Intracranial Localized Castleman’s Disease
—Case Report—

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Abstract

A 68-year-old woman presented with generalized clonic seizure following a 2-month history of initiative loss, incoherent speech, headache, and left hemiparesis. No systemic signs or symptoms were seen and laboratory studies were within normal range. Computed tomography and magnetic resonance imaging demonstrated a well-delineated small mass with homogeneous enhancement in the right parietal convexity, associated with unusually extensive perifocal edema compared to the size of the mass. Cerebral angiography showed a faint stain fed by the middle meningeal artery. These imaging features were very similar to those of meningioma. Full recovery from the symptoms was achieved by total removal of the lesion and no recurrence was found after 3 years. Histological examination identified the hyaline-vascular type of angiofollicular lymph node hyperplasia (Castleman’s disease). Castleman’s disease involving the central nervous system is rare, with only 12 previous cases, but should be considered in the diagnosis of intracranial meningeal tumors. The treatment of choice for localized Castleman’s disease is complete surgical resection, which is curative in most of the cases.

Key words: Castleman’s disease, angiofollicular lymph node hyperplasia, meningeal mass, meningioma, neuroradiological feature

Introduction

Castleman’s disease or angiofollicular lymph node hyperplasia is a rare pathologic process of unknown etiology, characterized by nonneoplastic reactive proliferation of lymphoid tissue. Two histological types of Castleman’s disease are recognized. The hyaline-vascular type accounts for about 85–90% of all cases, and manifests as small, hyalinized follicular centers with radially penetrating vessels and prominent interfollicular capillary proliferation. The plasma cell type occurs in only 5–10% of cases, and consists of larger hyperplastic lymphoreticular follicles separated by sheets of polyclonal mature plasma cells and less vascular stroma. In addition, an intermediate type has occasionally been described consisting of both types.

The clinical features of Castleman’s disease are also classified into two categories, localized and generalized. Most patients with localized Castleman’s disease are usually asymptomatic at presentation, although symptoms due to compression of adjacent structures may occur. The localized form is typically the hyaline-vascular type and the prognosis is thought to be good as recurrence after radical resection is rare. This form may represent reactive lymphoid hyperplasia due to chronic antigenic stimulation from viral infection or developmental disturbance such as hamartomatous processes. Generalized Castleman’s disease is a more aggressive multifocal form with a potentially malignant profile, for example, in association with polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinemia, and skin changes (POEMS), Hodgkin’s disease, Kaposi’s sarcoma, and acquired immunodeficiency syndrome. Most patients with the generalized form present with systemic symptoms such as fever, weight loss, anemia, and hypergobulinemia. The plasma cell type is preponderant in this form. Generalized Castleman’s disease is thought to involve dysregulation of interleukin-6 which stimulates B lymphocytes to transform immunoglobulin-producing plasma cells and dysplastic or neoplastic lymphoproliferative processes.
Castleman's disease may occur at any site with lymph nodes and extranodal areas, and most frequently involves the mediastinum, abdomen, neck, and axillae, and less commonly, the retroperitoneum, mesentery, and pelvis, although extranodal lesions have also occurred in the lungs, thymus, pericardium, and vulva. Intracranial involvement is extremely rare, with only 12 previously reported cases. Careful analysis of the clinical and radiological data is necessary to identify and treat this uncommon disease appropriately.

We describe a case of localized intracranial Castleman's disease and discuss the diagnostic features with particular emphasis on neuroimaging.

**Case Report**

A 68-year-old woman presented with a 2-month history of initiative loss and incoherent speech. Later she noticed slight weakness of her left arm and leg associated with mild headaches. Two weeks before admission, her verbal responses became ambiguous and the intensity of her headaches abruptly increased. Neurological examination on admission revealed somnolence, disorientation, and mild left hemiparesis. On the day after admission, she suffered generalized clonic seizure that required intravenous administration of phenytoin for control. Seizures were subsequently controlled with oral phenytoin therapy. Chest radiography, electrocardiography, and peripheral blood cell and biochemical laboratory examinations found no abnormalities.

Computed tomography (CT) showed a small mass with homogeneous enhancement after injection of contrast material in the right parietal convexity (Fig. 1), surrounded by localized edema in the right parietal white matter. No calvarial change was found near the mass. Magnetic resonance (MR) imaging demonstrated a tiny mass of about 7 mm diameter in the right parietal convexity that was homogeneously enhanced by administration of contrast material (Fig. 2A). No abnormal meningeal enhancement continuous to the mass was apparent. The mass was isointense to the gray matter on fluid-attenuated inversion recovery (FLAIR), T1-weighted, and T2-weighted MR images, and high intensity on diffusion-weighted MR images (Fig. 2B, C). The interface between the mass and the brain appeared as a hypointense rim on FLAIR, T2-weighted, and diffusion-weighted MR images (Fig. 2B, C). Brain

![Fig. 1 Preoperative computed tomography scans showing a small mass in the right parietal convexity as an isodense mass (arrow, A), with homogeneous enhancement (arrow, B).](image1)

![Fig. 2 A: T1-weighted magnetic resonance (MR) image showing a tiny mass in the right parietal convexity with homogeneous enhancement (arrow). B: T2-weighted MR image showing a small isointense mass (arrow) with a hypointense rim and notable brain edema in the surrounding white matter (arrowheads). C: Diffusion-weighted MR image revealing a small mass with hyperintense center and thick hypointense periphery (arrow).](image2)
edema surrounding the mass was extensive in comparison to the size of the mass (Fig. 2B). CT and MR imaging detected no sign of calcification in the mass. Right external carotid angiography revealed a faint stain fed by the frontal branch of the middle meningeal artery (Fig. 3), whereas right internal carotid angiography showed no abnormality. Thallium-201 chloride single photon emission computed tomography indicated no abnormal uptake.

Based on the neuroradiological findings, the diagnosis was convexity meningioma. The mass seemed to be a metastatic tumor because of the remarkable perifocal edema compared to the tiny lesion, so various systemic examinations were performed. However, gallium and bone scintigraphy of the whole body, abdominal echography, and endoscopy of the digestive organ found no abnormalities. The levels of tumor markers (α-fetoprotein, carcinoembryonic antigen, squamous cell carcinoma-related antigen, neuron-specific enolase, and carbohydrate antigen 19-9) were also within normal limits.

A right parietal craniotomy was performed and the dural-based solid mass was carefully separated from the underlying brain. No significant adhesion was seen between the mass and the brain. The mass was totally removed together with the dura mater around the attachment. The surgical findings were compatible with meningioma. The patient had an uneventful postoperative course. Postoperative MR imaging confirmed total removal of the mass. She was discharged without neurological deficit 2 weeks after surgery. MR imaging obtained 6 months later showed the brain edema had disappeared. After follow up for 3 years, she remained seizure free without anticonvulsant medication and MR imaging found no recurrence of the mass.

**Fig. 3** Right external carotid angiogram showing a faint stain (arrow) fed by the middle meningeal artery.

**Fig. 4** A: Photomicrograph showing concentric rings of small lymphocytes surrounding germinal centers and numerous hyalinized vessels. Hematoxylin-eosin stain, original magnification ×80. B, C: Photomicrographs of immunohistochemical staining for CD 3 (B) and CD 20 (C) showing mature T and B cells mainly distributed in the interfollicular area. Original magnification ×100.
Table 1  Clinical findings of intracranial Castleman’s disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author (Year)</th>
<th>Age/Sex</th>
<th>Clinical sign</th>
<th>Location</th>
<th>Treatment</th>
<th>Outcome*</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lacombe et al. (1983)</td>
<td>18/F</td>
<td>seizure, increased ICP</td>
<td>rt posterior fossa</td>
<td>TR</td>
<td>ND/NR (8 yrs)</td>
<td>IM</td>
</tr>
<tr>
<td>2</td>
<td>Severson et al. (1988)</td>
<td>25/M</td>
<td>seizure</td>
<td>rt parietal convexity</td>
<td>TR</td>
<td>ND</td>
<td>HV</td>
</tr>
<tr>
<td>3</td>
<td>Severson et al. (1988)</td>
<td>82/F</td>
<td>seizure</td>
<td>rt parietal convexity</td>
<td>TR</td>
<td>ND</td>
<td>HV</td>
</tr>
<tr>
<td>4</td>
<td>Gianaris et al. (1989)</td>
<td>63/F</td>
<td>focal sign, seizure</td>
<td>lt occipital convexity</td>
<td>TR</td>
<td>hemianopsia</td>
<td>PC</td>
</tr>
<tr>
<td>5</td>
<td>Gulati et al. (1998)</td>
<td>63/F</td>
<td>focal sign</td>
<td>bifrontal parafalx</td>
<td>TR, IR</td>
<td>ND/NR (3 yrs)</td>
<td>HV</td>
</tr>
<tr>
<td>6</td>
<td>Gulati et al. (1998)</td>
<td>47/F</td>
<td>headache</td>
<td>lt frontal parafalx</td>
<td>PR, IR</td>
<td>ND</td>
<td>HV</td>
</tr>
<tr>
<td>7</td>
<td>Hashimoto et al. (1999)</td>
<td>47/F</td>
<td>focal sign</td>
<td>rt tent</td>
<td>TR</td>
<td>ND/NR (5 mos)</td>
<td>HV</td>
</tr>
<tr>
<td>8</td>
<td>Cummings et al. (2000)</td>
<td>42/F</td>
<td>headache</td>
<td>rt frontal convexity</td>
<td>TR</td>
<td>ND/NR (5 yrs)</td>
<td>PC</td>
</tr>
<tr>
<td>9</td>
<td>Ropponen et al. (2002)</td>
<td>31/F</td>
<td>seizure</td>
<td>cerebral falx</td>
<td>TR</td>
<td>not described</td>
<td>IM</td>
</tr>
<tr>
<td>10</td>
<td>Sotrel et al. (2003)</td>
<td>65/M</td>
<td>seizure</td>
<td>frontal convexity</td>
<td>TR</td>
<td>ND</td>
<td>HV</td>
</tr>
<tr>
<td>11</td>
<td>Sotrel et al. (2003)</td>
<td>8/F</td>
<td>seizure</td>
<td>lt parietal convexity</td>
<td>TR</td>
<td>ND</td>
<td>HV</td>
</tr>
<tr>
<td>12</td>
<td>Delmont et al. (2003)</td>
<td>26/F</td>
<td>focal sign</td>
<td>paracavernous sinus</td>
<td>PR, IR</td>
<td>ND</td>
<td>HV</td>
</tr>
<tr>
<td>13</td>
<td>Present case</td>
<td>68/F</td>
<td>focal sign, seizure</td>
<td>rt parietal convexity</td>
<td>TR</td>
<td>ND/NR (3 yrs)</td>
<td>HV</td>
</tr>
</tbody>
</table>


Histological examination of the surgical specimens revealed numerous lymphoid follicles with germinal centers of varying sizes. Hyalinized vascular proliferation was seen in the interfollicular zone that consisted mainly of small lymphocytes with scattered eosinophils and plasma cells (Fig. 4A). Sporadic foci of chronic hemorrhage containing hemosiderin deposits were seen in the capillaries of the fibrous capsule. Immunohistochemical staining showed a normal distribution of B and T cells (Fig. 4B, C) and the polyclonal nature of the lymphocytes. The histological diagnosis was the hyaline-vascular type of Castleman’s disease.

Discussion

Castleman's disease involving the central nervous system has been reported in 12 cases in the intracranial area[^8][^11][^13][^14][^18][^29][^30][^32] and four in the spinal epidural space.[^1][^9][^15][^20] The clinical findings of intracranial Castleman's disease are summarized in Table 1. All patients with intracranial Castleman’s disease had the localized form. The 11 female and two male patients were aged 8 to 82 years (mean 50.2 years). The clinical manifestations at presentation included seizure (n = 8) and focal neurological sign (n = 5). Only one patient had symptoms due to increased intracranial pressure. Nine cases were the hyaline-vascular type, two were the plasma cell type, and two were the intermediate type. Gross total removal of the lesion was achieved in all but two cases and the surgical outcome was excellent in all cases. Follow-up study was possible in five cases including the present case. No recurrence was found. The clinical features such as good prognosis after surgical removal, predominance of middle-aged patients and the hyaline-vascular type are similar to those of localized Castleman’s disease at other sites,[^10][^25] whereas all patients had symptomatic signs in contrast to the usually asymptomatic cases of the localized form at other sites.

The neuroimaging findings of intracranial Castleman’s disease are shown in Table 2. The most distinctive feature is the location of the lesion, as a solitary mass arising from the dura mater or leptomeninges in all patients. The most common site was the cerebral convexity (n = 7) followed by the parafalcine dura mater (n = 3). Although the origin of the dural or leptomeningeal lymphoid tissue is unknown, clonal proliferation of follicular dendritic cells has been reported in the hyaline-vascular type.[^5]
<table>
<thead>
<tr>
<th>Case No.</th>
<th>CT</th>
<th>MR imaging</th>
<th>Cerebral angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>not described</td>
<td>not described</td>
<td>no stain, no feeder</td>
</tr>
<tr>
<td>2</td>
<td>6.5 cm round mass</td>
<td>not described</td>
<td>normal findings</td>
</tr>
<tr>
<td>3</td>
<td>5 × 3 × 1 cm mass, perifocal edema, midline shift</td>
<td>not described</td>
<td>no stain, mass effect</td>
</tr>
<tr>
<td>4</td>
<td>3.5 × 2.5 × 2 cm mass, perifocal edema</td>
<td>not described</td>
<td>not described</td>
</tr>
<tr>
<td>5</td>
<td>mass with HE, perifocal edema</td>
<td>significant perifocal edema</td>
<td>no stain, no feeder</td>
</tr>
<tr>
<td>6</td>
<td>5 × 5 × 2 cm mass with HE, perifocal edema, mass effect</td>
<td>mass with HE, invasion into the sulcal space, significant perifocal edema, mass effect, dural enhancement</td>
<td>not described</td>
</tr>
<tr>
<td>7</td>
<td>small mass with HE, perifocal edema</td>
<td>small mass with HE, T1: iso, T2: iso, dural enhancement, perifocal edema</td>
<td>not described</td>
</tr>
<tr>
<td>8</td>
<td>not described</td>
<td>3 cm mass with HE</td>
<td>not described</td>
</tr>
<tr>
<td>9</td>
<td>tumor-like lesion (few cm diameter, 2 cm thick)</td>
<td>not described</td>
<td>not described</td>
</tr>
<tr>
<td>10</td>
<td>not described</td>
<td>large frontal meningeal mass</td>
<td>not described</td>
</tr>
<tr>
<td>11</td>
<td>small mass with calcification, perifocal edema</td>
<td>small mass with HE, T2: low, significant perifocal edema, focal cortical enhancement</td>
<td>not described</td>
</tr>
<tr>
<td>12</td>
<td>mass with HE</td>
<td>mass with HE, T1: iso, T2: iso, dural enhancement</td>
<td>not described</td>
</tr>
<tr>
<td>13</td>
<td>small mass with HE, perifocal edema</td>
<td>T1: iso with HE, T2 &amp; FLAIR: iso with low rim, DW: high with low rim, perifocal edema</td>
<td>faint stain, feeder = MMA</td>
</tr>
</tbody>
</table>


A large number of dendritic cells participate in inducing and regulating immune responses against pathogens and/or autoantigens in the dura mater, leptomeninges, and choroid plexus in the rat. In addition, both myeloid and plasmacytoid dendritic cells were detected in the brain tissue of mice with infection and autoimmune encephalitis, and also in the cerebrospinal fluid of humans with primary inflammatory disorders of the central nervous system. Ultrastructural analysis of surgical specimens obtained from localized leptomeningeal Castleman’s disease demonstrated 100-nm viral-like particles within follicular dendritic cells as well as intercellular spaces. Presumably the dendritic cells develop from the cells resident in the dura mater or leptomeninges, and/or migrate to the dura mater or leptomeninges from the peripheral tissue via the blood mediated by some chemical effect induced by inflammation and/or dysregulation of the immune system.

Another characteristic neuroimaging finding was the extensive brain edema compared with the size of the mass. Seven patients presented with perifocal edema and four had remarkable edema in spite of the small mass without apparent compression of the underlying brain. Various factors are correlated with edema associated with meningioma, including tumor size, location, histological subtype, growth rate, and vascularity of the tumor. The pathogenesis of peritumoral brain edema in meningioma may involve impaired microcirculation and/or venous drainage of the surrounding brain due to mechanical compression, hydromechanical concepts of vasogenic edema based on the hydraulic pressure between the tumor and the underlying brain, and secretion of fluid or chemical factor inducing brain edema from the tumor. Recently, a significant correlation was found between the amount of peritumoral edema and vascular endothelial growth factor (VEGF) expression in some brain tumors including meningioma. Most patients with intracranial Castleman’s disease had neither invasion into the brain parenchyma nor significant compression of the brain parenchyma, so chemical substances released from the mass such as VEGF presumably caused the extensive brain edema.

CT showed the mass as isodense except in one patient with a mineralization nodule within the mass appearing as hyperdense. MR imaging showed well-defined solid masses appearing as

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The hypointensity of the peripheral rim was more prominent on the $T_2$- and diffusion-weighted images, and histological examination confirmed chronic hemorrhage within the fibrous capsule. The hypointensity of the peripheral rim may reflect preferential $T_2$ proton relaxation enhancement due to the paramagnetic effect of hemosiderin deposit. Localized Castleman’s disease may be associated with insidious hemorrhage showing MR imaging findings similar to those of cavernous angioma.

The typical angiographical appearance of Castleman’s disease is remarkable neovascularity with homogeneous capillary blush but previous intracranial cases showed no staining. The present case is the first to show staining of the mass supplied from the middle meningeal artery. Based on the view that all cases of intracranial Castleman’s disease contain abundant vessels and originate in the dura mater or leptomeninges, the mass is likely to show staining fed by the dural meningeal artery.

Localized intracranial Castleman’s disease manifests as seizure or focal signs attributed to the involved area and appears as a solid extraxial mass with significant enhancement by contrast medium. These findings are similar to those of meningioma. CT and MR imaging show extensive perifocal brain edema compared to the size of the mass. Castleman’s disease is a rare entity in the central nervous system, but should be considered in the differential diagnosis of intracranial meningeal tumors.

References


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