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## Intracranial extramedullary hematopoiesis associated with pilocytic astrocytoma: a case report

Received: 30 June 2003 / Revised: 4 August 2003 / Accepted: 4 August 2003 / Published online: 30 September 2003  
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**Abstract** Intracranial EMH is only occasionally found in primary brain tumors (mostly hemangioblastomas) and, to our knowledge, this is the first case of EMH associated with an astrocytoma. Intracranial extramedullary hematopoiesis (EMH) is described in a 29-year-old man with a recurrent pilocytic astrocytoma in the tectal region. Special stains confirmed the identities of erythroid, myeloid and megakaryocytic cells. The patient had no evidence of a predisposing bone marrow disorder or systemic EMH. Although the presence of multinucleated and blastic cells associated with a low-grade brain neoplasm is unusual, recognition of hematopoietic lineages allows EMH to be readily identified. Another tumor resection after a year of follow-up confirmed the absence of malignant progression in this recurrent astrocytoma. The small number of cases describing intracranial EMH in the absence of systemic hematologic abnormalities are correlated with the findings in this case. The low incidence of intracranial EMH indicates that cells with hematopoietic potential are seldom exposed to a supportive microenvironment within the central nervous system. However, intracranial EMH should be included as a potential, ancillary diagnosis when considering brain lesions. This may be particularly true if medical therapies involving growth factors or stem cells are found to promote hematopoiesis.

**Keywords** Extramedullary hematopoiesis · Pilocytic astrocytoma · Hematopoietic factors · Tectal region · Megakaryocytes

### Introduction

We report a case of extramedullary hematopoiesis (EMH) associated with a recurrent pilocytic astrocytoma. While uncommon, when EMH does occur in the CNS, it is usually associated with hematologic disorders rather than primary brain lesions. It is well known that bone marrow failure predisposes patients to developing EMH. Intracranial EMH has been described many times in patients with disorders such as polycythemia vera, thalassemia, osteopetrosis, etc., but it is an uncommon finding in patients without bone marrow or bone disorders. We report an unusual case of intracranial EMH associated with a pilocytic astrocytoma in a patient without evidence of bone marrow failure.

### Case report

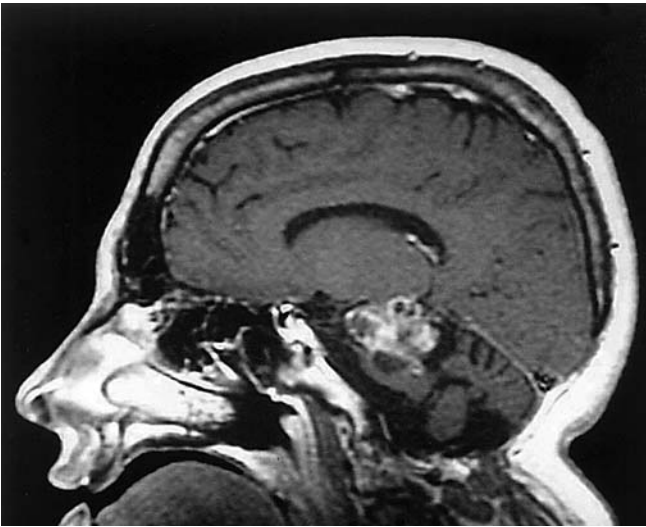
A 24-year-old man presented with a 2 year history of worsening headaches, dizziness and ataxia. He had also developed blurred vision. On physical examination the patient had nystagmus on lateral gaze and an abnormal gait. A CT scan disclosed a large, cystic posterior fossa lesion associated with a contrast-enhancing nodule in the brainstem. A pilocytic astrocytoma was surgically debulked, and the patient underwent external beam radiation. Two years later, MRI scans showed recurrence of a cystic, enhancing, tectal tumor (Fig. 1). He underwent Gamma Knife Boost radiosurgery at that time. Four years after the initial surgery, worsening of his symptoms led to a second resection of the pilocytic astrocytoma. EMH was detected in the second tumor resection specimen. His hematocrit at this time was 41.5%. The patient has been followed for 1 year and recently underwent a third tumor resection specimen (performed 5 years after the initial surgery). The specimen again showed a pilocytic astrocytoma with no evidence of malignant progression. There was no evidence of a bone or hematologic disorder in the patient. No evidence of systemic EMH, including hepatosplenomegaly, was found at any time.

Following standard formalin fixation and paraffin processing, hematoxylin and eosin-stained histologic sections were prepared.

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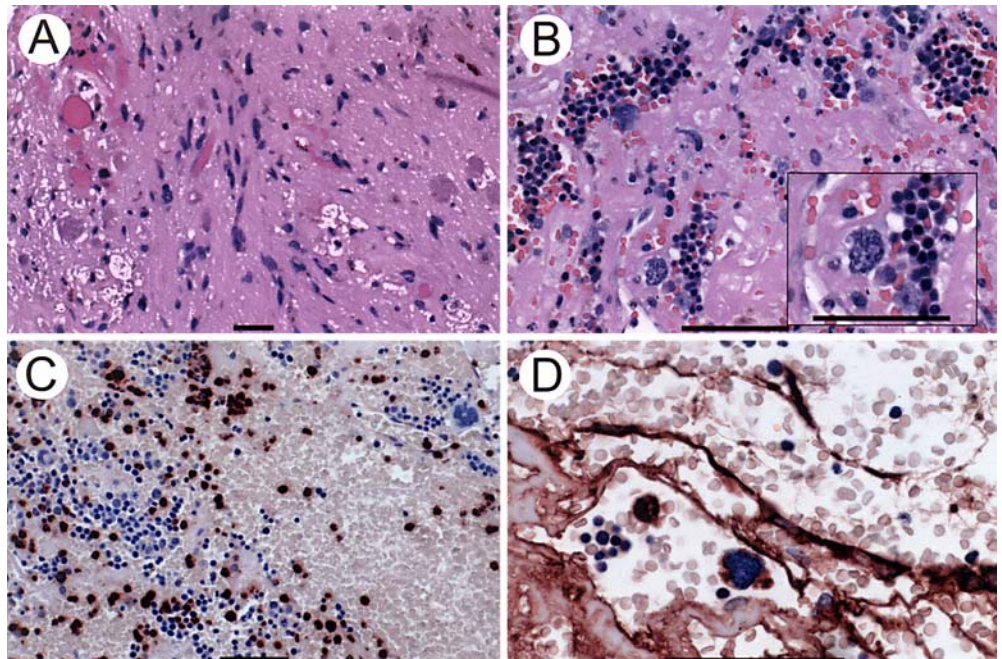
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**Fig. 1** Sagittal T1-weighted MRI scan with contrast. Recurrent/residual tumor in the tectal region. The tumor is cystic with regions of enhancement. Compression of the midbrain is better seen on other views. The MRI was performed 2 years after the initial tumor resection and 2 years prior to the second tumor resection that included EMH

Immunohistochemical stains were performed using antibodies directed against leukocyte common antigen (1:25), glial fibrillary acidic protein (1:200), glycophorin (1:200), myeloperoxidase (1:1000), Factor VIII-related antigen (1:500) and Ki67 (1:100) (all from DAKO, Carpinteria, Calif.). Antibodies for placental alkaline phosphatase (1:70) (Biogenex, San Ramon, Calif.) were also used. A cocktail of antibodies against pankeratin included those for AE13 (1:2,000) and keratin (1:80) (DAKO) and CAM5.2 (1:1,000) (Becton-Dickinson, San Jose, Calif.).

**Fig. 2** Microscopy of the pilocytic astrocytoma with associated extramedullary hematopoiesis. **A** Abnormal astrocytic cells infiltrating brain parenchyma with eosinophilic granular bodies, Rosenthal fibers, slight microcystic changes and hemosiderin pigment present. Hematoxylin and eosin stain. **B** Islands of hematopoietic cells, including megakaryocytes, are present in granulation tissue. The insert shows an enlarged view. Hematoxylin and eosin stain. **C** Myeloperoxidase reactive myeloid cells mixed with other hematopoietic cells. Hematoxylin counterstain. **D** Factor VIII-related antigen-reactive megakaryocytes and endothelium. Cluster of hematopoietic cells of other lineages stain negatively. Factor VIII-related (von-Willebrand factor) antigen. Hematoxylin counterstain. Magnification bars in **A–D** represent 100  $\mu$ m for each figure



## Results

### Gross examination

The initial tumor resection yielded 15 ml of amber-colored fluid and dark red and tan tissue, measuring in aggregate approximately 2.0×0.5×0.5 cm. The second tumor resection (with EMH) yielded two fragments of solid red-tan tissue (0.2×0.1×0.1 cm and 0.5×0.3×0.2 cm) and blood clot (4.5×2.5×1.0 cm) containing small tissue fragments. The third tumor resection (5 years after the initial surgery) yielded tan-brown tissue fragments measuring 1.0×0.8×0.7 cm in aggregate.

### Microscopic examination

The cyst fluid removed at the time of the first resection was proteinaceous and acellular. Tissue and cytologic smears from the first and second tumor resections showed features of pilocytic astrocytoma. Neoplastic cells with long fibrillar processes, elongated nuclei with moderate pleomorphism, Rosenthal fibers and eosinophilic granular bodies were present (Fig. 2A). The neoplastic cells were strongly immunoreactive for glial fibrillary acidic protein. Mitoses were not seen, and the cellular proliferation index, assessed using a Ki67 immunostain, was 3–4% in the second tumor resection specimen. Evidence of hemorrhage, consisting of hemosiderin and pigment-laden macrophages, was present in the first and second tumor resection specimens. Fibrosis with thickened hyalinized blood vessels was noted in the first resection specimen. Tissue fragments embedded in the blood clot from the second tumor resection specimen showed granulation tissue with

foci of EMH, consisting of multinucleated megakaryocytes and mononuclear hematopoietic cells (Fig. 2B). EMH was recognized in three of eight 4X microscopic fields of tissue scanned at low power, excluding fields containing only blood. Multiple foci of mature and immature hematopoietic cells of erythroid, myeloid and megakaryocytic lineages [confirmed with stains for glycoporphin, myeloperoxidase (Fig. 2C) and Factor VIII-related antigen (Fig. 2D), respectively] were present. A stain for leukocyte common antigen also revealed a few lymphocytes. The hematopoietic cells were immunonegative for pankeratin, glial fibrillary acidic protein and placental alkaline phosphatase. No fragments of choroid plexus or evidence of contaminating bone marrow (such as adipose tissue, bone spicules or bone dust) from the skull were found.

A third tumor resection (5 years after the initial surgery) also showed the microscopic features of a pilocytic astrocytoma, including eosinophilic granular bodies, without any evidence of malignant progression. The Ki67 proliferation index was 3%. Hemosiderin and collections of foamy macrophages in solid tissue fragments were present, but no hematopoietic cells were found.

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## Discussion

Intracranial EMH occasionally occurs without predisposing bone marrow disorders. Although isolated intracranial EMH occurs most often in association with hemangioblastomas, it has also been observed in two intracranial lipomas, a meningioma, a few subdural hematomas, an encephalocele, a tumor-like mass of papillary endothelial hyperplasia and a pilocytic astrocytoma (this case). The potential for cerebellar hemangioblastomas to be associated with EMH was first suggested by studies of explanted tumor cells in culture [7], and later confirmed by reports of at least ten reported cases [12, 14, 24, 33]. Two reports noted a predominance of red cell precursors or normoblasts in the EMH foci, presumably the result of erythropoietin produced by hemangioblastomas [12, 33]. No adverse effects on prognoses have been attributed to EMH [12, 14, 33].

Rubinstein was the first to note that hematopoietic tissue can occur within a lipoma, but did not describe specific cases [23]. Since then two patients with EMH in lipomas of the tectal region have been described [15, 21]. One case of EMH in a meningioma with atypical features (diagnosed as a malignant meningioma) has been reported [11].

Although EMH has been recognized by experienced neuropathologists as occurring in the outer membranes of subdural hematomas [5], documentation of specific cases in the literature is scant. A case of localized intracranial erythropoiesis was reported in an infant with large subdural hematomas and anemia that resolved following multiple procedures for fluid removal [28]. An encephalocele with EMH in the frontal lobe was reported in another infant born with semilobar holoprosencephaly, a subdural hematoma and anemia [8]. A case of extensive intracranial papillary endothelial hyperplasia associated with thrombotic material and EMH has been reported in a fraternal twin

neonate, possibly associated with an underlying vascular malformation or hemangioma [26].

Although the association of EMH with pilocytic astrocytoma in our case is unique, some of its features are shared with other cases of intracranial EMH. The pilocytic astrocytoma in this case and two lipomas reported earlier involved the tectal region [15, 21]. A prominent vascular component (granulation tissue in our case) was associated with intracranial EMH in several cases [8, 11, 12, 14, 26, 33]. This case had localized hemorrhage, which was also noted previously [8, 11, 26, 28]. Although subdural hemorrhage has been attributed to EMH that occurred in a patient with a hematologic disorder [3], it is not established whether loculated blood can be an etiologic factor for EMH in a non-osseous site or if localized hemorrhage represents a secondary effect. Although our patient received radiation treatments, irradiation of intracranial tissues has not been associated with EMH. While hypoxia and ischemia may be associated with increased erythropoietin production in brain tissue [19, 27], irradiation damage to blood vessels is not a recognized etiologic factor of EMH to our knowledge. Importantly, responsiveness of EMH to radiation therapy has been reported [4, 6, 13, 16, 18].

Giant cells, sometimes multinucleated, and immature cells displaying high nuclear to cytoplasmic ratios are features of high grade astrocytomas. Thus, the presence of multinucleated giant cells and blastic cells in a recurrent astrocytoma specimen can be cause for concern. Recognition of the histologic features of EMH, with immunohistological confirmation of hematopoietic lineages, is essential for proper management of the patient. As noted for other intracranial tumors in the literature, intracranial EMH did not alter the prognosis for this patient.

Historically, the intracranial cavity has been included as a potential site for EMH based on recapitulation of hematopoietic sites found in lower vertebrates and mammalian embryos. Intracranial EMH occurs normally in adults of some fish species as a relatively large, organ-like tissue mass of hematopoietic tissue located behind the cerebellum with involvement of the choroid plexus overlying the fourth ventricle. The hematopoietic cells become recognized as bone marrow in small foci where this tissue extends into bony cavities found inside the cartilaginous skulls of ganoid fish [25, 31]. EMH has been found in the choroid plexus of marmosets [22] and dogs [1, 17, 25], and the possibility of EMH occasionally occurring in the human choroid plexus is generally accepted [10]. Intracranial EMH occurs during mammalian embryologic development. In rat embryos, large aggregates of erythroblasts are routinely found in several characteristic CNS locations (lamina terminalis, the fifth cranial ganglion and the thoraco-lumbar sympathetic ganglia). Smaller foci are also found in the thalamus, ventral portions of the cerebral hemispheres and elsewhere. However, this tissue disappears by the 20th day of development [2]. In humans erythroblasts have been found around meningeal nerves [2, 9]. Intracranial EMH found in some infants with anemia may thus represent persistence of fetal EMH.

Other predisposing factors are also suggested. Maximow proposed in 1909 that multipotential mesenchymal cells differentiate into hematopoietic cells in a variety of extramedullary sites [2, 20]. Low numbers of hematopoietic stem cells from the bone marrow have been found to circulate in the peripheral blood [32]. Hematopoietic stem cells could potentially arrest their migration and proliferate when exposed to a favorable environment within the CNS.

Central nervous system cells are capable of producing hematopoietic growth factors that may promote the development of EMH. Erythropoietin is sometimes produced by hemangioblastomas, as mentioned earlier. Human astrocytic cells can produce granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor, and these cells can stimulate human bone marrow stem cells to proliferate in vitro [29, 30].

Although the CNS is capable of producing hematopoietic growth factors, the constitution of a microenvironment that successfully promotes development of intracranial EMH appears to seldom occur. Nevertheless, intracranial EMH should be included as a potential, ancillary diagnosis when considering CNS lesions, even in the absence of bone marrow failure or systemic EMH. This may be especially true in the future if anticipated therapies involving growth factors and stem cells exhibit any potential for promoting EMH.

**Acknowledgements** We would like to thank Leslie Viramontes, HT, and colleagues at the University of Pittsburgh Medical Center Immunohistochemistry Laboratory for their technical assistance with special stains. We thank The Nick Eric Wichman Foundation for financial support.

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