Human Herpesvirus Type 8-positive Multicentric Castleman Disease

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Abstract

Castleman disease (CD) is rare lymphoproliferative disorder with local lesionsor with multiple lessions (multicentric CD [MCD]—usually with plasma cell or mix cell morphology). Patients with human herpesvirus (HHV) type 8-positive MCD were included in a separate group owing to its extremely aggressive course and the high risk of transformation into HHV8$^+$ plasmablastic lymphoma. At our hematologic center, from 1996 to the present, the clinical and morphologic features of 87 patients with CD were analyzed. Immunohistochemical examination revealed DNA HHV8$^+$ lymph node tissue in patients with plasma cell and mixed cell morphology. In 45 patients, plasma cell or mixed cell variant CD was diagnosed. In 21 patients (8%), the manifestation of CD was local and in 29 (9%), it was multicentric. HHV8 was identified in only 6 cases (23.1%) of MCD (5 men and 1 woman, with a median age of 48.2 years; range, 36-77 years). The median follow-up point was 39.2 months. In 4 patients, the mixed cell variant was diagnosed and in 2, the plasma cell variant was diagnosed. In all the patients, constitutional symptoms, generalized lymphadenopathy, and hepatosplenomegaly were detected. Various laboratory changes were observed, but the most significant were anemia, thrombocytopenia, hypergammaglobulinemia, M-component, increased erythrocyte sedimentation rate, and circulating immune complexes. In 2 cases of HHV8$^+$ CD, MCD was combined with autoimmune hemolytic anemia and in 2 cases with non-Hodgkin lymphoma. At the last follow-up point, 2 patients were still alive after CHOP (cyclophosphamide, prednisone, Adriamycin, vincristine) and R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate [Oncovin], prednisone) therapy with rituximab maintenance. HHV8$^+$ MCD results in aggressive multiorgan lesions and pronounced changes in laboratory test results. It is characterized by an unfavorable prognosis with a high risk of transformation to plasmablastic lymphoma and a lethal outcome. Timely chemotherapy for patients with HHV8$^+$ MCD can result in remission and prolong life.

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Introduction

Castleman disease (CD; also known as angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder of unknown etiology. It was first described in 1954 by histologist Castleman as a case of benign neoformation of mediastinal lymph nodes in a 41-year-old man with a significant medical history. A solid mass in the mediastinum with regional lymph nodes was successfully removed. The histologic findings were unusual and did not fit any of the known diseases. Gross total resection of the mass led to a full recovery.[1,2] In 1972, Keller et al[3] analyzed the clinical and morphologic data from 182 patients and identified 2 histologic variants of the disease: a hyaline vascular variant, which occurs in 91% of cases, and a plasma cell variant (PCV).

The investigators showed that HVV is, in most cases, localized, with tumors growing slowly over years or even decades. The disease will be asymptomatic until the tumor starts to compress nearby organs. Therefore, the symptoms will be local. With chest localization, the symptoms will include cough, shortness of breath, palpitations, and hemoptysis. With retroperitoneal localization, the symptoms will include abdominal pain, dyspepsia, and/or urinary disorders. The typical histologic pattern of HVV$^+$ CD is characterized by nodal architectural obliteration resulting from abnormal follicles with reduced hyalinized germinal centers surrounded by a broad mantle zone, consisting of concentric layers of lymphocytes with an "onion-skin" appearance and hypervascularization of the interfollicular zone. These modified follicles will usually be

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penetrated by ≥ 1 blood vessels, resembling a "lollipop." Surgical excision of the tumor leads to recovery.[3]

The PCV is characterized by marked constitutional symptoms, including weight loss, sweating, fever, pain, organomegaly, and lymphadenopathy, and laboratory tests changes that include anemia, hypergammaglobulinemia, acceleration of the erythrocyte sedimentation rate, increased levels of C-reactive protein, and circulating immune complexes. The PCV most often manifests as generalized lymph node hyperplasia and hepatosplenomegaly.[3] Morphologic study revealed hyperplastic follicles with a narrow mantle zone and marked plasma cell infiltration of the interfollicular space. PCV has a more aggressive course and a worse prognosis. This variant of the disease requires cytostatic therapy.[3] A number of investigators have identified a mixed cell morphologic variant of CD, with symptoms of both hyaline vascular and plasma cell types and the clinical course of PCV.[4-7] The research by Keller et al,[3] and others,[4-7] led to the introduction of additional clinical classification factors for CD that distinguishes the local (unicentric) and generalized (multicentric) variations.

CD is a disease of unknown etiology. Studies of the CD etiopathogenesis are currently ongoing. First, the pathogenetic theories linking disease progression with lymph node hamartoma, dystopic thymoma, and non-Hodgkin lymphoma have not been confirmed.[2,8,9] In the 1990s, investigators began to study the pleomorphic cytokine interleukin-6 (IL-6) as an etiopathogenetic factor in CD progression. Yoshizaki et al[10] conducted a study of IL-6 expression in the germinal centers of cells in the reactive lymph nodes and the serum IL-6 levels stratified by the morphologic variant of CD. They concluded that dysregulated gene IL-6 expression might be implicated in the etiology of CD.[10]

IL-6 production can be mediated by virus in the case of multicentric CD (MCD). In 1994, Chang et al,[11] in studying the skin areas affected by Kaposi sarcoma, identified DNA fragments of the new gamma-herpesvirus, human herpesvirus type 8 (HHV8), or Kaposi sarcoma-associated herpesvirus, which belongs to the group of oncogenic viruses, capable of producing the viral analogue of endogenous human IL-6, viral IL-6.[12] This virus is most often diagnosed in patients with CD who are seropositive for human immunodeficiency virus (HIV). El-Osta and Kurzrock[13] reported the virus was found in 100% of cases. However, cases of HHV8 infection in HIV-negative patients have also been described.[14-19] The first studies to detect a relation between HHV8 infection and the development of CD were conducted by Soulier et al.[20] In their study, HHV8 was detected in all cases of MCD in HIV-positive patients (14 cases), regardless of the morphologic variant, and in 7 of 17 patients with HIV-negative status, including 2 with HVV, 3 with PCV, and 2 with a mixed cell morphology.[20] Suda et al[21] studied sections from lymph node paraffin blocks using polymerase chain reaction (PCR) from 82 patients with MCD for the presence or absence of latency-associated nuclear antigen-1 (LANA-1) HHV8. In only 3 cases (4%) was the staining positive, and all 3 patients were HIV-positive.[21] Further studies showed that HHV8 infection in HIV-negative patients occurs only in multicentric cases, regardless of the morphologic variant. The most sensitive method for its detection is PCR in real time performed on fresh-frozen lymph node sections or peripheral blood mononuclear cells. However, the PCR method performed on sections from paraffin blocks should not be use because it can result in false-positive and false-negative test results.[22,23]

HHV8$^+$ CD cases are very aggressive and characterized by marked constitutional symptoms, laboratory test changes, and a high risk of plasmablastic lymphoma transformation. Therefore, recently a "variation" in the group of patients with MCD was identified as plasmablastic HHV8-associated MCD. This "variation" was first described in the group of patients with CD complicated by POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome. The morphologic pattern of the lymph nodes resembled that of the PCV, but with a difference: the mantle zone was infiltrated by large plasma cells—plasmablasts with abundant cytoplasm and prominent (≥ 1) nucleoli.[24,25] Therefore, we currently prefer to classify CD in accordance with its histopathogenic type to HVV, PCV, MCD, and HHV8-associated (plasmablastic) variants.[14-19]

CD can be associated with a variety of pathologic conditions, including multiple myeloma, Hodgkin disease and non-Hodgkin lymphoma, POEMS syndrome, and IgG4-associated lymphoproliferative diseases[26] and can transform into Kaposi sarcoma, aggressive plasmablastic lymphoma, and follicular dendritic cells.[27] The differential diagnosis of these pathologic conditions is crucial for patients with CD.

The number of patients with CD in Russia has been increasing annually; however, no common database is available to any hematologist. Malygin and Frank[28] were the first to report a case of CD in Russia in 1975. All subsequent studies have focused on descriptions of single cases of the local hyaline vascular variant. Only in 2005 did Melikyan et al[29] present the first description of a group of 12 patients with different types of CD, including HVV-associated, PCV, and multicentric variant.

Recently, in Russia, an increased scientific interest in CD has occurred, primarily because of its connection to HIV and HHV8. Because of the lack of data on the incidence, clinical course, and factors indicating a poor prognosis, Melikyan et al[30] performed a study that included a large group of HIV-negative patients with a proven diagnosis of CD to detect the clinical course and morphologic features of the HHV8-associated variant of CD.

Materials and Methods

The present study included 87 HIV-negative patients with CD observed in the scientific and clinical department of outpatient care at the National Research Center for Hematology from 1996 to the present. We analyzed the following clinical characteristics: the presence or absence of B-symptoms, generalized lymphadenopathy, organomegaly (hepato- and/or splenomegaly), edema, and autoimmune complications (autoimmune hemolytic anemia and immune thrombocytopenia). The laboratory tests included red blood cell, white blood cell, and platelet counts, serum creatinine, total protein, bilirubin and liver enzyme (aspartate aminotransferase, alanine aminotransferase) tests, erythrocyte sedimentation rate, C-reactive protein, circulating immune complexes, normal immunoglobulin concentration, and the detection of monoclonal secretion.

In all cases, morphologic study of the resected lymph nodes or tumors was performed. The antibody panel for the