Epithelioid hemangioendothelioma of the spine

Report of two cases


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Epithelioid hemangioendothelioma (EH) is a rare tumor of vascular origin. The authors describe two cases of spinal EH, one involving the T-10 vertebra and the second involving the upper cervical spine. In the first case the patient underwent resection of the tumor; this case represents the longest reported follow-up period for spinal EH. In the second case, extensive involvement of C-2, C-3, and C-4 as well as encasement of both vertebral arteries precluded safe tumor resection, and posterior occipitocervical stabilization was performed. The patient subsequently died of metastatic disease. The findings in these two cases underscore the difficulty in predicting the clinical behavior of spinal EH based solely on histological and clinical features as well as the uncertainty of the roles of surgery, chemotherapy, and radiotherapy in the oncological management of a spinal tumor for which clinical data are very limited.

KEY WORDS • epithelioid hemangioendothelioma • vertebral tumor • axis tumor

Case Reports

Case 1

Presentation and Examination. This 17-year-old man presented with a 1-year history of nocturnal thoracic low-back pain in May 1993. A CT scan of the thoracic spine revealed a mixed sclerotic and osteolytic lesion in the T-10 VB, extending into both pedicles (Fig. 1a). Results of a needle biopsy procedure were nondiagnostic.

Operation. A radical subtotal resection was performed, in which we removed the T-10 VB and its right pedicle via a left thoracotomy. For spinal stabilization, we then placed an iliac crest strut graft secured with a stainless-steel plate screwed into the T-9 and T-11 VBs. Several nodules of tumor were noted in the pleura and lungs adjacent to the T-10 VB. A biopsy sample of one of these lesions was obtained.

Histological Examination. Histological examination of the tumor showed a fibrotic neoplasm infiltrating and replacing bone. The tumor cells were large, had eosinophilic cytoplasm, and lined several vascular channels. In addition to standard H & E and reticulin staining, sections were immunostained for factor VIII–related antigen, CD31, CD34, smooth-muscle actin, vimentin, and the epithelial markers MNF 116 and CAM 5.2 (all Dako Corp., Carpinteria, CA). The cells were positive for vimentin, factor VIII, CD31, and CD34. The histological profile of the pleural nodule was identical to that of the VB lesion (Fig. 2).

Postoperative Course. Postoperatively the patient was asymptomatic for 16 months; his thoracic low-back pain then recurred.

Second Examination and Operation. A 99mTc isotope bone scan revealed increased tracer uptake in the left T-10 pedicle. A CT scan demonstrated a tumor in the left paravertebral region, infiltrating the soft tissues anterior to the graft, up to the aorta. We noted partial collapse of the bone graft. A left thoracotomy was performed. Intraoperatively
we observed additional lung and pleural lesions. The main bulk of the tumor, to the left of the T-10 bone graft, was stuck firmly to bone and the surrounding soft tissue, infiltrating the anterior longitudinal ligament and close to the aorta; it was firm, rubbery, and avascular. Extensive resection of the visible tumor was performed. A Hartshill rectangle was placed posteriorly to stabilize the spine at this level.

Second Histological Examination. The histological features of this tumor were similar to those of the initial specimen; however, the tumor cells were more pleomorphic, varying from spindle-shaped to plump cells with eosinophilic cytoplasm, resembling endothelial cells. The tumor also exhibited extensions into connective tissue.

Radiotherapy and Chemotherapy. In view of the recurrence and the change in histology, a 30-Gy course of radiotherapy was undertaken and a chemotherapy regimen, including ifosfamide, carboplatin, etoposide, and vincristine, was initiated.

Second Posttreatment Course. The Hartshill rectangle, the cause of severe mechanical interscapular pain, was removed 3 years later, leading to resolution of symptoms. The patient has remained well and asymptomatic during the past 7 years. The quality of serial CT and MR imaging has consistently been poor because of the stainless-steel plate–related artifacts; however, lateral spinal plain radiography has confirmed that there is no collapse of the bone graft, nor any change in the T-9 and T-11 VB characteristics (Fig. 1b).

Case 2

Presentation and Examination. This 60-year-old man presented in October 2000 with a 1-year history of neck pain. The range of movement of the cervical spine was restricted, particularly in extension. No neurological deficits could be identified on examination. On MR images we observed destruction of the C2–4 VBs with a large infiltrating soft-tissue mass adjacent to these vertebrae and encasing both VAs laterally. The spinal cord was displaced to the left and was slightly compressed. The tumor also involved the pedicles and laminae at these levels and significant angulation and subluxation were evident (Fig. 3). A CT-guided percutaneous needle biopsy procedure was performed.

Histological Examination. Histopathological examination showed a cellular tumor that caused bone destruction. The tumor was composed of uniform epithelioid cells within a fibrous stroma, lining small vascular channels or having intracytoplasmic microlumina (Fig. 4). The tissue was examined with a similar panel of antibodies used in Case 1. These cells stained positively with CD31, CD34, factor VIII, and vimentin. The tumor extended beyond the borders of the vertebrae into the paravertebral tissue.

Operation. Because of the severe flexion deformity, gentle skull traction was applied and we attempted a posterior occipitocervical stabilization procedure. The bone quality was poor, and obtaining satisfactory purchase was difficult. To achieve adequate stabilization, then, we placed a left-sided rod, which was secured with screws into the occipital bone, and C1–5 sublaminar wires (Fig. 5).

Postoperative Radiotherapy and Course. The patient underwent postoperative radiotherapy and was advised to wear a sternococpitomandibular immobilizing brace. He was asymptomatic for 17 months, but then presented with right upper-quadrant abdominal pain. Imaging revealed multiple hepatic and abdominal metastases; examination

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>Presentation</th>
<th>Treatment</th>
<th>FU Period/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maruyama, et al., 1985</td>
<td>43, F</td>
<td>T-3 VB w/ compression fracture; multicentric bone involvement outside the spine</td>
<td>pain &amp; neurological deficit; cord compression caused by pathological fracture</td>
<td>resection, steroids, radiotherapy</td>
<td>1 mo; neurological deficit resolved</td>
</tr>
<tr>
<td>Tsuneyoshi, et al., 1986</td>
<td>73, M</td>
<td>T-10, T-12, &amp; L-1 vertebrae</td>
<td>pain, pathological fracture</td>
<td>curettage, radiotherapy</td>
<td>not stated</td>
</tr>
<tr>
<td></td>
<td>16, M</td>
<td>T-9 vertebra; solitary</td>
<td>pain</td>
<td>curettage, resection, radiotherapy</td>
<td>4 yrs; alive &amp; well</td>
</tr>
<tr>
<td></td>
<td>26, M</td>
<td>T-11 vertebra; solitary</td>
<td>pain</td>
<td></td>
<td>20 mos; alive &amp; well; abdominal wall metastases</td>
</tr>
<tr>
<td>Boutin, et al., 1996</td>
<td>24, M</td>
<td>multiple lesions in cervical, thoracic, &amp; lumbar spine</td>
<td>neck stiffness, back pain</td>
<td>radio- &amp; chemotherapy</td>
<td>36 mos; asymptomatic</td>
</tr>
<tr>
<td>Ellis, et al., 1996</td>
<td>31, F</td>
<td>anterior L-2 VB</td>
<td>low-back pain</td>
<td>L-2 vertebrectomy, strut grafting</td>
<td>18 mos; alive &amp; well</td>
</tr>
<tr>
<td>Brennan, et al., 2001</td>
<td>58, M</td>
<td>C5–6 VBs</td>
<td>neck pain, progressive myelopathy</td>
<td>C5–6 vertebrectomy; C6–7 laminectomy &amp; stabilization</td>
<td>6 mos; myelopathy improved</td>
</tr>
<tr>
<td>present cases</td>
<td>17, M</td>
<td>T-10 VB &amp; pedicles</td>
<td>low-back pain</td>
<td>T-10 vertebrectomy, radiotherapy</td>
<td>11 yrs; asymptomatic</td>
</tr>
<tr>
<td></td>
<td>60, M</td>
<td>C2–4 vertebrae</td>
<td>neck pain, progressive flexion deformity</td>
<td>pst stabilization, radiotherapy</td>
<td>20 mos; died of hepatic metastases</td>
</tr>
</tbody>
</table>

* FU = follow-up; pst = posterior.
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![Image](SpineNovember2005_10/14/05_2:09_PM_Page_395)

of a needle biopsy specimen confirmed metastatic tumor identical to the primary vertebral lesion. Conservative treatment was elected by the patient and his family. Palliative care was instituted, and the patient died 2 months later.

**Discussion**

A rare tumor of endothelial origin, EH was initially identified in the lung as an intravascular bronchioloalveolar tumor. In additional studies of the histogenesis, its endothelial origin was confirmed. The term “EH” was coined by Weiss and Enzinger in 1982; this phrase reflects the tumor cells’ similarity to epithelium. It has since been demonstrated in other tissues including liver, soft tissue, spleen, bone, heart, and pleura as well as intracranially. It is regarded as a low-grade malignancy, and its biological behavior is intermediate between that of hemangioma and angiosarcoma.

Histologically, EH is characterized by epithelioid endothelial cells forming nests or cords within a loose hyalinized stroma. These cells are round to cuboidal and usually have abundant eosinophilic cytoplasm (Fig 2. upper left). They often contain intracytoplasmic vacuoles; this represents a primitive attempt at vascular formation at the cellular level (Fig 4. right). Erythrocytes are sometimes visible within the vacuoles. Mitotic activity is absent or minimal.

The tumor cells express the endothelial markers factor VIII, Ulex europaeus agglutinin, CD31, and CD34. Unlike normal endothelial cells, those of EH have numerous intermediate filaments and stain positive for vimentin. A positive response to focal immunostaining for cytokeratin is not uncommon. Electron microscopy confirms the endothelial nature of these cells, demonstrating Weibel-Palade bodies, junctional complexes, basal laminae, and pinocytic vesicles.

Epithelioid hemangioendothelioma is a neoplasm that exhibits intermediate vascular differentiation between that of a hemangioma and that of an angiosarcoma. In a hemangioma the vascular channels are well formed and lined by a single layer of endothelial cells. There are no intracellular channels or a significant spindle-cell component. Hemangioma is less frequently multifocal and invariably runs a benign clinical course. An angiosarcoma typically consists of solid sheets of cells with only coarse and irregular vascular or sinusoidal channels. The extent of endothelial cell pleomorphism and the incidence of mitotic figures are much greater than in EH. Foci of necrosis are typically present in angiosarcoma.

The pathological diagnosis of EH and its differentiation from other vascular tumors, as well as from metastatic carcinoma, is often difficult. The endothelial nature of the tumor cells—and therefore their factor VIII positivity—is central to the diagnosis. The principal factor VIII–positive tumors are hemangiomas and angiosarcomas. Atrial myxomas are also positive for factor VIII, and the authors of one report described a presumed intracranial EH subsequently discovered to be a metastatic atrial myxoma. Mitotic activity and desmoplastic reaction in EH is less
than would be expected of a metastatic adenocarcinoma. Other differential diagnoses include chondromyxoid fibroma, fibrous dysplasia with myxoid change, and chondrosarcoma.

In a recent review of 40 cases of EH arising in bone, investigators reported that local bone pain was the most common presenting symptom; in three patients pathological fractures were present. Twenty-two patients presented with multicentric disease, in six of whom multifocal tumor was demonstrated within a single bone and in 16 of whom multiple bones were involved. In only four patients was clustering of the multifocal lesions absent in one anatomical area. Seven patients (18%) also harbored lesions of the parenchymal organs. There were seven VB lesions, although neither the precise distribution nor the clinical course and treatment were stated. Neuroimaging evaluation of the bone-involved lesions revealed varying degrees of sclerosis; the typical lesion consisted of small luencies surrounded by extensive sclerosis in the adjacent bone. There were twofold as many poor marginated tumors as distinct marginated ones. Areas of cortical destruction as well as expansion were common. Soft-tissue extension was evident in nine cases. Macroscopically, the tumors were typically observed to be soft red nodular masses associated with bone fragments.

The clinical course and management of spinal EH has only been documented in seven cases (Table 1). The longest reported follow-up period has been 4 years; the mean age of the patients was 39 years (range 16–73 years). All patients presented with local neck or back pain; in two patients with thoracic lesions, pathological fractures were also observed. Two patients presented with neurological deficits: in one patient the deficit was due to a pathological T-3 fracture; in the other case with cervical compressive myelopathy, the deficit was caused by the tumor’s mass effect. Preoperative fine needle aspiration was attempted in two patients, but in both cases the findings were nondiagnostic.

Of the seven previously published cases, four patients underwent resection. In three cases, surgery was fol-
lowed by radiotherapy.\textsuperscript{10,16} One patient, who presented with multicentric disease involving 45 bones, underwent chemo- and radiotherapy.\textsuperscript{4} One patient with localized L-2 EH underwent an L-2 vertebrectomy; clear surgical margins were confirmed intraoperatively by examination of a frozen section.\textsuperscript{6} This patient was asymptomatic 18 months postoperatively. In one other patient, complete tumor excision was not possible because of circumferential VA encasement.\textsuperscript{5} Spinal decompression and anterior and posterior stabilization were performed. Tumor involvement of the C-5 and C-6 lateral masses precluded their incorporation in the posterior stabilization. The tumor was intensely vascular, and significant intraoperative blood loss occurred despite preoperative embolization of an estimated 50\% of the tumor’s blood supply. Adjuvant radiotherapy was undertaken 2 months postoperatively. The patient’s myelopathy improved and a solid fusion mass was evident on imaging at 6 months.

As in the case reported by Brennan and colleagues,\textsuperscript{5} the lesion in our Case 2 also involved the cervical spine; however, the extensive involvement of C-2, as well as C-3 and C-4, renders our case unique. The tumor involved all four surgical zones of the axial vertebra, as described by Piper and Menezes,\textsuperscript{13} and also encased both VAs. Stringent patient selection based on the lesion’s complexity and the patient’s prognosis is essential to minimize the high morbidity rate associated with resecting cervical tumors involving the axis.\textsuperscript{13} Resection via a transoral approach would have been limited bilaterally by the VAs. Involvement of the C-3 and C-4 VBs would have posed significant difficulties for anterior fixation. Complete tumor resection would have nonetheless required a lateral extrapharyngeal

\textbf{FIG. 3.} Case 2. Various imaging studies. Sagittal T2-weighted (upper left) and T1-weighted (upper right) MR images as well as coronal (lower left) and axial (lower right) CT scans of the upper cervical lesion.
and a posterolateral procedure. It was thus believed that the lesion was too extensive to allow for total resection without risking significant morbidity. Because the cervical spine was unstable at both the atlantoaxial and the upper subaxial levels, a posterior occipitocervical stabilization, the most common procedure for stabilizing the spine at this level, was performed.

The authors of recent publications have identified the value of en bloc resection in spinal tumor surgery. En bloc resection, defined as the removal of the entire tumor in one piece together with a layer of healthy tissue, significantly lengthens the time until local recurrence, and is to be attempted whenever possible; however, few patients present with tumors amenable to en bloc resection; in a series of primary and metastatic spinal sarcomas, tumors in only 15% of patients were suitable. Patients in whom there was bilateral pedicle or multiple VB involvement were unsuitable for this treatment and thus underwent intraliteral resection only.

Based on its histological features, the biological behavior of EH is not predictable with certainty. According to Weiss and Enzinger, patients in whom there is evidence of metastases or histology characterized by nuclear atypia, mitotic figures in excess of one per 10 hpf, focal spindling of cells, and foci of necrosis are more likely to be subjected to a tumor-related aggressive course. These latter histological features are present in up to 25% of patients. In one study of bone EH, however, histological atypia and mitotic index did not correlate with outcome; visceral involvement was the most important adverse prognostic factor. Also unclear is whether the survival rate is higher for uni- or multicentric bone disease; the authors of two studies involving bone EH reached contradictory conclusions. The lack of correlation between outcome and histology is supported by the findings in our Case 1; this patient survived 11 years after presentation, despite an increase in cellular pleomorphism at first recurrence.

Epithelioid hemangioendothelioma is generally associated with favorable prognosis, with long-term survival possible even in the presence of metastases. In soft-tissue EH, during a 4-year period, 13% of patients sustained local recurrence, metastases developed in 31%, and caused death in 13%. Because the number of patients has been small and the follow-up period short, the indications for adjuvant radio- and chemotherapy in spinal EH are still unclear. Management guided by the basic oncological principles of maximal safe resection and subsequent radiotherapy for residual disease is the usual course of action. Diffuse disease is probably best treated with chemotherapy.

Conclusions

We present two additional cases of spinal EH, underlining the variation in the clinical behavior of this tumor. To the best of our knowledge, our Case 1 represents the longest reported follow-up period of any patient with a spinal
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EH. In Case 2 the poor prognosis was associated with metastatic EH as well as the difficulties of stabilizing the upper cervical spine because of extensive tumor involvement. The management of spinal EH (particularly the indications for and the timing of adjuvant radio- and chemotherapy) is still unclear. It would appear from our limited experience, however, that because these lesions are potentially aggressive, en bloc resection should be attempted whenever possible. Given the propensity of these lesions to recur, intralesional or subtotal resection should be followed by radiotherapy.

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References

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