Cystic Tumor of the Cerebellum With Megaloblastic Erythropoiesis

Annika M. Svensson, MD, PhD; Yijun Pang, MD, PhD; Nicholas J. E. Moore, MD; Barbara H. Tindle, MD

A 52-year-old man suffered an accidental 4.5-m fall from a ladder while trimming trees; he sustained a fracture of the left femur. During the workup following the trauma, a computed tomographic scan of the neck and spine incidentally revealed a 3.4 × 3.6-cm solitary cystic lesion in the right inferior cerebellar hemisphere with some hemorrhage and an enhancing mural nodule. Magnetic resonance imaging confirmed this finding (Figure 1). The patient had no previous medical history. He denied symptoms from any organ system, including neurologic problems. Physical examination was unremarkable except for the skin, on which were found a few scattered soft, nontender lumps on the back, forearms, and chest. The patient conveyed that the lumps had been classified as lipomas in the past. There were no nevi or other discoloration. Family history was negative for phakomatoses, including von Hippel-Lindau (VHL) syndrome.

At the time of surgical removal of the lesion, several arteries were seen entering into the mural nodule. Frozen section showed cyst wall with increased cellularity, collagen, and hemosiderin deposition. The cyst wall and the mural nodule were grossly removed in toto and submitted for evaluation, along with fluid from the cyst. On gross examination, the specimen consisted of a tan-pink to red, hemorrhagic, 0.8 × 0.6 × 0.3 cm piece of soft tissue. Hematoxylin-eosin-stained sections revealed a hypervascular and hypercellular lesion containing epitheloid cells with vesicular cytoplasm (Figure 2). Rosenthal fibers were observed in the cyst wall (Figure 3). Immunohistochemical evaluation revealed that the cells were positive for neuron-specific enolase, negative for epithelial membrane antigen, and negative for CD10. The cystic fluid specimen was composed of blood containing lymphocytes and megaloblastic erythropoiesis (Figure 4). There was no evidence of myelopoiesis or megakaryopoiesis.

What is your diagnosis?
Pathologic Diagnosis: Hemangioblastoma With Megaloblastic Hematopoiesis

Abstract

Cerebellar hemangioblastomas constitute 1% to 2% of all primary nervous system tumors and are generally considered to be benign. Hemangioblastoma is the most common presenting manifestation of von Hippel-Lindau disease. However, most cerebellar hemangioblastomas are not associated with von Hippel-Lindau disease. The main differential diagnosis is metastatic renal cell carcinoma, which may be distinguished from hemangioblastoma by staining with glucose transporter 1 or, as recently described, by inhibin α-subunit (inhibin A). Although extramedullary hematopoiesis is a rare finding in tumors of the central nervous system, several cases of hemangioblastoma with hematopoiesis in the central nervous system have been described previously. However, to our knowledge this is the first observation of megaloblastic erythropoiesis in a cerebellar hemangioblastoma.

Cerebellar hemangioblastomas represent 1% to 2% of all primary tumors of the central nervous system. They are considered to be benign neoplasms, but may cause major morbidity. Hemangioblastoma is the most common presenting manifestation of the autosomal-dominant VHL disease (OMIM 193300), which is associated with a germ-line mutation of the VHL tumor suppressor gene. This diagnosis should be considered in patients with more than one tumor or a tumor in an unusual location. In this case, computed tomographic imaging of the thorax, abdomen, and pelvis to rule out VHL lesions was unremarkable. The majority of cerebellar hemangiomas are not associated with VHL. Somatic inactivation of the VHL gene has been shown in sporadic cases of hemangioblastoma. Cerebellar hemangioblastomas occur most often in adults aged 30 to 50 years; there is a slight male predominance. Symptoms depend on localization and size, and may include signs of cerebellar dysfunction as well as hydrocephalus. Major hemorrhages are rare. Although hemangioblastomas associated with VHL are often multiple, and may present significant surgical challenges, the prognosis for a radically excised solitary, sporadic cerebellar hemangioblastoma is considered favorable.

Four types of hemangioblastoma have been described: type 1 (6%), simple cyst form with no macroscopic evidence of mural nodule; type 2 (65%), macrocystic form, consisting of a variably sized cyst with a mural nodule 0.502.5 cm in size; type 3 (25%), solid tumor; and type 4 (4%), predominantly solid with several small cysts. Histologically, hemangioblastomas typically show a mixture of variably sized capillary vessels and epitheloid stroma cells containing lipid vacuoles, the latter feature allowing for differentiation from angiomia. Hemangioblastomas are slow-growing and typically display no mitotic figures. The origin of the neoplastic stromal cells is not well defined. These cells seem to represent a heterogeneous population of mesenchymal cells of angiogenic lineage. Immunohistochemical studies have shown frequent expression of vimentin, S100 protein, neuron-specific enolase, and cytokeratin; less expression of desmin, factor XIIIa and Ricinus communis lectin receptors; occasional expression of factor VIII and ulex europaeus lectin; and negativity for other markers of endothelial, neuronal, glial, neuroendocrine, and smooth muscle differentiation. Electron microscopy has demonstrated a clear relationship of stromal cells with endothelial cells, smooth muscle cells, and pericytes. The current World Health Organization classification of brain tumors lists hemangioblastoma as a single entity in the tumors of uncertain histogenesis.

The main differential diagnosis is metastatic renal cell carcinoma, which shares the clear cell features of the hemangioblastoma cells. Compared with the tumor cells of renal cell carcinoma, the hemangioblastoma cells tend to have more uniform nuclear chromatin, smaller nucleoli, and a more intimate arrangement of capillaries and stromal cells. The absence of necrosis is also a distinguishing feature. Immunohistochemically, glucose transporter 1 immunoreactivity has been used to distinguish hemangioblastoma from metastatic renal cell carcinoma. In addition, immunohistochemical staining of inhibin A, which is expressed in the stromal cells of hemangioblastoma but rarely in renal clear cell carcinoma, has recently been used for this purpose. In the present case, a panel consisting of neuron-specific enolase, epithelial membrane antigen, and CD10 was used for diagnosis. Hemangioblastoma, in contrast to renal cell carcinoma, tends to stain for neuron-specific enolase but not for epithelial membrane antigen. The tumor in this case was positive for neuron-specific enolase but negative for epithelial membrane antigen. In addition, the tumor was negative for CD10 (whereas it was positive in more than 90% of renal cell carcinomas). Sampling of the cyst wall of hemangioblastomas may show gliosis, and Rosenthal fibers may be prominent, mimicking pilocytic astrocytoma. Furthermore, during processing for frozen section, lipid contained in the vacuoles may vanish. In cases in which frozen sections show cyst wall with fibroid cells, the surgeon should be asked to inspect for mural nodules. In this case, the nodule had already been observed on the neuroimaging studies and tissue was submitted for routine processing.

Extramedullary hematopoiesis is rarely found in primary brain tumors. However, hemangioblastoma is the central nervous system tumor that is most commonly associated with extramedullary hematopoiesis, with approximately 10 cases documented in the literature. For instance, a previous study revealed hematopoiesis in 4 of 26 hemangioblastoma specimens examined. One case was associated with erythrocytosis. Approximately 20% of cerebellar hemangioblastomas display polycythemia caused by local production of erythropoietin. Disruption of VHL-mediated degradation of hypoxia-inducible factors may increase the expression of erythropoietin. Hypoxia-inducible factors may also act to stimulate angiogenesis by increased levels of vascular endothelial growth factor and platelet-derived growth factor-β. Our patient, however, did not display erythrocytosis (data not shown).

Megaloblastic erythropoiesis is characterized by erythroblasts larger than normal at all stages of maturation, dissociation between nuclear and cytoplasmic maturation, and the presence of macrocytes in the peripheral blood. Although the erythropoietic cells found in the cyst fluid in this case were clearly megaloblastic, the patient did not display megaloblastosis of the peripheral blood (mean corpuscular volume, 85 fl [reference range, 81–95 fl] with normal red cell morphology). The megaloblastosis was thus restricted to the tumor area. To our knowledge, megaloblastic erythropoiesis has not previously been ob-
served in hemangioblastomas. Reporting hematopoiesis in hemangioblastomas is important in light of frequent recurrences of the tumor. New treatments, including growth factors, may work to expand intracranial extramedullary hematopoiesis.9

References