Primary Capillary Hemangioblastoma of Bone: Report of a Case Arising in the Sacrum

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Abstract
Capillary hemangioblastoma (CHB) is a benign, highly vascularized tumor that generally occurs in the central nervous system either in the setting of von Hippel-Lindau (VHL) disease or, more often, as a solitary sporadic lesion that is increasingly recognized in extraneural sites. We present the case of a 72-year-old woman with low back pain and a well-demarcated lytic lesion of the sacrum, which at histological and ultrastructural examination was indistinguishable from central nervous system CHB. The patient had no signs of VHL disease and died of another cause with no evidence of disease 57 months after curettage of the lesion. To our knowledge, this is the second case of CHB reported to occur in bone.

Keywords
capillary hemangioblastoma, bone, immunohistochemistry, electron microscopy

Capillary hemangioblastoma (CHB) is a WHO grade I tumor of the central nervous system of uncertain histogenesis, composed of stromal cells and abundant capillaries,¹ which involves intracranial or intraspinal sites either sporadically or in association with von Hippel-Lindau (VHL) disease. Sporadic CHB usually occurs in adults, whereas the VHL-associated tumors affect significantly younger patients. Examples of CHB developing in extra CNS sites, including peripheral nerves, parenchymal organs, soft tissues, and skin, are increasingly recognized. We present a case of primary intraosseous CHB arising in the sacrum with immunohistochemical and ultrastructural characterization.

Case Report
Clinical Findings
A 72-year-old woman with no history of trauma complained of persistent pain in the lower back. Radiographic examination and computed tomography (CT) scan revealed a well-demarcated lytic lesion of the sacrum (Figure 1). The patient’s past medical history was remarkable for a previously treated cancer of the uterine cervix. In light of the above-mentioned findings, a clinical diagnosis of metastasis versus schwannoma was proposed. Computed tomography–guided needle core biopsy of the lesion was carried out, and a diagnosis of “benign vascular tumor” was rendered. Curettage of the lesion was performed; the recovery was uneventful. The patient had no signs of VHL disease and died of another cause with no evidence of disease 57 months after curettage of the lesion.

Microscopic Findings
At low-power magnification, the tumor appeared as a well-vascularized cellular lesion composed of numerous blood vessels ranging in size from small capillaries to large ectatic vessels, some of which had a staghorn shape, with single-layered flat endothelial lining, and sheets of stromal cells (Figure 2). The latter were of variable size, with multivacuolated amphophilic or clear cytoplasm and round to oval, centrally placed nuclei with inconspicuous nucleoli (Figure 3). Focal nuclear enlargement and hypercromasia were observed. Mitoses and necrosis were not...
and alpha smooth muscle actin (clone 1A4; Cell Marque) stains were negative. The endothelial cells were highlighted by CD31 (clone 1A10; Cell Marque) and CD34 (clone Qbend 10; Ventana) stains (Figure 4).

**Immunohistochemistry**

The stromal cells stained positively for vimentin (clone V9; Ventana, Tucson, Ariz), protein S-100 (polyclonal rabbit; Dako, Glostrup, Denmark), CD57 (clone NK1; Cell-Marque, Rocklin, Calif), neuron-specific enolase (NSE) (clone E27; Cell-Marque) and α-inhibin (clone R1; Cell-Marque) (Figure 4). Epithelial membrane antigen (EMA), cytokeratins AE1/AE3 (Ventana), CAM5.2 (Becton Dickinson, San José, Calif), GFAP (clone ZCG29; Zymed, San Francisco, Calif), HMB45 (Cell Marque), CD68 (clone KP1; Ventana), and alpha smooth muscle actin (clone 1A4; Cell Marque) stains were negative. The endothelial cells were highlighted by CD31 (clone 1A10; Cell Marque) and CD34 (clone Qbend 10; Ventana) stains (Figure 4).

**Electron Microscopy**

Tissue fragments for electron microscopic examination were obtained from formalin-fixed material. The stromal cells were characterized by the presence of several...
cytoplasmic droplets of varying size and probable lipid nature, which appeared electron lucent (Figure 5). In addition, the cytoplasm contained few organelles, glycogen deposits, and occasional myelin bodies. The hyaline bodies observed at light microscopic level consist of collagen fibrils.

Discussion

Capillary hemangioblastoma is a benign, highly vascularized tumor that generally occurs in the central nervous system and arises either in the setting of VHL disease or, more often, as a solitary sporadic lesion.\(^2\) von Hippel-Lindau disease patients often have multiple CHB that can be found in the cerebellum, medulla, spinal cord, or retina, while sporadic lesions occur predominantly in the substance of the cerebellum. Sporadic CHB is a tumor of adulthood generally occurring between 30 and 65 years of age, while VHL-associated tumors affect significantly younger patients with a mean age of 29 years.\(^1\) Patients usually present symptoms of increased intracranial pressure or spinal cord compression.

Histologically, CHB is characterized by the presence of large vacuolated stromal cells interspersed between a rich capillary network. On the basis of the abundance of the stromal cell component, cellular and reticular variants have been described. The stromal cells represent the neoplastic component of the tumor. They are usually polygonal and contain lipid, much of which may be lost during processing, resulting in the typical “clear cell” morphology of CHB. Nuclei are often variable in size. Atypical or hyperchromatic features may be present, but mitotic activity is uncommon. Because of its high vascularity, CHB may present intraleisonal hemorrhage and cystic changes. However, necrosis is usually not seen.

Immunohistochemical studies have demonstrated expression of S-100 protein, NSE, CD57, vimentin, α-inhibin, and factor XIIIa within the stromal cell component, whereas there is negativity for vascular markers CD31, CD34, factor VIII, and for epithelial markers such as keratin and EMA. Stromal cells generally do not contain glial fibrillary acidic protein (GFAP), but on occasion they are unequivocally, although not uniformly, positive.\(^2\)

The origin of CHB is unclear. As the name indicates, it was originally believed to be a vascular neoplasm because of its conspicuous microvascular component. The histogenesis of the vacuolated stromal cells, which are regarded as the neoplastic component, is still unsettled. Based on immunohistochemical and electron microscopic studies, endothelial, astrocytic, fibrohistiocytic, myoid, and pericytic lines of differentiation have been proposed.\(^3-6\) Currently a mesenchymal origin remains the most widely accepted, but no definitive conclusions have yet been reached.

Capillary hemangioblastoma developing in extra CNS sites are increasingly recognized.\(^7\) They have been described in peripheral nerves,\(^8,9\) kidney,\(^10\) liver,\(^11\) lung,\(^11\) retroperitoneum,\(^4\) soft tissues,\(^12,13\) and skin,\(^14\) all being unassociated with VHL disease. Herein we presented a case of primary intraosseous CHB arising in the sacrum of a 72-year-old female patient with no family history of VHL disease. In consideration of the patient’s history (treated cancer of the uterine cervix), a clinical diagnosis of a metastasis involving the sacrum was taken into consideration. However, the morphological findings did not support this diagnosis. In light of the histological findings and the site of involvement, the differential diagnosis included metastatic clear cell carcinoma of the kidney, hemangioma, hemangiopericytoma, schwannoma, and chordoma.

Renal cell carcinoma is recognized by its epithelial characteristics. The expression of S-100 protein, NSE, and α-inhibin, and the absence of epithelial markers (keratin and EMA) are decisive in distinguishing CHB from the clear variant of renal cell carcinoma. Considering primary vascular lesions of bone, hemangioma may simulate the capillary network of CHB, but the former lacks the characteristic vacuolated cells of CHB and does not exhibit expression of S-100 protein. So-called hemangiopericytoma of the bone may arise in the sacrum\(^15\) and has some histological features in common with CHB, including a prominent
vascular network with staghorn-shaped large vessels. However, it lacks the vacuolated stromal cells of CHB, and the neoplastic cells are diffusely positive for CD34, a marker not expressed by the stromal cells of CHB. Schwannoma of bone is extremely well circumscribed, composed of spindle cells with wavy-appearing nuclei frequently arranged in a palisading fashion, and classically has a biphasic appearance with Antoni A and B areas. More than 50% of chordomas involve the sacrococcygeal region. The tumor cells are arranged in strands and cords, have small, round, uniform nuclei and abundant pale vacuolated cytoplasm. The expression of EMA, low molecular cytokeratins and, less consistently, of S-100 protein by chordomas, further helps to differentiate them from CHB.

In conclusion, we report a case of primary intraosseous CHB arising in the sacrum, not associated with VHL disease, with immunohistochemical and ultrastructural characterization. Capillary hemangioblastoma developing in extra CNS sites is increasingly recognized, but to our knowledge, only one case originating in the bone has been previously reported. Considering the anatomy of the sacrum, it is possible that the tumor originated from a peripheral nerve, although this could not be demonstrated with certainty by imaging or at the time of surgery. This entity should be considered in the differential diagnosis of tumors featuring vacuolated epithelioid cells intimately associated with a prominent vascular component. The combination of the histological, immunohistochemical, and ultrastructural findings ensures proper diagnosis.

References