Pyrogenic cytokine interleukin-6 expression by a chordoid meningioma in an adult with a systemic inflammatory syndrome

Case report and review of the literature

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Chordoid meningioma is a rare meningothelial tumor characterized by chordoma-like histological features with lymphoplasmacellular infiltration. This tumor is often seen in children, but not in adults, with a systemic inflammatory syndrome (iron-resistant microcytic anemia and/or dysgammaglobulinemia) and very rarely with a persistent moderate hyperthermia.

In the present report the authors describe a temporal chordoid meningioma in a 30-year-old woman who presented with fever, headache, and a serological inflammatory syndrome. The clinical symptomatology, chiefly the fever, disappeared immediately after removal of the tumor. To our knowledge, only one similar patient with such clinical presentation and response to surgery has been mentioned in the literature. Interestingly, at immunohistochemical examination, the neoplasm showed focal positivity for the pyrogenic cytokine interleukin-6. The capacity of the tumor to produce this pyrogenic cytokine could explain both the patient’s clinical presentation and her response to the surgical management.

KEY WORDS • chordoid meningioma • pyrogenic cytokine • interleukin-6 • tumor necrosis factor • inflammatory syndrome

Chordoid meningioma is a rare tumor characterized by chordoma-like histological features and lymphoplasmacellular infiltration. In pediatric patients, but not in adults, chordoid meningioma is often associated with a systemic inflammatory syndrome that dramatically improves after tumor removal. To our knowledge, only one adult patient with chordoid meningioma and systemic inflammatory syndrome characterized by fever has been reported in the literature (Table 1).

Here, we report on a 30-year-old woman with a 3-month history of persistent fever, which was a part of a systemic inflammatory syndrome of unknown origin. After numerous examinations conducted at another institution, MR imaging revealed a right temporal mass. Excision of the mass, a chordoid meningioma, was followed by immediate resolution of the fever. Considering that in a child with a rhabdoid atypical meningioma with similar clinical presentation and response to tumor excision, the systemic manifestations were related to tumor-produced pyrogenic cytokines IL-6 and TNFα, we searched for the expression of these cytokines in the tumor samples obtained in our patient. Only expression of the pyrogenic cytokine IL-6 was found.

Case Report

History. This 30-year-old woman was admitted to our department in January 2003. She had a 3-month history of headache, diffuse myalgia and arthralgia, and fever (38 to 38.5°C) that were unresponsive to antiinflammatory drugs and broad-spectrum antibiotic agents. In another hospital, blood and CSF had been cultured, and serological autoantibodies research, skeletal scintigraphy, and abdominal and thoracic computerized tomography scanning were performed, all with negative results. An MR image of the brain revealed a round, right 3-cm-diameter temporal lesion. On T1-weighted MR images, the lesion was iso- to slightly hypointense and enhanced homogeneously with administration of Gd; no “dural-tail” was detected (Fig. 1A and B). On
TABLE 1
Synopsis of chordoid meningiomas reported in the literature*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Mean Age in Yrs (range)</th>
<th>Associated Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kepes, et al., 1988</td>
<td>7</td>
<td>14.7 (8–19)</td>
<td>anemia</td>
</tr>
<tr>
<td>Glässer, et al., 1993</td>
<td>1</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Zuppan, et al., 1994</td>
<td>1</td>
<td>10</td>
<td>none</td>
</tr>
<tr>
<td>Kumar, et al., 1996</td>
<td>1</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Civit, et al., 1997</td>
<td>1</td>
<td>21</td>
<td>anemia, fever, elevated ESR</td>
</tr>
<tr>
<td>Kobata, et al., 1998</td>
<td>1</td>
<td>15</td>
<td>anemia</td>
</tr>
<tr>
<td>Kajiwara, et al., 1999</td>
<td>1</td>
<td>52</td>
<td>none</td>
</tr>
<tr>
<td>Shino, et al., 1999</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Couce, et al., 2000</td>
<td>42</td>
<td>47.4 (12–77)</td>
<td>none</td>
</tr>
<tr>
<td>Yano, et al., 2000</td>
<td>1</td>
<td>44</td>
<td>none</td>
</tr>
<tr>
<td>Lee, et al., 2001</td>
<td>1</td>
<td>55</td>
<td>increased gammaglobulinemia</td>
</tr>
<tr>
<td>Mori, et al., 2001</td>
<td>1</td>
<td>62</td>
<td>none</td>
</tr>
<tr>
<td>de Tella, et al., 2003</td>
<td>2</td>
<td>52 &amp; 19</td>
<td>none</td>
</tr>
<tr>
<td>Varma, et al., 2003</td>
<td>2</td>
<td>20 &amp; 33</td>
<td>elevated ESR in 1 patient</td>
</tr>
<tr>
<td>Yeon, et al., 2003</td>
<td>1</td>
<td>33</td>
<td>none</td>
</tr>
<tr>
<td>Inagawa, et al., 2004</td>
<td>1</td>
<td>57</td>
<td>none</td>
</tr>
<tr>
<td>Salinero, et al., 2004</td>
<td>1</td>
<td>45</td>
<td>none</td>
</tr>
<tr>
<td>Soo, et al., 2004</td>
<td>1</td>
<td>60</td>
<td>none</td>
</tr>
</tbody>
</table>

* NA= not available.

T1-weighted MR images, the mass was hyperintense and surrounded by edema (Fig. 1C). The patient was therefore transferred to our department.

**Examination and Further Assessment.** At admission, the patient had a temperature of 38.5°C, a stiff neck, sore muscles and joints, and normal fundus oculi and internal organs, including liver and spleen. No peripheral lymph nodes were noted. Laboratory findings included a 36.8% hematocrit level, a hemoglobin count of 10.9 g/dl, mean corpuscular volume of 84 fl, mean corpuscular hemoglobin of 25 pg, and mean corpuscular hemoglobin concentration of 29.4 g/dl. The white blood cell count showed a neutrophilic leukocytosis (10.89 × 10⁹/L). An infectious disease was excluded by serological findings had returned to normal. Control MR studies confirmed the total excision of the tumor.

**Histopathological Findings.** The tumor was fixed in formalin and embedded in paraffin according to standard procedures. Histological studies were performed with hematoxylin/eosin and reticulin silver staining. Slides were processed for immunohistochemistry on an automated staining system (Autostainer; Dako Cytomation, Glostrup, Denmark) by using antibodies for CD3 (dilution 1:100; Ylem, Avezzano, Italy), CD20 (dilution 1:200; Ylem), CD68 (PGM-1, dilution 1:400; Dako Cytomation), S100 (dilution 1:200; Ylem), CD34 (dilution 1:50; Dako Cytomation), SMA (dilution 1:100; Ylem), cytokeratin (ae1/ae3, dilution 1:100; Ylem), EMA (dilution 1:100; Ylem), GFAP (dilution 1:1000; Ylem), and vimentin (dilution 1:200; Ylem). The proliferation index was evaluated using the antibody against MIB-1 antigen (dilution 1:100; Dako Cytomation).

On microscopic examination, the tumor displayed two different components. The first component was that of elongated spindle cells with irregular nuclei, arranged in whorls and nests. The second component (80% of the tumor) consisted of chordoidlike features formed by epithelial-like cells, which were arranged in chords and dispersed in a myxoid background (Fig. 2A). Both components were positive for vimentin and EMA. The CD34, S100, SMA, GFAP, and cytokeratins were negative. The tumor showed a proliferation index (MIB-1 staining) of 8 to 10%. The mitotic range varied from 5 to 7 per 20 hpfs. A moderate inflammatory component was present throughout the tumor and was composed mainly of macrophages (CD68 positive) and T lymphocytes (CD3 positive). Only a few B lymphocytes (CD20 positive) were identifiable in the tumor.

The tumor specimens were also tested for the expression of IL-6 (dilution 1:20; R&D, Minneapolis, MN) and TNFα (dilution 1:50; Santa Cruz Biotechnology, Inc., Santa Cruz, CA). The tumor was focally positive for IL-6 (Fig. 2B) but not for TNFα; isolated inflammatory cells, including macrophages and lymphocytes, were stained with anti–IL-6 antibody.

**Discussion**

Here we present an unusual case of an adult woman who developed a systemic inflammatory syndrome, mainly characterized by a febrile status and diffuse muscle and joint

![Fig. 1. Magnetic resonance images. A: Axial T1-weighted MR image without Gd enhancement, revealing hypointensity in the mesial aspect of the right temporal lobe. B: Coronal Gd-enhanced T1-weighted image revealing the mass. C: Axial T1-weighted image demonstrating the right temporal mass and the surrounding brain edema.](image)
Pyrogenic cytokine IL-6 expression by a chordoid meningioma

Fig. 2. Histological and immunohistochemical features of the tumor. A: Microscopically, the tumor shows frank chordoid features composed by epithelial-like cells that are dispersed in a myxoid background. H & E. B: The immunohistochemical analysis showed a cluster of neoplastic cells presenting cytoplasmatic staining for IL-6. Scale bar = 50 μm (A), 30 μm (B).

pain. After negative results of numerous examinations, an MR image of the brain revealed a right temporal mass for which the patient was transferred to our neurosurgical department. Immediately after excision of the tumor, which was a chordoid meningioma, the patient’s febrile state resolved. To our knowledge, this case involves the second adult patient with a systemic inflammatory syndrome associated with a space-occupying intracranial mass but not to any systemic inflammatory syndrome. In three cases, information on systemic manifestations was not provided.

The role of lymphocyte infiltration in chordoid meningiomas is still unclear. Kobata, et al., reported that the infiltration was mainly constituted by B lymphocytes and plasma cells in chordoid meningiomas whereas it was from T cells in all meningiomas. Moreover, it has been observed that the lymphocyte infiltration of chordoid meningiomas consisted mainly of B cells in young patients with systemic inflammatory syndrome and T cells in adult cases. It has been hypothesized that B-cell infiltration of the tumor could be characteristic in young patients with a systemic inflammatory syndrome. In our adult patient with a systemic inflammatory syndrome, however, the lymphocyte infiltration of the tumor consisted mainly of macrophages and T cells with a few B cells.

The cause of the systemic inflammatory syndrome in patients with chordoid meningioma is also still unclear. As the main pathophysiological mechanism, an immunological reaction associated with the characteristic lymphocytic infiltration has been suggested. Civit and colleagues proposed a chemical antigenic stimulus due to tumor cells.

Regarding a 9-year-old child affected by a rhabdoid atypical meningioma, Ritterodt and associates suggested that the fever, headache, arthralgia, and hepatosplenomegaly could be caused by the pyrogenic cytokines TNFα and IL-6 produced by tumor cells. Similarly, in our case, the pyrogenic IL-6 was detected in the chordoid meningioma samples. It seems that IL-6 acts at the end of the cytokine cascade, leading to fever, with the target being the anterior hypothalamus by signaling thermoregulatory neurons via prostaglandin-dependent pathways. The removal of the mass, that is the elimination of the source of IL-6, could explain the immediate subsiding of the fever in our patient. Considering that fever may be caused by many types of pyrogens produced by inflammatory cells, such as inflammatory cytokines, prostaglandins, and free radicals, and that the tumor in our patient was also infiltrated by inflammatory cells, we cannot attribute the fever only to IL-6 production.

Conclusions

Chordoid meningioma is mainly a tumor found in adults,
and it is generally not associated with a systemic inflammatory syndrome. Conversely, in young patients, chordoid meningioma is frequently associated with a systemic inflammatory syndrome, mainly expressed by hypochromic/microcytic anemia and/or fever, which usually disappear rapidly after tumor removal. In our case, although affecting an adult, the chordoid meningioma was associated with a systemic inflammatory syndrome. This syndrome was chiefly characterized by fever that completely disappeared after tumor excision. This pattern could be related to the production of IL-6 by tumor cells.

References