• CASE REPORTS •

Pilomyxoid Astrocytoma in Unusual Location in a Child with Neurofibromatosis Type 1: Case Report and Review of the Literature

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Pilomyxoid astrocytoma (PMA) is a recently defined brain tumor believed to be a variant of pilocytic astrocytoma (PA), but with a more aggressive course. Most PMAs occur in the optic-chiasmatic/hypothalamic (OCH) region but they have also been described in the posterior fossa, temporal lobe, and in the spinal cord. We report a girl with history of neurofibromatosis type 1 (NF-1) who presented with a PMA located in the left lateral ventricle. Despite the fact that most of PMAs occur in the hypothalamic region, high awareness should be given to lesions in unusual locations, thus expanding the current epidemiologically known locations for this tumor. [_P R Health Sci J 2010;2:123-126_]

Key words: Astrocytoma, Pilocytic, Pilomyxoid, Neurofibromatosis

In 1999, Tihan and colleagues reported for the first time the pilomyxoid astrocytoma (PMA) as a histological variant of the pilocytic astrocytoma (PA) in children(1). It was described as monomorphous piloid cells loosely arranged, displayed in a uniform and extensive myxoid background. In contrast to PA, PMA lacks Rosenthal fibers and eosinophilic granular bodies, and has a frequent angiocentric pattern (1-2). They also have a relatively higher proliferation index and a significant propensity for CSF dissemination and recurrence than PA, purporting a more aggressive clinical behavior (1, 3).

Though PMA was first described in the pediatric population affecting more commonly very young children, it has also been reported lately in adult patients (4-6), and in association with NF1 in one patient (7). Most PMAs occur in the optic chiasm-hypothalamic (OCH) area but they have also been reported in the posterior fossa, temporal lobe, and spinal cord (1, 8, 2, 9). Though PA, PMA's closest relative, (1, 9-11) can occur anywhere along the neuraxis, to our knowledge PMA has never been reported in the lateral ventricles. We present the clinical manifestations, radiological characteristics, histological features, management and progression of this unusual case.

Case Report

A 9 year old girl with neurofibromatosis type I had been complaining of headaches since she started school at age 6. Due to persistent headaches and episodes of absence-like behavior at school, she was evaluated and referred to a neurologist who recommended an electroencephalogram that revealed an epileptogenic cortical dysfunction. She was started on anticonvulsants with no improvement. A brain magnetic resonance imaging (MRI) revealed an intraventricular tumor. She had no history of nausea, vomiting or any type of neurologic deficits. There is history of neurofibromatosis in the mother and maternal grandmother but no history of cancer in the family. Past history revealed a term baby born via vaginal delivery without complications. She has two healthy siblings born from different fathers. She was referred to our institution for neurosurgery evaluation and treatment.

On physical exam, she was an alert, active and communicative girl, 1.21 m tall (< 5 percentile for age), with a body weight of 24 kg (5 percentile). She had a blood pressure of 98/53 mm Hg, heart rate of 89 beats per minute and a respiratory rate of 22 per minute. Multiple café au lait spots were seen in the face, extremities and trunk in addition to freckling in the axillary and inguinal regions. No abdominal or pelvic masses, nor neurological deficits were observed.

On computerized tomography sagittal T1 images, a heterogeneous lesion at the left lateral ventricle with a central area of decreased intensity probably representing necrosis was noted. Coronal T1 post gadolinium showed an oval mass occupying the

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left ventricle which was isointense to the gray matter with a central rounded area of decreased intensity with peripheral enhancement (Figure 1). An endoscopic biopsy was performed.

The biopsy was received fresh and had a mucoid focally hemorrhagic appearance. The tissue fragments measured 3 x 2 x 0.1 cm in aggregate. On microscopy, tumor cells were uniformly small and bipolar embedded in a myxoid stroma. Some of the cells were oriented around blood vessels to produce an ependymoma-like appearance (Figure 2). Immunohistochemistry revealed positive immunoreaction to glial fibrillary acidic protein (GFAP), weak positive immunoreaction for synaptophysin, and tumor presented a proliferative index (Ki67) of approximately 3% (Figure 3). Neurofilament was negative. The diagnosis was that of a pilomyxoid astrocytoma.

Discussion

Neurofibromatosis is one of the inherited tumor syndromes involving the nervous system with a prevalence of 2-3 cases per
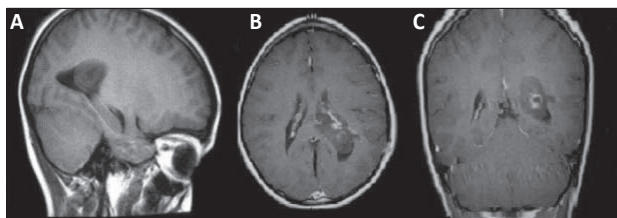

Figure 1. **A**. Sagittal T1 images reveal an heterogeneous lesion in the left lateral ventricle with a central area of decreased intensity probably representing necrosis. **B**. Axial T1 post gadolinium shows a mass in the left lateral ventricle which is isointense to gray matter and shows a rounded area of similar intensity within, with peripheral rim enhancement. **C**. Coronal T1 post gadolinium shows an oval mass occupying the left ventricle which is isointense to gray matter with a central rounded area of decreased intensity with peripheral enhancement.
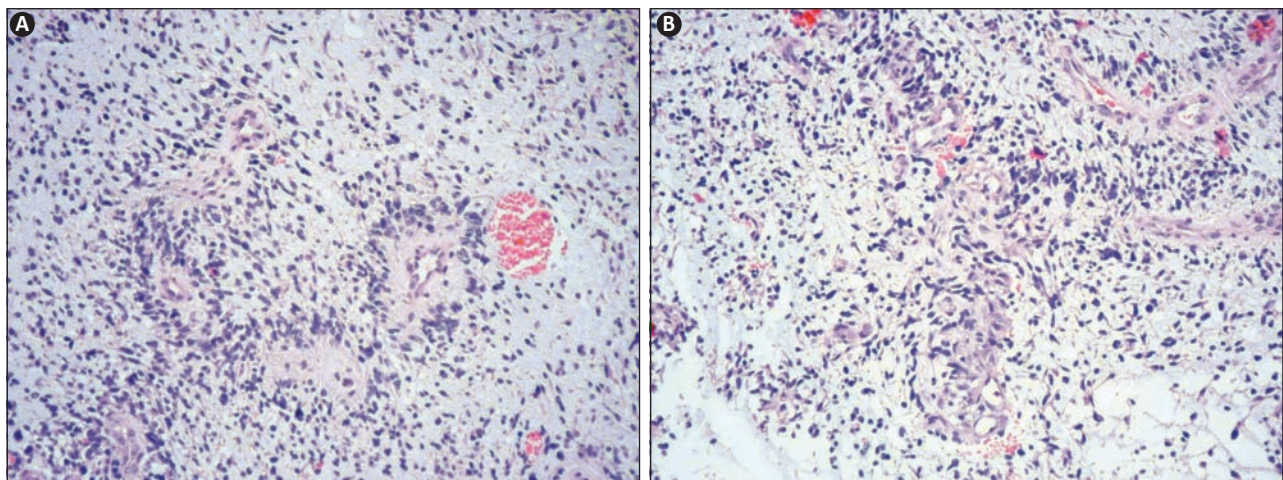
10,000 people (12). At least eight different types (13), have been identified with neurofibromatosis type 1 (NF1; also known as von Recklinghausen's disease), being the most common one. Diagnostic criteria for NF1, as revised by Gutmann et al. in 1997, was met by our patient (13), and as it is known, NF1 is associated to brain tumors, especially gliomas, seen in 20% of these patients (14).

Affected individuals born with this autosomal dominant disorder have a germline mutation affecting the NF1 gene which codes for neurofibromin, a protein that serves as a tumor suppressor gene by binding the growth-promoting GTP-bound form of RAS (15). Loss of neurofibromin in astrocytes has been shown to lead to hyperactivation of one of the RAS isoforms, which may lead to the formation of astrocytomas (16). It has been also observed that NF1 gene is located on chromosome 17, the most common chromosome involved in pilocytic astrocytomas (PA) and neurofibromatosis type 1 (17).

PMA, first described as an infantile form of PA, and named pilocytic astrocytoma, infantile type, is now accepted to be a different and more aggressive type of glioma in view of the clinical, histological differences, higher rate of recurrence, and CSF dissemination (1, 3, 9-10, 17-18) compared to PA which has a more indolent behavior. In 2007, PMA was officially designated a grade II tumor by the World Health Organization (WHO) (19).

Pilomyxoid astrocytomas typically present within the first two to three years of life with a mean age at diagnosis of 10-18 months compared to 58 months for PA (1-2, 5-6). Rarely they present in older children and adults (4-6, 20). Khanani et al. (7) presented a 9 year-old girl with NF1 and PMA similar to our patient. From this information we can suggest that PMA in NF1 tends to occur at an older age than the sporadic counterpart. In general, brain tumors have a better outcome if they appear during late childhood (21). Nevertheless, more research and adequate screening are needed to define the epidemiology of

Figure 2. **A**. Note tumor cells oriented around blood vessels to produce an ependymoma-like appearance within a myxoid background. H & E 20X. **B**. Focal areas of vascular proliferation, H & E 20X.

PMA in NF1 and non NF1 patients, and its implications in the management and prognosis of both populations.

Regarding to the most usual location, PA may occur anywhere along the neuraxis, but in patients with NF1, it usually presents in the optic pathway. It may also be found in the hypothalamus, thalamus, cerebral or cerebellar hemispheres, spinal cord and brainstem (14). PMAs on the other hand, are reported to be located in the optic chiasmatic hypothalamic (OCH) area, with rare cases encountered in the suprasellar region, thalamus, posterior fossa, fronto-callosal and temporal area and the spinal cord (1, 2, 5, 8-9, 19, 22).

MRI images describe PMA as a predominantly solid and/or cystic tumor, with homogeneous enhancement, with or without extension into the deep white mater and gray mater, with peritumoral edema, and cerebrospinal fluid (CSF) dissemination (2, 23). Magnetic resonance spectroscopy (MRS) is also being studied as a tool for the differentiation of PMA from PA; PMA presenting decreased concentrations of total choline (Cho), creatine (Cr), and N-acetyl aspartate (NAA), in contrast to PA which has elevated Cho, and decreased Cr, and NAA (22, 24). Our patient presented an MRI with similar findings as those described above. No MRS was performed. Despite MRI findings, no reliable radiographic images have yet been defined to differentiate PMA from PA with the exception of a higher incidence of CSF seeding.

The diagnosis of PMA is based on the histologic features defined by various authors (1-2, 9, 11, 25). Typically PMA presents a monomorphous population of spindle bipolar (piloid) cells in a myxoid background whereas classic PA consists of a biphasic architecture demonstrating densely cellular areas alternating with loose cystic regions. In contrast to PA, Rosenthal fibers, eosinophilic granular bodies and calcifications tend to be absent or uncommon in PMA, though Gottfired et al., described a PMA case with Rosenthal fibers, and microcalcifications (5). Another characteristic of PMA is the angiocentric pattern of neoplastic cells (Figure 2B) that resembles the perivascular pseudorosettes

of ependymomas. Mitotic figures may be present in PMA but are rare or absent in PA. MIB-1 index has been described as an average of 4% and 1% for PMA and PA respectively (1, 7, 9). The tumor cells show strong GFAP positivity and negative immunostaining for synaptophysin. One case of PMA has shown a divergent population of cells, with positive immunohistochemistry for GFAP and synaptophysin, leading to the conclusion of a possible glioneuronal component of some PMAs.

The postoperative survival rate for PA is 70-80% at 20 years (26-27) compared to PMA which has an overall survival rate of 38.7% at 2 years (1). Komotar et al. reported a mean overall survival in an age-matched PMA and PA groups of 60 and 233 months respectively (2) and mortality caused by the disease was 33% for PMA and 17% for PA. The same authors found, in the same group of patients, that local recurrence rate was 76% for PMA and 50% for PA, and CSF dissemination for PMA and PA was 14% and 0% respectively.

The aggressive behavior of PMA could be related to multiple factors including a higher MIB-1 index, a greater rate of recurrence, its capacity for CSF dissemination, and the location where they occur. A recent published report revealed an insertion of chromosome 17 to be associated to PMA (17). Though, the gene affected was not the NF1, this finding could unravel the molecular pathology and biology of PMA, its relation to PA, and a future alternative treatment approach. In 2006, Khanani et al., reported the first case of NF1 associated to PMA (7). We report the second case of NF1 and PMA in the medical literature. We suggest that a close survey of NF1 patients is warranted to better ascertain the incidence of PMA in these patients and hence offer the proper management for this tumor.

Our case, presents the radiological and histological features currently known for PMA with the exception of the location in the lateral ventricle making this a unique case. No study has officially reported the importance of the location of PMA and its prognostic value. Certainly, location has a value in the preoperative and postoperative setting as well as in the amount of residual tumor.
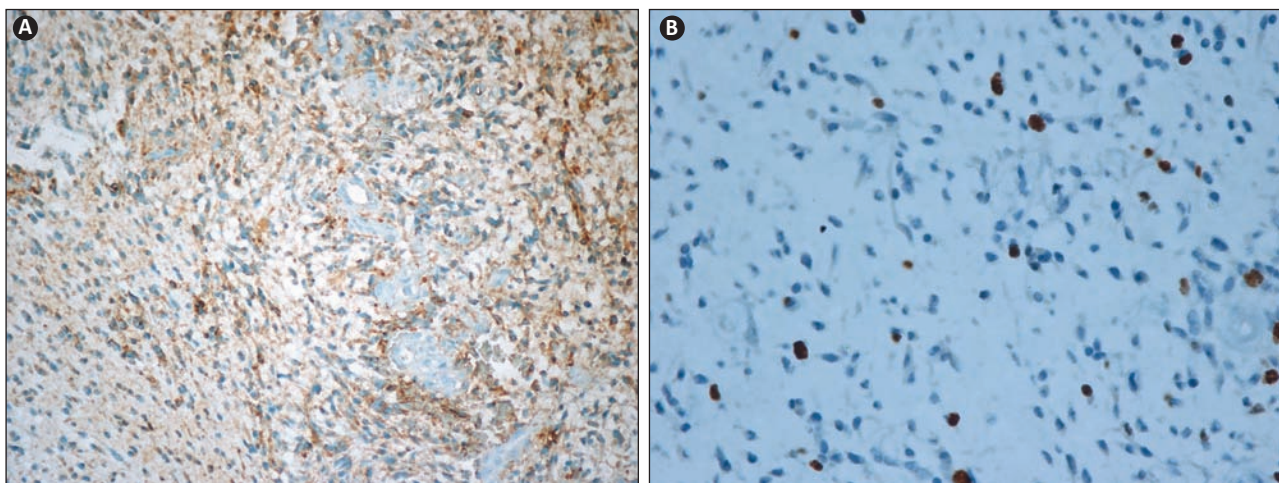

Figure 3. **A**. Positive immunoreaction to glial fibrillary acidic protein (GFAP), 20X. **B**. Proliferative index (Ki67), of approximately 3%, 40X.

After the biopsy, significant intraventricular tumor remained with invasion into the splenium of the corpus callosum. Follow up MRI two months later, revealed a slight increase in the size of the lesion, therefore patient was started on Vincristine and Carboplatin as per protocol used for low grade gliomas. On periodic follow up MRI studies, there was no change in the lesion size and the patient was asymptomatic with no headaches or seizures, and with good quality of life. However, after 10 months of chemotherapy, cystic signal intensity was present and surgery was offered. The histology in this treated tumor was mostly pilocytic with areas of pilomyxoid astrocytoma. The histology was no different from previously treated PMAs since the ability of PMA to recur as classical PA has been published (1, 9, 11). In view that this finding does not imply a better prognosis, close follow up was recommended.

From January 2002 to May 2006 we have operated 33 new cases of PA in the pediatric population in our institution; one associated to NF1, and one patient with tumor recurrence. This is the first case of pilomyxoid astrocytoma diagnosed at our institution. A better understanding of PMA's molecular biology and genetics will be important in the management and prognosis of patients with this entity. As to date, clinical suspicion and histological findings are the only tools to diagnose this tumor. More studies are required to develop guidelines for the diagnosis, management and treatment of PMA in both NF1 and non-NF1 patients. NF1 patients should be properly screened for early diagnosis.

Resumen

Astrocitoma pilomixoide es un tumor descrito recientemente que se cree es una variante del astrocitoma pilocítico pero con un curso clínico mas agresivo. La mayoría de estos tumores ocurre en la región óptico-quiasmática/hipotalámica pero también se han descrito en la fosa posterior, lóbulo temporal y cordón espinal. Presentamos el caso de una niña con historial de neurofibromatosis tipo I que presentó con este tumor en el ventrículo lateral izquierdo. A pesar de que la mayoría de los astrocitomas pilomixoide presentan en el área hipotalámica, debemos tener presente que pueden verse en otras localizaciones no esperadas.

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