Castleman's Disease Confined to the Leptomeninges

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Abstract. We report a rare case of the plasma cell variant of Castleman's disease confined to the leptomeninges in a 42-year-old female. Flow cytometry demonstrated a minor monoclonal kappa light chain population, and conventional Southern blotting confirmed clonal rearrangement of the JH immunoglobulin heavy-chain gene. Polymerase chain reaction for Epstein-Barr virus and Kaposi's sarcoma-associated herpes virus was negative. The patient is disease-free five years after surgical resection. To our knowledge, clonal gene rearrangement has not been previously reported in the plasma cell variant of localized intracranial Castleman's disease.

Keywords: Castleman's disease, angiofollicular lymphoid hyperplasia, heavy-chain gene rearrangement

Introduction

Castleman's disease (CD), or angiofollicular lymphoid hyperplasia, is rarely diagnosed in the central nervous system (CNS), with only nine cases in the literature. We report a 42-year-old female with a nodular, dural-based mass that progressed in size during 3 yr. She underwent craniotomy and complete resection of the mass, which was histologically confirmed as CD of the plasma cell type. At 5 yr after diagnosis, she remains asymptomatic and without evidence of systemic disease. Although plasma cells stained in a polyclonal fashion with antibodies for kappa and lambda light chain, flow cytometry revealed a minor monoclonal kappa light chain population. Conventional Southern blotting confirmed clonal rearrangement of the JH immunoglobulin heavy-chain gene. Polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpes virus (HHV-8) was negative. This is the first report of combined pheno-typic and gene rearrangement studies in the plasma cell variant of CD localized in the intracranial leptomeninges.

Case Report

The patient is a 42-year-old black female with a history of hypertension and asthma, who presented to her primary care physician with complaints of headache and sinusitis. Magnetic resonance (MR) imaging of the brain showed a 3.0 cm homogenously enhancing right frontal dural-based mass thought to be a meningioma. She was followed with serial MR scans over 3 yr, during which a mild increase in the size of the mass was noted. She then underwent a right fronto-temporal craniotomy. Intraoperatively, the greater wing of the sphenoid bone was noted to be hypervascular, and the dura mater was stuck to the underlying cortex. The mass was completely resected over the left superior temporal gyrus, and the patient was discharged from the hospital with no neurological deficits.

Hematoxylin and eosin (H&E) stained sections of the dural-based mass showed numerous well-formed lymphoid follicles with large reactive germinal centers containing tingible body histiocytes (Fig. 1) and some follicles that had small or burned-out germinal centers. The interfollicular regions were populated by a dense and diffuse population of plasma cells that exhibited varied degrees of maturity and extensive single cell necrosis (Fig. 2). Special stains, including the Brown-Brenn stain for bacteria, Dieterle stain for spirochetes, PAS-fungus stain, and Grocott methenamine silver
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Fig. 1. The dural mass shows a lymphoid pattern consisting of secondary lymphoid follicles with reactive germinal centers and intact mantle zones (H&E, original x68).

Fig. 2. The interfollicular areas demonstrate sheets of plasma cells exhibiting varied degrees of maturity and extensive single cell necrosis (H&E, original x680).

stain for fungi did not demonstrate organisms, and no granulomas were identified. Microbiological cultures did not reveal growth. Immunophenotypically, B cells (L26+) and T cells (CD3+) were present, with the B-cell population predominating within the follicles. Immunomarkers for kappa and lambda light chains showed a polyclonal population of plasma cells; however, flow cytometric studies demonstrated a minor monoclonal kappa light chain phenotype. Gene rearrangement studies were performed using Southern blot analysis and confirmed the presence of clonal rearrangement of the J_{H} immunoglobulin heavy-chain. PCR analyses for EBV and HHV-8 were negative.

Thorough postoperative staging studies were performed to rule out the presence of multicentric CD. An iliac crest bone marrow biopsy and aspirate were normal. Serum protein and immunoelectrophoresis, markers for collagen vascular disease, human immunodeficiency virus (HIV), quantitative immunoglobulins, and a Coomb's test were within normal range. MR of the brain revealed no other evidence of disease, and a positron emission tomography (PET) scan showed no abnormal areas of metabolic activity. Currently, at 5 yr post-operation, the patient shows no signs of intracranial recurrence or systemic involvement of CD.

Discussion

In 1954 Castleman described an unusual lymphoid proliferation in the mediastinum which he termed "angiofollicular lymphoid hyperplasia" [1,2]. Subsequently, the disease has been observed in a number of locations as both a localized and a systemic disease. Two main histologic variants are recognized:
Table 1. Ten cases of Castleman's disease involving the central nervous system.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Localized</th>
<th>CD type</th>
<th>Clonality</th>
<th>HHV-8</th>
<th>EBV</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulati et al [6]</td>
<td>47 y</td>
<td>F</td>
<td>parafalcine</td>
<td>yes</td>
<td>H-V mono, κ</td>
<td>neg</td>
<td>neg</td>
<td></td>
<td>3 mo</td>
</tr>
<tr>
<td>Hashimoto et al [7]</td>
<td>62 y</td>
<td>F</td>
<td>tentorium</td>
<td>yes</td>
<td>H-V yes</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>5 mo</td>
</tr>
<tr>
<td>Lacombe et al [8]</td>
<td>30 y</td>
<td>F</td>
<td>tentorium</td>
<td>yes</td>
<td>inter</td>
<td>NA</td>
<td>NA</td>
<td>10 y</td>
<td></td>
</tr>
<tr>
<td>Gianaris et al [9]</td>
<td>63 y</td>
<td>F</td>
<td>parafalcine</td>
<td>yes</td>
<td>H-V mono, κ</td>
<td>NA</td>
<td>NA</td>
<td>3 y</td>
<td></td>
</tr>
<tr>
<td>Severson et al [10]</td>
<td>25 y</td>
<td>M</td>
<td>parietal</td>
<td>yes</td>
<td>H-V poly</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Severson et al [10]</td>
<td>82 y</td>
<td>F</td>
<td>parietal</td>
<td>yes</td>
<td>H-V poly</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Severson et al [10]</td>
<td>73 y</td>
<td>F</td>
<td>occipital</td>
<td>yes</td>
<td>PC mono, κ</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Alper et al [11]</td>
<td>10 y</td>
<td>M</td>
<td>C6-T2</td>
<td>yes</td>
<td>NA poly</td>
<td>NA</td>
<td>NS</td>
<td>8 mo</td>
<td></td>
</tr>
<tr>
<td>Stanley et al [12]</td>
<td>64 y</td>
<td>M</td>
<td>CSF</td>
<td>no</td>
<td>PC poly</td>
<td>NA</td>
<td>NA</td>
<td>2 y</td>
<td></td>
</tr>
<tr>
<td>This report</td>
<td>42 y</td>
<td>F</td>
<td>frontal</td>
<td>yes</td>
<td>PC mono, κ</td>
<td>neg</td>
<td>neg</td>
<td>5 y</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: inter = intermediate; mono = monoclonal; poly = polyclonal; k = kappa light chain restriction; neg = negative; NA = not available; H-V = hyaline-vascular type; PC = plasmacellular; C = cervical vertebra; T = thoracic vertebra.

the more common hyaline-vascular or angiofollicular type, and the less common plasma cell type [3]. Clinically, CD may be divided into a solitary or unicentric form, and a multicentric form. Most cases of the solitary form are histologically of the hyaline-vascular type and occur in asymptomatic patients, whereas the plasma cell type of the solitary form may be associated with patients who exhibit fever, anemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, and hypoalbuminemia [3]. The multicentric form is commonly of the plasma cell type, and patients usually present with generalized lymphadenopathy. The natural progression of the multicentric form is generally poor, with eventual renal or pulmonary complications. Some patients with systemic CD seem at risk for the development of plasmacytoma and large B-cell lymphoma, with frequent evidence of clonal rearrangements of immunoglobulin and T-cell receptor genes [4,5].

Nine reported cases of CD in the CNS are summarized in Table 1 [6-12]. Seven cases had intracranial involvement [6-10], one was a spinal epidural mass [11], and one had negative neuroimaging although CNS involvement was confirmed by cytological examination of the cerebrospinal fluid [12]. Two cases were described as the plasma cell variant, one of which was multicentric [12]; the other was isolated to the leptomeninges [10]. Neither case report, however, described confirmation of a monoclonal component with flow cytometry, gene rearrangement with Southern blotting, or PCR analyses for EBV and HHV-8. One case involved the cervicothoracic epidural space and the report did not describe the presence of a monoclonal component [11]. Five cases were described as hyaline-vascular CD confined to the leptomeninges [7,10]. One case, which was described as intermediate, had a 10-yr disease-free followup [8]. A monoclonal kappa light chain population was confirmed in three cases by flow cytometry [6,9,10], and none used PCR to detect EBV and HHV-8. In all intracranial cases, MR typically demonstrated nodular, contrast-enhancing, dural-based masses similar to meningioma.
The histopathologic differential diagnosis of intracranial CD includes plasma cell granuloma, sarcoidosis, inflammatory meningeal masses of unexplained origin [13], infectious agents including syphilis, and plasmacytoma. When considering the differential diagnosis, the classical Castleman lesion typically develops independent of other masses or neoplasms. Chronic inflammatory infiltrates can be identified in conventional meningiomas, especially the lymphoplasmacytic variant and the chordoid variant [14]. The lymphoplasmacytic variant of meningioma shows lobules of meningothelial cells accompanied by a prominent chronic inflammatory response composed of lymphocytes, plasma cells, and germinal centers. The polyclonal nature of the inflammatory cells indicates that they are reactive rather than neoplastic. The chordoid variant of meningioma has been associated with massive peritumoral polyclonal lymphoplasmacellular infiltrates with follicles, germinal centers, and thick-walled blood vessels with an onion-skin pattern. These features were described by Kepes et al [14] as reminiscent of angiofollicular hyperplasia. Young patients with the chordoid variant of meningioma and peritumoral lymphoplasmacellular follicle-forming reaction preoperatively demonstrated various systemic manifestations of CD, including iron-resistant hypochromic microcytic anemia and dysgamma-globulinemia [14]. The reason for this is unclear, and none of the patients had evidence of a primary lymphoplasmacellular proliferative mass.

CD of plasma cell type is characterized histologically by multiple discrete lymph nodes with a recognizable nodal architecture, germinal center hyperplasia, and marked plasmacytosis defined by sheets of plasma cells in the interfollicular tissue. Although numerous plasma cells may be found in some cases of the hyaline-vascular type, they are admixed amongst a mononuclear cell population and do not form solid sheets [3]. In CD of the plasma cell type, two characteristic patterns have been described that appear to represent distinct phases in the evolution of the disorder: an early "proliferative" pattern, with marked proliferation of venules and plasmacytoid immunoblasts that leads to a blurring of architectural marking; and a later "accumulative" pattern, with distinct germinal centers separated by sheets of mature plasma cells and no excess of blood vessels or immunoblasts [15]. Evidence suggests that CD might be a disorder of auto-antibody producing CD5-positive B cells [16]. The hypothesis is that these cells, under the effect of interleukin-6 produced by germinal center cells, undergo unregulated proliferation and differentiation into plasma cells.

Human herpesvirus 8, also known as Kaposi's sarcoma–associated herpesvirus, is a member of the g-herpesvirus family which encodes oncoproteins or cell signaling proteins. This DNA tumor virus is the causative agent of HIV-associated and non-HIV-associated Kaposi's sarcoma, and it is also present in a large proportion of extracranial multicentric CD, particularly those associated with HIV infection [17]. Additionally, HHV-8 has been implicated in the pathogenesis of primary effusion lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, sarcoidosis, and pemphigus. It has been suggested that the pathogenesis of monoclonal gammopathies may be related to HHV-8 infection of bone marrow stromal dendritic cells [18]. Viral particles suggestive of a D-type retrovirus have been reported in a case of isolated leptomeningeal hyaline-vascular CD, possibly indicating that a viral infection other than HHV-8 may cause an extranodal lymphoproliferative reaction [6].

The incidence of CD is increased in immunodeficient patients, and in patients with associated autoimmune phenomena such as the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma, skin changes), temporal arteritis, and autoimmune cytopenias. Nonetheless, the present case, as others [6], have occurred in patients without immunodeficiency or autoimmune disease. Although the presence of a monoclonal population of plasma cells has been suggested to portend a malignant potential [10], disease-free survival for 5 yr in the present case suggests that clonality in localized CD may not be a poor prognostic feature.

References


