a total of 20 fractions, cumulating 36 Gy at the level of the remaining mediastinal formation, with a diameter of 26/15 mm. Control PET/CT after autotransplant and radiotherapy showed a complete metabolic response.

Again in May 2021, the patient presented to the Hematology department, with a dry cough, itching, and asthenia, raising the suspicion of a relapse of Hodgkin's lymphoma. The PET-CT examination was performed that revealed the appearance of metabolically active ganglion images located in the right external iliac (SUV= 3.42 and maximum diameter of 9 mm) and bilateral inguinal (SUV=2.08 and diameter 8 mm on the right, respectively SUV =4.24 and diameter 7 mm on the left).

A lymph node biopsy was performed. Histopathological examination highlighted frequent reactive hyperplastic germinal centers, partially polarized with zonal follicculosis, diffuse paracortical hyperplasia with the frequent presence of large, mononucleated, immunoblastic type cells, small lymphocytes, paracortical interdigitated cells, and Largenhans histiocytes. Numerous plasma cells were arranged in cords, both between the dilated medullary and paracortical sinuses along with groups of monocytoid cells and perivascular plasmacytoid.

Immunohistochemistry showed that CD20 was positive in reactive germinal centers and in frequent large mononucleated cells of the immunoblastic type which expressed CD38 whereas CD3 was positive in frequent small paracortical reactive T cells. EBV/LMP1 was positive in isolated small lymphocytes and plasma cells showed a kappa/lambda ratio of approximately 8/1 and were negative for IgG4 and HHV8.

Paraclinical findings demonstrated mild anemia (Hb = 11.1 g/dl), inflammatory biological syndrome (C-reactive protein = 56 mg/L; ferritin = 395 ng/ml; fibrinogen = 670 mg/dl), protein electrophoresis with immunofixation highlights IgG with the secretion of kappa chains. The following were additionally evaluated: virological status: HIV test negative, HHV 8 negative, EBV IgG positive 750 U/ml; immunological evaluation: negative rheumatoid factor and ANA. Pulmonary function was evaluated with normal spirometry, renal function with GFR = 142 ml/min, and cardiac ultrasound showed FE = 60%. In conclusion, the histopathological and immunohistochemical aspects suggested the diagnosis of plasmacytic subtype, HHV8 negative, multicentric Castleman's disease.

For the treatment therapy, we decided to use Siltuximab, 11 mg/kg, administered once every 3 weeks. However, after the second dose, adverse reactions such as mild thrombocytopenia, neutropenia grade I, asthenia, and arthralgias with a migratory character appeared after administration which spontaneously remitted after a few days. Follow-up after six administrations of Siltuximab treatment therapy showed complete remission on PET/CT evaluation in the patient.

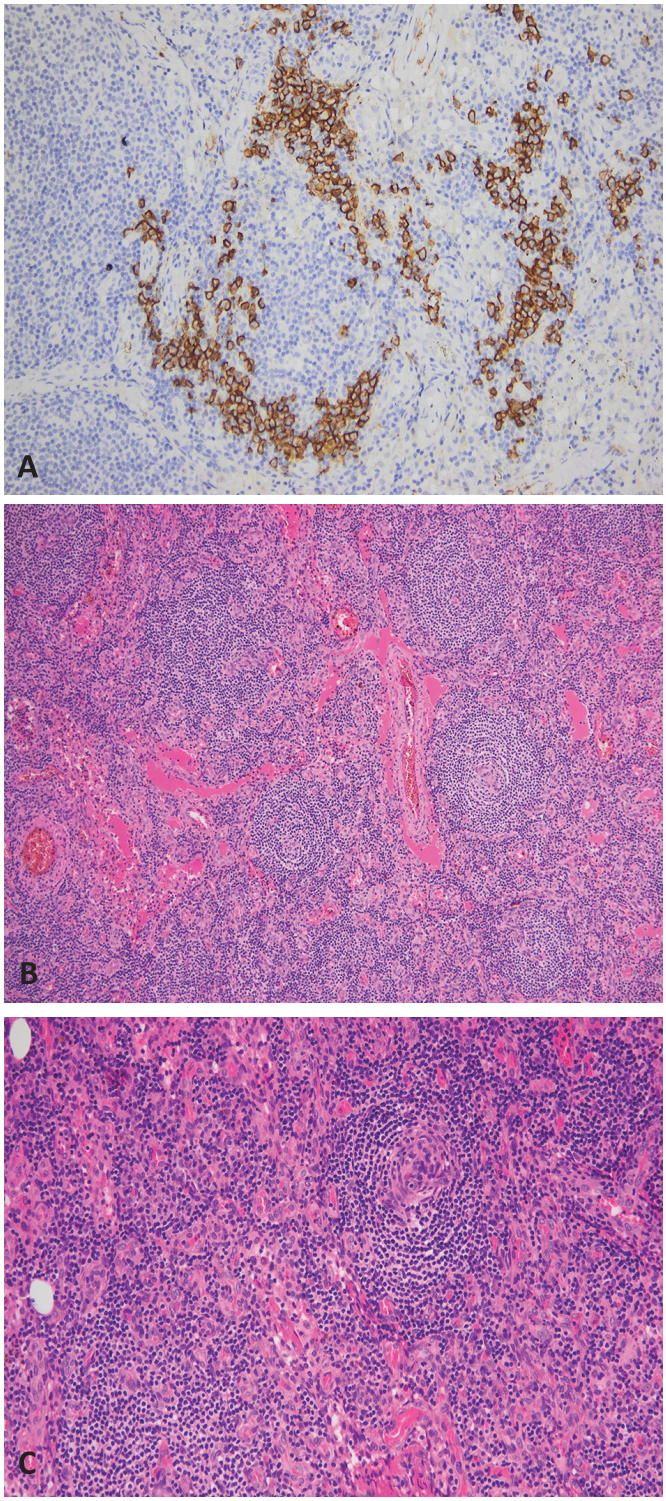

Fig 3. Castleman disease, plasmacytic subtype showing diffuse plasma cells. A. CD138 immunostaining revealing abundent small mature plasma cells in interfollicular areas. B. Lymph node with distorted architecture due to small follicles with atretic centers with thickened mantle areas composed of layers of small, typical lymph cells with onion-skin appearance. Many hyalinized small vessels, some of them penetrating germinal centers, others occupying interfolicullar areas. Hematoxylin-eosin, 100x. C. Detail of a small follicle with atretic germinal center and onion-skin appearance of mantle area. Parafollicular areas with vascular proliferation and small groups of plasma cells. No atypia is present. Hematoxylin-eosin, 200x.

DISCUSSION AND CONCLUSION

The clinical prevalence varies greatly between localized and multi-centric forms of Castleman's disease. Almost 90% of cases of CD are localized in nature, with the majority being asymptomatic unless the enlarged lymph nodes compress any vital organ. Only 3% of localized cases develop symptoms such as fever, sweats, fatigue, and anemia. The multi-centric type of CD is reported in only 9% of cases, however, 50% of such patients exhibit symptoms [11]. Patients with MCD demonstrate a progressive course of the disease which is often complicated with other lymphoma or sarcoma. In this study, we presented the evolution of a case of a 48-year-old patient with Hodgkin's disease, early stage, with an unfavorable prognostic outlook. The patient did not respond to the initial therapy and required rescue therapy and autotransplantation. Although the patient obtained complete remission after autotransplantation and radiotherapy, apparently remission was not sustained considering the reappearance of the general symptoms of the disease and adenopathies. Upon further investigations, we confirmed it as a plasmacytic subtype, HHV8 negative, multicentric Castleman's disease. For treatment therapy, we opted for Siltuximab which culminated in remission in the patient.

Our therapeutic interventions were in-line with Falchi et al. who propagated that Hodgkin lymphoma co-occurring with CD should be treated with standard lymphoma chemotherapy. They also concluded that Rituximab could be effective in eliminating CD20-positive cells [12]. Similar findings were shared by El-Osta et al. who demonstrated the efficacy of Siltuximab, an anti-IL-6 antibody treatment for the management of Castleman's disease [13]. Nishi et al. reported that the therapeutic mode of action of rituximab involves the depletion of CD-20 positive B cells which is a contributing factor to IL-6, VEGF, and other cytokines dysregulation [14].

In the current study, partial response was seen after the treatment with ABVD courses; however, Mohtaram et al. reported a complete response after four courses of ABVD in patients with coexisting Hodgkin's Lymphoma and Castleman's Disease [15]. Selvaraj and Gudipudi reported two recurrent cases of Hodgkin's lymphoma-associated multicentric Castleman's disease that were managed by radiotherapy and rituximab. Both cases demonstrated remission after 15 months and 42 months of follow-up [16]. Our biopsy examination showed hyperplastic germinal centers with diffused paracortical hyperplasia along with the frequent presence of large, mononucleated immunoblastic-type cells, and small lymphocytes. Maheswaran et al. biopsy findings showed typical follicles and interfollicular plasma cells of the

plasma cell variant in Castleman's disease [17]. Similar findings were exhibited by Osorno et al. who highlighted the presence of reactive follicular hyperplasia with small germinal centers in Hodgkin's disease with Castleman's disease [18]. Gong et al. revealed various follicles with atrophic germinal centers [19].

The extent of the clinical symptoms, as mentioned earlier, can vary greatly, the symptoms being non-specific, from asymptomatic forms to symptoms such as lymphadenopathy accompanied by fever, anemia, fatigue, abdominal or chest pain, and weight loss. Cases with skin symptoms such as paraneoplastic pemphigus, erythema multiforme, or lichen planus have also been described [20].

In conclusion, significant evidence demonstrated the efficacy of rituximab in imparting positive outcomes in patients coexisting with Hodgkin's Lymphoma and Castleman's Disease. In this report, we showed the evolution of multicentric Castleman's disease after autologous stem cell transplantation for Hodgkin's disease. Our findings suggest that histopathological examination is vital for a confirmatory diagnosis of Castleman's disease, and each relapse after a bone marrow transplant should undergo a biopsy for a confirmatory diagnosis of the disease.

AUTHOR CONTRIBUTIONS

Conceptualization, M.A.; methodology, M.A.; validation, M.A.; formal analysis, M.A.; investigation, M.A., N.I., A.L., L.T., V.P. resources, M.A. and A.D.T.; data curation, M.A. and T.T.A.; writing—original draft preparation, M.A.; writing—review and editing, M.A., T.T.A., E.I.; visualization, M.A., N.I., A.L., L.T., V.P.; supervision M.A. and A.D.T.;. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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