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LETTER TO THE EDITOR

Intra-Axial Frontal Cyst with Ependymoma-Like Proliferation: Neuroectodermal or Neurenteric?

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To the Editor:

Intracranial cysts are classified into 3 main categories based on their embryologic origin: ectodermal (such as epidermoid and dermoid cysts), neuroectodermal (including arachnoid, choroid plexus, and ependymal/glioependymal cysts), and endodermal (neurenteric/enterogenous, colloid, and Rathke cleft cysts). The anatomic location of each lesion provides useful information for an accurate diagnosis. Ependymal/glioependymal cysts may be intraventricular, leptomeningeal, or intraparenchymal (1), whereas neurenteric cysts are characteristically located in the subarachnoid space anterior to the spinal cord, most commonly in the cervical region. They have also been reported in the third or fourth ventricles, the cerebellopontine angle, brainstem, and cerebral hemispheres (2).

Ependymal/glioependymal and neurenteric/enterogenous cysts can be readily differentiated by their localization, the histological features of the cyst epithelium and immunohistochemical profile (1). In addition, both ependymal/glioependymal or neurenteric/enterogenous cysts can harbor adjoining glial or glioneuronal elements; however, detailed descriptions of these elements are unusual (1, 3). Here, we present a case of an intracranial cyst with an associated ependymoma-like component.

A 58-year-old man who was a kidney donor at the age of 51 presented with a one-month history of intense headache. Computed tomography and magnetic resonance imaging (MRI) demonstrated a large non-enhancing superficial mass measuring 49 mm × 27 mm within the right frontal lobe, with remodeling of the inner table of the frontal bone, suggesting an extra-axial location. The lesion had a main septated cystic component and 2 discrete solid mural foci without associated edema. These were hyperintense on T1 and T2 in MRI. The patient underwent brain surgery with gross total tumor resection. The intraoperative neurosurgical impression was of an intracranial lesion with a cystic component filled with dense material and a poorly defined solid component without a clear dissection plane between the lesion and the adjacent parenchyma.

In hematoxylin and eosin stain, the tumor on showed a pseudostratified epithelium composed of cuboidal (in the basal area) to columnar ciliated cells (in the luminal area), with round basal nuclei and luminal eosinophilic cytoplasm and lipofuscin granules (Fig. 1). There were no goblet cells detected despite careful evaluation with periodic acid-Schiff, mucicarmine, and Alcian blue stains. The epithelium rested on a basal membrane and a variable glial component. This component ranged in appearance from well-delimited subepithelial areas of variable thickness to macroscopically nodular areas. It was composed mainly of cells with round to oval nuclei with scant atypia and small inconspicuous nucleoli. They were distributed unevenly, with areas of fascicular fibrillar background devoid of nuclei interspersed and others with mild nuclear aggregation. The fibrillar background seemed focally hyalinized, and intralesional vessels with hyalinized mural change were present. There were Rosenthal fibers and hemosiderin deposits but no inflammatory cells. No mitoses, necrosis, or microvascular proliferation was observed.

Immunohistochemistry showed the epithelial cells to be diffusely and intensely reactive for CK AE1–AE3 and CK7. Isolated cells were positive for S-100, GFAP, and EMA, whereas they were negative for CK20 and transthyretin. Collagen-IV immunostain showed a homogeneous basement membrane beneath the epithelial cells. The solid underlying component was diffusely positive for GFAP, negative for Olig2, and EMA showed an inconspicuous paranuclear dot positivity. Ki67 was positive in 1% of the glial cells, IDH-1 was negative and ATRX showed nuclear retention. Electron microscopy demonstrated an epithelial component

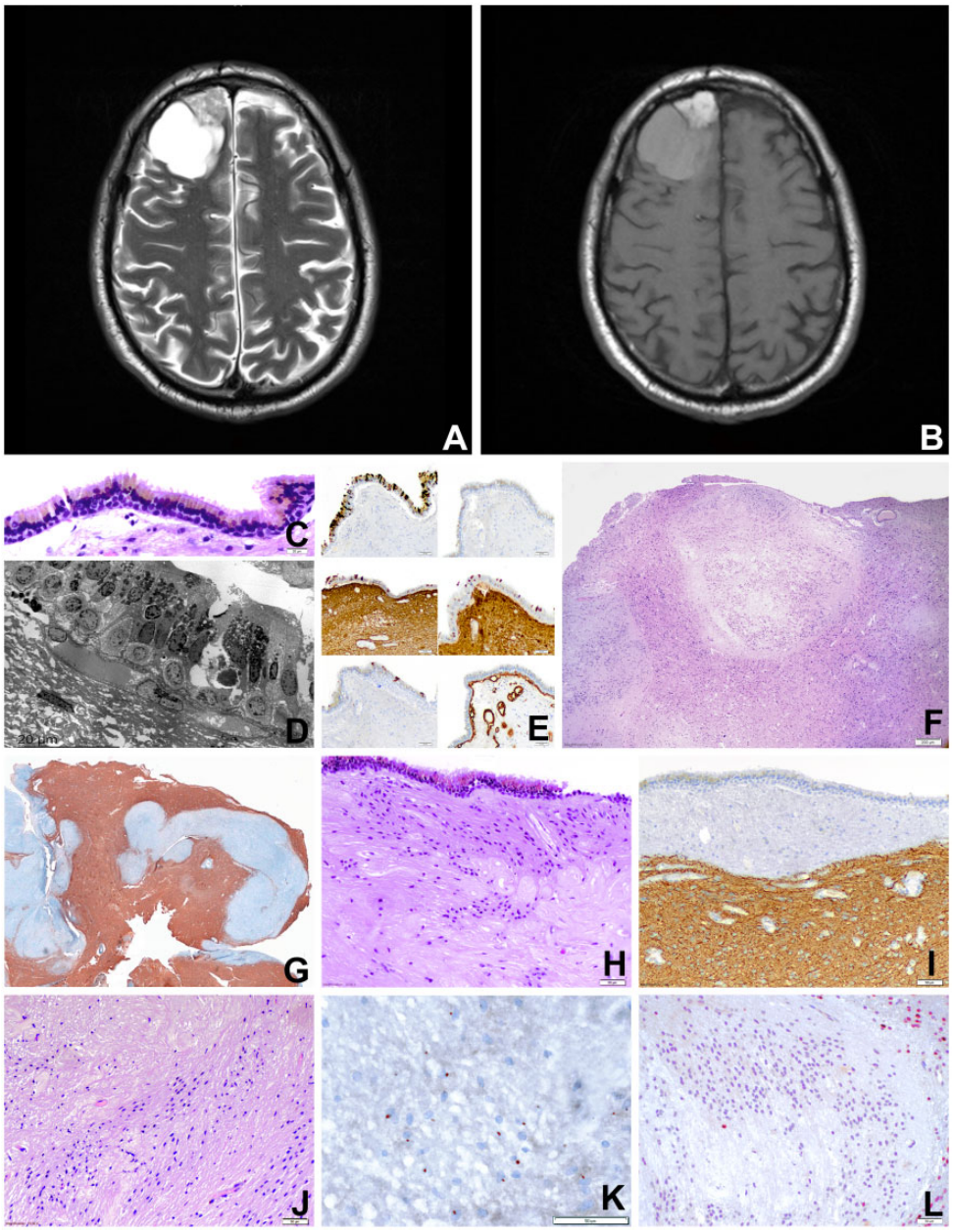

FIGURE 1. (**A, B**) Axial views of preoperative MRI showing a non-enhancing frontal mass hyperintense of T2 **(A)** and T1 **(B)**, composed of a main septated cystic component and 2 discrete solid mural foci without associated edema. **(C)** The cyst was lined by a pseudostratified ciliated epithelium (H&E, 400×). **(D)** Electron microscopy showed epithelial cells resting on a basal membrane with no rupture or cytoplasmic extensions (×3000). **(E)** The epithelial cells were reactive for CK7 (upper left) while negative for CK20 (upper right). Immunostains for GFAP (middle left) and S-100 (middle right) showed focal positivity (×100). The cyst wall had focal positivity for EMA (lower left). Immunostain for collagen-IV showed a homogeneous basement membrane (lower right). **(F)** The ependymoma-like proliferation showed nodular foci (H&E, ×20). **(G)** These were well-delimited, as seen with anti-neurofilaments stain (10×). **(H)** The fibrillar background harbored intralesional hyalinized vessels (H&E, ×100). **(I)** This proliferation was closely related to the cyst wall, as shown with the anti-neurofilaments stain (×100). **(J)** The cells were arranged in areas of fascicular fibrillar background devoid of nuclei interspersed with others with mild nuclear aggregation (H&E, ×100). **(K)** EMA immunostain showed a paranuclear dot positivity (×400). **(L)** Olig2 immunostain was negative (×100).

that was pseudostratified to focally stratified with a cuboidal basal component and a columnar apical component. The cells had apical cilia and multiple electrondense granules in the apical compartment, suggestive of lipofuscin but secretory granules could not be ruled out. The epithelium rested on a basal membrane; serial samples showed no focal ruptures or

cytoplasmic extensions of the epithelia to the underlying vessels, a feature seen in ependymal cells. The glial component had artifacts due to the fact that the original sample was formalin-fixed, paraffin-embedded tissue; hence, signs of ependymal differentiation such as cytoplasmic microlumina could not be ascertained. The cyst was diagnosed as glioependymal cyst with ependymoma-like proliferation. Postoperative MRI confirmed total resection and no adjuvant therapy was given to the patient. Seven months after surgery, the patient remained in remission.

We present a case of an intra-axial cyst with a well-defined cyst epithelium and a subepithelial glial component clearly suggestive of ependymoma-like differentiation. Ependymal and glioependymal cysts are considered to be of neuroectodermal origin, along with choroid plexus and arachnoid cysts. Those cysts are characterized by a lining that ranges from cuboidal to columnar ciliated cells that are negative for cytokeratins and positive for S-100 and patchy for GFAP, with no collagen IV-positive basement membrane present and no intraepithelial mucin-producing goblet cells (1). In contrast, neurenteric or enterogenous cysts are considered to be of endodermal origin. They are lined by a ciliated, pseudostratified columnar to cuboidal epithelium with goblet cells that lies on a basement membrane; the underlying stroma may contain other elements such as seromucinous glands, lymphoid tissue, or glioependymal tissue (4). The epithelial cells are immunoreactive for EMA and cytokeratins, including CK7 but not usually CK20, with a variable positivity for CEA and negative for GFAP and S-100 protein (2).

The etiology of intracranial neurenteric cysts remains uncertain and it has been suggested to represent endodermal entrapment during embryonal development (5). This theory would not explain the location of some intracranial neurenteric cysts, such as in the present case. The ependymoma-like component underlying the cyst wall has features partially suggestive of a subependymoma or a tanycytic ependymoma. However, frontal lobe hemispheric parenchyma is not a common location for these entities as subependymomas usually have an intraventricular location, most frequently the fourth ventricle followed by the lateral ventricles and tanycytic ependymomas are most commonly found in the spinal cord (6, 7). In the present case, the location in the frontal lobe, the immunopositivity for S-100 and GFAP, as well as the ependymal-like proliferation strongly suggest an ependymal origin of the lesion. Therefore, it would be reasonable to suggest that the neurenteric cyst features may be secondary to posterior metaplasia. Indeed, ependymomas may show metaplastic changes (8, 9), and the literature provides variable histological descriptions for ependymal cyst histology, including some that are similar to those of our case (10). This further suggests that there is a grey zone between both cyst types.

There is a case report of a neurenteric cyst associated with an intraparenchymal subependymoma that had a similar histologic appearance to our case but there was a limited histopathological description (11). The authors described a cystic frontal lesion with a solid component, where the cyst is lined with a respiratory-like stratified ciliated epithelium very similar to our case but there was no mention of the presence or absence of goblet cells; they were not evident in the images in that report. Moreover, immunohistochemistry findings of the epithelial lining are also lacking. They also stated that the underlying glial component was suggestive of subependymoma but with a multi-nodular pattern. One year after resection there was a recurrence of the cyst and a second surgery was performed; after 19 months of follow-up there was no evidence of recurrence was noted. The authors reviewed the previously reported cases of intraparenchymal subependymomas and noted that they have an overall good prognosis (6, 12). This is an interesting point because cyst-associated ependymoma-like proliferations seem to be exceptional, and we do not know whether they show the biological behavior of ependymomas, such as seeding through the neuraxis, especially after surgical resection. Hence, complete surgical excision with follow-up could be the most sensible approach to these lesions.

In conclusion, we describe an intraparenchymal cyst in the frontal lobe of a patient with a glial element of ependymal differentiation and a cyst lining that resembles a neurenteric cyst, but with features reminiscent of a glioependymal cyst.

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