Central nervous system leiomyosarcoma in patients with acquired immunodeficiency syndrome

Report of two cases

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Leiomyosarcomas (LMSs) of the central nervous system are extremely rare; however, they are becoming more prevalent in immunocompromised patients. The authors present the cases of two patients with acquired immunodeficiency syndrome: one with LMS of the thoracic vertebral body and the other with LMS originating from the region of the cavernous sinus. The epidemiological and histological characteristics of LMS and its association with latent Epstein–Barr virus are discussed, as well as the treatments for this neoplasm.

KEY WORDS • leiomyosarcoma • central nervous system • acquired immunodeficiency syndrome • Epstein–Barr virus

MALIGNANT mesenchymal tumors with myogenic components presenting in the CNS remain exceptionally rare. The majority of CNS LMSs are metastatic lesions that originate in the gastrointestinal tract or female reproductive system. The incidence of LMS occurring in the neural axis is infinitesimal. Recently, there has been an increasing incidence of primary malignant smooth-muscle tumors in immunocompromised patients.1,3,5,6,8,13,14,16,18,22–24,26–28,30 Literature suggests there is an association between the occurrence of EBV and LMS in patients with HIV and in patients who have received transplanted tissue.4,15,20,22,29,33 Our present report focuses on two immunocompromised patients with CNS LMS who harbor EBV.

Case Reports

Case 1

History. This 5-year-old girl had received a diagnosis of AIDS when she was 18 months of age, after having recurrent interstitial pneumonia, clostridium difficile colitis, and esophageal candidiasis. Yearly surveillance head CT scans were nondiagnostic until 1997, when a mass involving the left cavernous sinus was identified.

Examination. On physical examination, no neurological deficits were present. Magnetic resonance imaging revealed a dura-based, brightly enhancing lesion within the cavernous sinus (Fig. 1). Magnetic resonance angiography revealed a patent cavernous carotid artery.

Operation. The patient underwent a pterional craniotomy. The sylvian fissure was split and a dural-based mass was visualized. The dura was opened with a scalpel, revealing a firm, rubbery, whitish-gray tumor that appeared to be located between the inner and outer dural layers of the cavernous sinus. A Caviton ultrasonic surgical aspirator was used to resect a majority of the avascular tumor except that which lay against the carotid artery.

Pathological Findings and Postoperative Course. A diagnosis of meningioma was made after analysis of frozen-section tissue. Following review of the permanent pathological sample, a diagnosis of LMS was made. Adjuvant radiotherapy or chemotherapy was deferred in this patient because of her age and immunological state. Follow-up head CT scanning has demonstrated minimal progression of the residual tumor.

Abbreviations used in this paper: AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; CT = computerized tomography; EBNA2 = Epstein–Barr nuclear antigen 2; EBV = EB virus; HIV = human immunodeficiency virus; LMS = leiomyosarcoma; MR = magnetic resonance.
Case 2

History. This 35-year-old woman in whom AIDS was diagnosed 8 years prior to her presentation, presented with bilateral lower-extremity weakness.

Examination. Leg strength was determined to be 3/5 on the left side and 2/5 on the right side. Bilateral pinprick sensation was decreased and was more pronounced on the left side at T-5. There was a Babinski sign on the right side. Two MR images are presented in Fig. 2. A thoracic hemilaminotomy exposed the interspace between T-3 and T-4. The tumor appeared to originate in the vertebral body and pedicle with expansion, but not invasion, into the epidural space. The tumor was whitish gray and fibrous and tough in consistency. A gross-total resection of the epidural mass was accomplished.

Pathological Findings and Postoperative Course. Based on the analysis of a frozen section of tissue the diagnosis of meningioma was made. The patient underwent postoperative radiotherapy at which time the final diagnosis of LMS was verified.

Methods and Results of Pathological Studies

Case 1

Multiple small fragments of gray-to-pink, firm, somewhat rubbery tissue, approximately 2 × 0.5 × 0.5 cm in aggregate were preserved in 10% buffered formalin and processed for paraffin embedding. Five- to 8-μ-thick sections were stained with hematoxylin and eosin. The immunoperoxidase studies consisted of routine avidin–biotin complex analyses and used dianaminobenzidine as a chromogen. The antibodies selected were directed against vimentin (mouse monoclonal), smooth muscle–specific actin (mouse monoclonal), EBNA2 (mouse monoclonal), S-100 protein (rabbit/anti–bovine), desmin (mouse monoclonal), and epithelial membrane antigen (mouse monoclonal).

Light microscopic examination revealed a densely cellular tumor composed of wide intersecting fascicles of plump spindle cells. The cells were pleomorphic in nature with some having long cigar-shaped nuclei and others having rounded or irregular nuclei. Relatively few nuclei contained clumped chromatin. The cells had a moderate amount of eosinophilic cytoplasm and displayed indistinct borders (Fig. 3 left). Mitotic figures were rare (two per 10 high-power fields) and necrosis was absent. No evidence of brain invasion was identified.

Immunoperoxidase studies demonstrated nuclear staining with EBNA2 (Fig. 3 right). Vimentin and smooth muscle–specific actin stains were positive. Negative results were obtained with antibodies against desmin, S-100 protein, and epithelial membrane antigen. The diagnosis of LMS associated with EBV was made on the basis of these findings.

Case 2

Multiple fragments of whitish gray tissue measuring 4.5 × 3 × 1 cm were processed similarly to those described in Case 1 for hematoxylin and eosin staining and for immunoperoxidase studies for smooth muscle–specific actin, desmin, and EBNA2. Immunoperoxidase studies for cytokeratin (rabbit/anti–bovine) and factor VIII (rabbit/anti–human) were also used.

The hematoxylin and eosin–stained sections of tumor demonstrated interlacing fascicles of pleomorphic spindle cells that possessed a moderate amount of eosinophilic cytoplasm. The cell borders were indistinct. Moderate atypia and occasional mitotic figures (two or three per 10 high-power fields) were identified, and necrosis was absent (Fig. 4 left).

Nuclear staining with EBNA2 was verified by the immunoperoxidase study (Fig. 4 right). The tumor cells were also immunoreactive for smooth muscle–specific actin and desmin. Negative results were obtained for S-100 protein, cytokeratin, and factor VIII. The final pathological diagnosis was LMS associated with EBV.
Sources of Supplies

All antibodies and antisera used in Cases 1 and 2 were obtained from Dako Corp., Carpinteria, CA.

Discussion

Leiomyosarcomas are malignant neoplasms demonstrating smooth-muscle differentiation that arise primarily in the uterus, gastrointestinal tract, skin, and blood vessels. Metastases from these sites are unique, but may be directed to bone, lung, and liver. Even more uncommon is metastasis to the CNS. Lewis, et al., documented only six LMSs in 50 metastatic sarcomas to the brain. Thus, LMSs that originate in the neural axis are exceptional cases. Tumors discovered in the spine or brain are believed to originate from mesenchymal elements within blood vessels of the bone, dura, or subarachnoid spaces. Since the early 1980s there have been 11 reported cases of LMS involving the intracranial space and three involving the bone, soft tissue, or epidural space of the spine.

There are three reports in the literature of LMS involving the paraspinal region. De Vries, et al., described a partially intra- and partially extramedullary tumor that was also adherent to the leptomeninges. Others have documented a purely epidural LMS and an LMS that invaded a thoracic vertebral body with extension into the spinal canal. In 1991, Paulus and colleagues documented that 0.1% of all brain tumors are “primary leiomyosarcomas.” In their study of 19 cases of LMS, three patients, two males and one female, were between the ages of 4 and 9 years. No long-term follow-up observations or metastatic work-up was documented in that pathological report. There have also been sporadic reports of LMS involving the cerebellum, temporal dura, suprasellar region, and ventricle. The four additional, and most recent, cases of intracranial LMS have been discovered in immunodeficient patients. The earliest report by Mierau and associates in 1996 contained a description of an LMS in a 14-year-old child with common variable immunodeficiency syndrome. The tumor encompassed the posterior portion of the temporal lobe and the dura mater of the posterior fossa and extended into the transverse and sigmoid sinuses. Other authors have reported on three additional AIDS patients with LMS of the neural axis. Two of these tumors involved the cavernous sinus and the other was “within the pontine cistern.”
Although the incidence of LMS in the neuraxis may be small, there has been a robust increase in LMSs identified in other organ systems of adults and children. This parallels the increasing number of individuals with virally induced, acquired, and congenital immunodeficiency syndromes.1,15,16,24,26,28,29,30,35 Leiomyosarcoma and its benign counterpart, leiomyoma, have become the second most common cancer in children with HIV.6,24 Although LMS occurs in approximately 2 of 10 million children not infected with HIV,13 cases have been reported in approximately 6200 children with HIV. Reported sites of this tumor in children include the lung, spleen, liver, stomach, intestine, skin, and foot.6,19,21,24,27,30 Reported sites of LMS in HIV-positive adults, based on studies of biopsy and autopsy specimens, include the adrenal gland, liver, lymph nodes, pleura, pericardium, skin, and intestine.4,20,29,32,35

With the four previously reported cases of LMS in immunocompromised patients and the two present cases, the brain and spinal cord can be added to these lists. The incidence of LMS has also become more frequent in immunocompromised patients after tissue transplantation.10,28 Penn15 records that 7.4% of cancers identified in patients who received organ allograft transplants are sarcoma (5.7% Kaposi’s sarcoma and 1.7% other types). In Penn’s study, LMS was the second most common sarcoma and included 15 of 8724 malignancies. Of these 15, five tumors (33.3%) were found in children. Lee and associates15 described three cases of smooth-muscle tumors that developed in children after they received immunosuppression therapy for liver transplantation.

The increased prevalence of malignant myogenic tumors in immunocompromised patients has been linked to EBV.10,15,20,22,29,35 In situ hybridization and polymerase chain reaction have been used to identify EBV in malignant smooth-muscle cells obtained from individuals with HIV, but not in patients not infected with HIV.4,20 Mierau and associates22 presented the first case of CNS LMS in an immunocompromised patient that was associated with EBV. Epstein–Barr virus was also detected by in situ hybridization in cells obtained from three patients described by Brown,5 Blumenthal,1 and Kleinschmidt-DeMasters,13 and their colleagues. Epstein–Barr virus has also been discovered in patients who have received organ transplants or have congenitally compromised immune systems.15,21,28,35 Researchers have shown that EBV receptors are unregulated in the immunocompromised patient. This may facil-

Fig. 4. Case 2. Photomicrographs, original magnification × 1000. Left: Pleomorphic nuclei and a degree of cellular atypia are identified in the tumor cells. H & E. Right: Immunoperoxidase staining for EBNA2 identifying brown nuclear staining in tumor cells infected with EBV.
itate viral entrance into, and transformation of, the human cell.\textsuperscript{10,20} The reduction in tumor surveillance cells and the inability to remove EBV in immunocompromised patients can propagate this transformation.\textsuperscript{10,12,20}

Although the number of cases of LMS is increasing, there are still too few patients to formulate effective treatment regimens. Complete surgical removal together with radiotherapy is the mainstay for other non-CNS sarcomas. Gross-total resection and radiotherapy, depending on the site and age of the patient, are the treatment goal.\textsuperscript{1,2,15,18} Postoperative regimens of doxorubicin, vincristine, dacarbazine, cyclophosphamide, and/or interferon-\textalpha are considered palliative treatment.\textsuperscript{1,15,20}

In conclusion, the number of malignant myogenic tumors in the compromised host associated with EBV is expanding. This case report adds two patients to the growing number of cases of LMS of the CNS that are associated with EBV in patients with virally induced immunocompromise.

References