Primary intracranial β-human chorionic gonadotropin–producing leiomyosarcoma in a 2-year-old immunocompetent child

Case report

Brian C. Kelley, D.O.,1 Paul M. Arnold, M.D.,1 John A. Grant, M.B., B.Ch.,1 and Kathy L. Newell, M.D.2

Departments of 1Neurosurgery and 2Pathology & Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas

The authors present a rare case of primary intracranial leiomyosarcoma (LMS) in a young, immunocompetent boy. The patient presented with an expanding right forehead mass. Diagnostic workup revealed multiple large intracranial tumors. The largest mass was resected, and pathological analysis revealed LMS. Given the poor prognosis of this tumor, the family declined further care, and the child died 3 months later. Primary LMSs are extremely rare tumors in the pediatric population, especially in patients who are not immunocompromised. (http://thejns.org/doi/abs/10.3171/2012.4.PEDS1216)

Key words • primary leiomyosarcoma • β-hCG • pediatric • immunocompetent child • central nervous system • oncology

LEIOMYOSARCOMAS are rare tumors at any age, and a primary intracranial LMS is exceptionally rare. The majority of these neoplasms that occur in the CNS are caused by metastatic disease or radiation exposure. They are associated with HIV and EBV infections, and their occurrence in immunocompetent patients is exceptionally rare. We describe a previously healthy, HIV-seronegative, immunocompetent 2-year-old boy with a history of macrocephaly who presented with a right frontal scalp lesion. Computed tomography and MRI studies revealed multiple intracranial solid and partially enhancing cystic masses with extracranial extension.

Case Report

History and Examination. A 34-month-old boy presented to an outside facility for evaluation after his mother noticed an expanding soft-tissue mass on his right forehead. A review of his developmental history indicated age-appropriate achievement of physical, cognitive, and social milestones. He had a history of common childhood illnesses, was not taking any medications, and was considered a generally healthy and active boy. His mother reported no radiation or chemical exposures. A review of his systems was significant for unspecified cardiac atrial and ventricular septal defects, which were being monitored by a cardiologist, as well as a slight strabismus and what the mother had been told was macrocephaly. At 13 months of age, the boy weighed 14.1 kg with a length of 89.5 cm and a head circumference of 57.5 cm. At 15 months of age, his head circumference was 58 cm, well above 49 cm, the 95th percentile. Large heads were characteristic of 3 other family members. The family history included Asperger syndrome in both his 7-year-old sister and a first cousin.

On physical examination the patient was found to be somnolent but easily aroused with reactive irritability to disturbance. He had distinct superior vertical gaze palsy and a slight strabismus. His pupils were equal and symmetrically reactive to light. His head circumference was 65 cm (52 cm is the 95th percentile head circumference for 34-month-old boys). He was able to sit, stand, and ambulate without difficulty. His speech was age appropriate. There were multiple small, palpable, noncompressible, nontender, frontal cranial masses.

Computed tomography studies with and without con-
Contrast revealed 3 large extraaxial heterogeneous enhancing masses located in the right frontal, high left parietal, and left temporoparietal regions; these masses appeared to arise from bone or dura. Computed tomography studies also revealed 2 intraaxial lesions in the left subfrontal as well as the left occipital/supratentorial regions with large bilateral subdural hygromas (Fig. 1). Additional CT scans of the child’s chest, abdomen, and pelvis were unremarkable for an extracranial primary lesion or any metastatic lesions.

After transfer to our facility, axial, sagittal, and coronal postcontrast T1-weighted MR images of the brain were obtained with fiducial markers for treatment planning. Postcontrast axial T2, FLAIR, and diffusion-weighted imaging sequences were obtained, revealing multiple extraaxial enhancing masses, with the right frontal mass demonstrating osseous involvement. Also evident were large bilateral extraaxial fluid collections and a left posterior fossa lobulated fluid collection without marginal enhancement (Fig. 2). Magnetic resonance images of the cervical, lumbar, and thoracic spine were normal.

The serum markers and serological tests assessed preoperatively were β-hCG, AFP, CA125, and CEA; those assessed postoperatively were HIV-1 and EBV (Table 1).

**Intervention.** Biopsy sampling of the right frontal extracranial soft-tissue lesion revealed a malignant mesenchymal tumor with diffuse vimentin and smooth-muscle actin expression, suggestive of myogenic differentiation. Leiomyosarcoma was considered as a possible diagnosis, but rhabdoid areas were also present. Although a germ cell tumor had been suspected preoperatively given an elevated serum β-hCG level > 400 U/L, a germ cell component was not identified in the biopsy sample. Four days later the patient underwent a right frontal craniotomy with subtotal resection of the large right frontal mass.

**Pathological Findings.** The right frontal tumor specimen consisted of 2 disc-shaped masses, 7.0 × 6.0 × 1.5 and 7.0 × 6.0 × 1.8 cm thick. The grayish-white tissue was firm and rubbery with bosselated areas (Fig. 3).

Histological examination of the partially resected intracranial mass revealed highly cellular spindled and rhabdoid areas showing immunoreactivity to smooth-muscle actin, vimentin, glial fibrillary acidic protein, and β-hCG antisera. Abundant reticulin fibers were present, as were sparse PAS-positive macrophages. Immunostaining for INI1 protein revealed no loss of expression. No immunoreactivity was seen with antisera to desmin, myogenin, myoD1 (rabbit anti–human polyclonal [Ser200] antibody), muscle-specific actin, chromogranin, synaptophysin, pancytokeratin, CD117 antibody (stem cell factor receptor), AFP, CEA, CD31 (a 130-kD integral membrane protein), SI100 protein, epithelial membrane antigen, or EBV. Cytogenetic testing showed no chromosomal abnormalities via conventional techniques. Electron microscopy findings included some features observed in tumors with smooth-muscle differentiation, such as poorly defined external lamina and a few cells with thin filaments. The pathological impression was a primary high-grade sarcoma, primarily LMS, with immunohistochemical evidence of divergent differentiation. The source of the serum β-hCG elevation was attributed to the scattered tumor cells that showed immunoreactivity to this protein, an association rarely reported in some sarcomas, including LMS (Fig. 4).
Primary intracranial β-hCG-producing leiomyosarcoma in a child

TABLE 1: Preoperative and postoperative laboratory values*

<table>
<thead>
<tr>
<th>Value</th>
<th>β-hCG (U/L)</th>
<th>AFP (ng/ml)</th>
<th>CA125 (U/ml)</th>
<th>CEA (ng/ml)</th>
<th>HIV-1</th>
<th>EBV†</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference</td>
<td>0–3.0</td>
<td>0–15</td>
<td>&lt;35</td>
<td>&lt;3.0</td>
<td>positive/negative</td>
<td>positive/negative</td>
</tr>
<tr>
<td>preop</td>
<td>412‡</td>
<td>2.2</td>
<td>54</td>
<td>20.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>postop</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>negative</td>
<td>negative</td>
</tr>
</tbody>
</table>

* — = not applicable.
† The EBV testing included antibody to early D antigen, immunoglobulin (Ig) G; antibody to nuclear antigen, IgG; antibody to viral capsid antigen, IgG and IgM; and polymerase chain reaction.
‡ The β-hCG decreased to 82 U/L 10 days after surgery.

Postintervention Course. The pediatric oncology service was consulted for treatment options. Faced with the grim prognosis, the family declined further therapy, including chemotherapy. Following a 2-week hospitalization, the boy was discharged to home with hospice care and died 3 months later as a result of disease progression. No autopsy was performed.

Discussion

Most LMSs found in the CNS are metastases from primary sites in the gastrointestinal tract, uterus, and subcutaneous tissue, or result from radiation exposure. In comparison with other soft-tissue sarcoma subtypes, LMSs appear to have an increased tendency to metastasize to the brain. No evidence of an extracranial source for the child’s tumor was documented radiographically, and there was no history of radiation exposure.

Primary intracranial LMSs are exceptionally rare, with only a few cases documented in the literature. Sivendran et al. reviewed 14 cases found in the English literature between 1966 and 2006, and Fujimoto et al. conducted a similar review, including many of the same cases, and adding several others as well as their own.

Primary intracranial sarcomas commonly have sites of dural attachment, and thus a complete differential diagnosis for expansile cranial and dural tumors should be expanded to include sarcomas, such as LMS. In the present case, a dural origin might be suggested by the imaging studies, although a definitive site of origin is not possible given the multiplicity and complexity of the masses. Regardless of the site of origin, the ultimate cells of origin are likely pluripotent mesenchymal stem cells in the dura. Intracranial sarcomas can also originate in cerebral blood vessel epithelium as well as in the extradural blood vessels and extend to the meninges and skull.

Preoperative evaluation of our patient revealed a marked elevation in serum β-hCG and a few other tumor markers, leading to the clinical suspicion of choriocarcinoma or other germ cell neoplasm. As a result, clinicopathological confusion arose when the histological findings supported a sarcoma and not a germ cell tumor. The production of β-hCG in LMSs is a rare phenomenon and appears to be associated with ominous outcomes. The identification of scattered β-hCG-immunoreactive cells within the tumor ultimately confirmed that the source of the serum β-hCG elevation was the LMS.

In immunosuppressed patients, including those with HIV infection, co-infection with EBV is considered a causative factor for the development of LMS. The occurrence of LMS in immunocompetent patients is extremely rare. In our patient, EBV immunoreactivity was not detected within the tumor immunohistochemically at the time of analysis, nor was the patient immunocompromised.

Although our patient had a family history of macrocephaly, which may have been nothing more than a benign trait, the presence of his marked macrocephaly even before 16 months of age might suggest other possibilities. One such possibility is that a tumor, either LMS or a precursor lesion, had been present for an unknown interval prior to clinical presentation. During an evaluation for macrocephaly approximately 1 year before this presentation, a pediatric neurologist detected some subtle neurological signs and recommended MRI of the head, but the family did not obtain the study because of an insurance issue. An alternative possibility is related to the family history of Asperger syndrome. Early brain overgrowth, which may exceed more than 2 SDs in young children, has been recently recognized as a significant marker for autism spectrum disorder. To our knowledge, at the time of presentation an autism spectrum disorder had not been considered in this child; however, diagnosis may not be formally made until 4 or more years of age.

Our case appears to involve the youngest immunocompetent patient presenting with a primary intracranial LMS. A few other cases of young children (age range 4–9 years) with primary intracranial LMS are documented in the literature, although their immune status was not always detailed.

![Fig. 3. Photograph of gross findings. The tumor is tan-white with a firm rubbery consistency. The cut surface has a whorled appearance.](image)
Due in part to the rarity of primary intracranial LMS, there is no standard treatment regimen. Maximal resection has been the mainstay, with radiation therapy used as an adjunct to maintain local control. The role of adjunct systemic chemotherapy remains unclear, as the use of cytotoxic agents has not been consistent and clinical outcomes have been variable. The prognosis for intracranial sarcomas is unclear, although it is generally considered poor despite the use of postoperative radiotherapy and chemotherapy. Disease-free survival has ranged from 6–32 months to 8 years after the initial diagnosis.

In the sporadic reports of primary intracranial sarcomas, treatment plans and clinical outcomes have been variable. The use of radiation therapy after maximal resection of primary intracranial LMS has been documented by several authors and may be considered useful. The role of chemotherapy is unclear, and a particular regimen has not been established. In the 4 reported cases that included detailed descriptions of the chemotherapy administered, the treatment appeared to be successful in the 3 pediatric cases but was not successful in the adult case. Recent results of various studies have demonstrated the efficacy of doxorubicin, ifosfamide, and gemcitabine in combination with docetaxel. Other agents that appear promising include dacarbazine, temozolomide, and bevacizumab.

**Conclusions**

Primary intracranial LMSs are rare neoplasms in any age group, including the pediatric population. Of all reported cases of primary intracranial LMSs in the literature, very few have occurred in immunocompetent patients. Leiomyosarcomas, including those in the intracranial vault, have recently been linked to HIV and EBV infections. However, our patient had no evidence of HIV or EBV infection or other immunocompromise. In part because of the lesion’s rarity, the optimal treatment for primary intracranial LMS is as yet unknown.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author contributions to the study and manuscript preparation** include the following. Conception and design: Arnold, Kelley, Grant. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Kelley. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Arnold.

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**References**


