

Challenging Manifestations of Malignancies

CASE 1. Polycythemia and High Serum Erythropoietin Level As a Result of Hemangioblastoma

A 44-year-old white male was referred to our hospital for evaluation of asymptomatic polycythemia which had been detected on a routine checkup. On admission, the patient described a mild headache for about 1 month without nausea or vomiting. There was no history of thromboembolism and no pruritus. As a passionate cyclist, he was a nonsmoker and denied using stimulating drugs such as exogenous erythropoietin (EPO). On physical examination the patient seemed in good general health, his blood pressure was 150/100 mmHg, and his pulse rate 60 beats/min. Auscultation of the heart and lungs was unremarkable and no neurologic deficits were found. Laboratory studies showed markedly increased hemoglobin at 20.2 g/dL, a hematocrit of 63%, and slightly elevated uric acid. The white blood and platelet counts were normal. Bone marrow (Fig 1; hematoxylin and eosin, $\times 40$) revealed increased, left-shifted erythropoiesis, normal granulopoiesis and megakaryopoiesis, and no evidence of a myeloproliferative disorder. Measurement of the total RBC mass by isotope dilution with chromium-51-labeled red cells demonstrated marked erythrocytosis at 42.4 mL/kg body weight (normal expected value, 27 mL/kg body weight) and reduced plasma volume. The serum EPO level was elevated at 32 U/L (normal, 5 to 25 U/L). Evaluation for secondary erythrocytosis showed no evidence of an EPO-

producing tumor on the computed tomography scan of the chest and abdomen, or increased EPO due to hypoxemia. Eventually, because there is a known association of cerebral hemangioblastoma with elevated EPO levels, magnetic resonance imaging (MRI) of the cerebrum was performed. The MRI scan (Fig 2) disclosed a tumor measuring 3 \times 4 cm in diameter in the right cerebellar hemisphere (black arrow) with perifocal edema and mid-line shift (white arrow), resulting in obstruction of the fourth ventricle (thin arrow). Radiologic findings were consistent with the criteria of a solid cerebellar hemangioblastoma. With the clinical diagnosis of an EPO-producing hemangioblastoma in the posterior fossa, the patient was referred to neurosurgery. The tumor could be resected completely and the patient had no neurologic deficit postoperatively. Histology (Fig 3; $\times 40$) confirmed the diagnosis, showing the characteristic findings of a capillary hemangioblastoma WHO grade 1 (A, hematox-

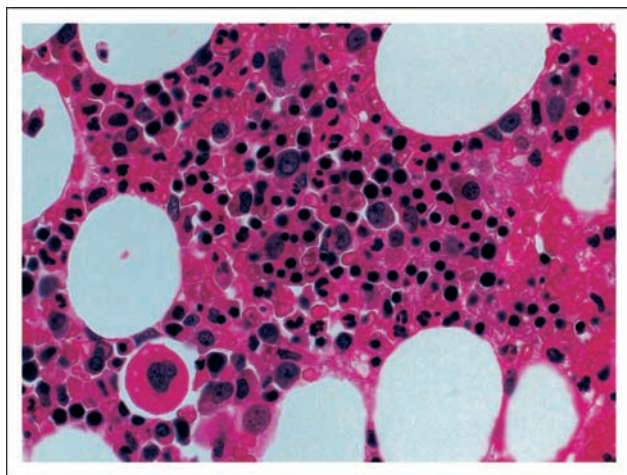


Fig 1.

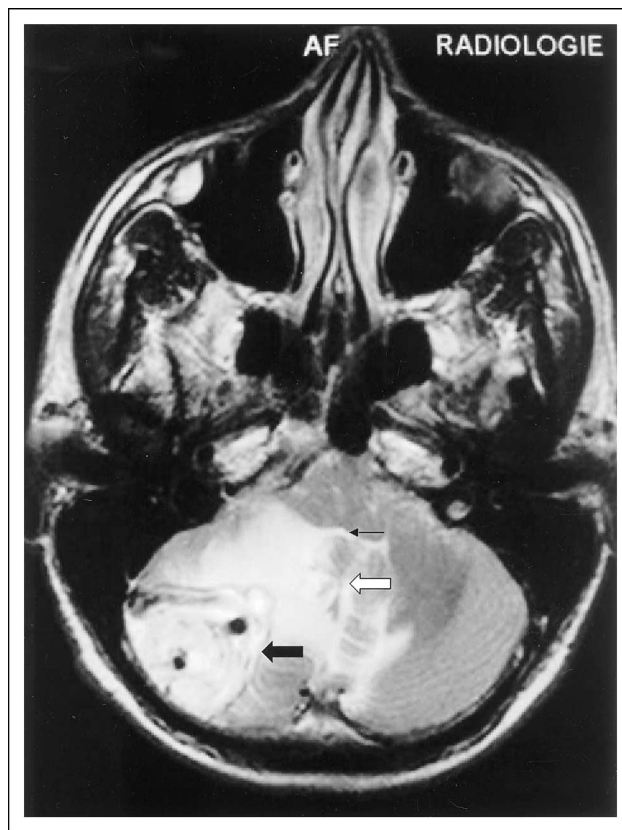


Fig 2.

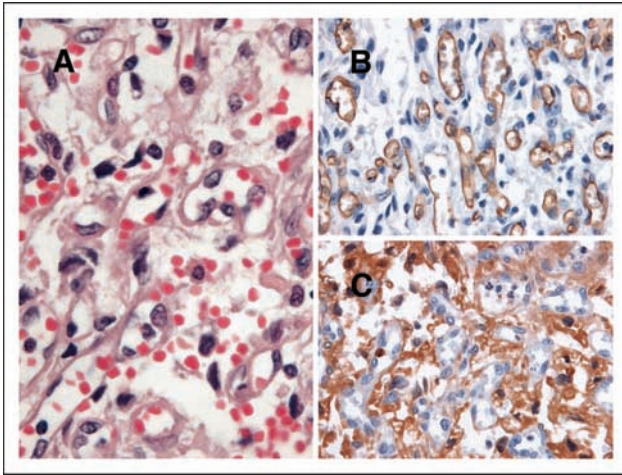


Fig 3.

ylin and eosin) with numerous capillaries (B, immunohistochemistry positive for CD34) and intermingled stromal cells (C, immunohistochemistry positive for S-100). Three months after surgery, the patient was in excellent condition with hemoglobin levels within normal range and no residual tumor on MRI of the cerebrum. Given that hemangioblastomas are strongly associated with Von Hippel-Lindau (VHL) disease, investigation for *VHL* mutation was performed and showed no mutated genes in all three exons.

Hemangioblastomas account for approximately 2% of intracranial tumors and are found especially in the cerebellar hemispheres and the vermis. Clinical features include signs of increased intracranial pressure or cerebellar deficits and in 10% to 20% of patients, a paraneoplastic erythrocytosis.^{1,2} The tumor originates most probably from endothelial cells, presents as a cystic, highly vascular lesion, and enlarges +slowly. Stromal cells have been identified as the site of EPO production by in situ hybridization.³ Hemangioblastomas may occur sporadically or as a manifestation of VHL disease, a heritable tumor syndrome caused by inactivation of the *VHL* tumor suppressor gene and characterized by the occurrence of neoplasias in multiple organs.⁴ Although in healthy individuals the VHL protein (pVHL) is inactivated by hypoxia, the mutated pVHL imitates hypoxia

on a molecular basis leading to dysregulation of the hypoxia-inducible factor and as a consequence overexpression of EPO.⁵ Other mutations in the molecular pathway leading to upregulation of EPO could be postulated in our patient. The fact that 35% to 58% of CNS hemangioblastomas are associated with VHL disease suggests that patients with apparently sporadic hemangioblastoma should be investigated for VHL, including molecular mutational testing, to ensure that the disease is not underdiagnosed.⁴

Our patient demonstrates that in the presence of unexplained polycythemia and elevated serum EPO levels, even in the absence of CNS symptoms, a CNS tumor has to be excluded by MRI of the brain.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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CASE 2. Langerhans Cell Histiocytosis Presenting With a Skin Rash

A 73-year-old white woman presented with a skin rash for 2.5 years. The rash initially began on her forehead as erythematous papules with crusting (Fig 1A). It progressed to involve her entire scalp, resulting in sebor-

rhea and mild alopecia. She also noted confluent erythematous patches involving skin folds of the trunk (beneath breasts and pannus), axilla, groin, and gluteal region. The rash worsened 6 months before admission and was described as pruritic and burning. She was initially treated with medicated shampoos and a variety of topical creams, including antifungal agents, without sig-