Spontaneous malignant transformation of a supratentorial pilocytic astrocytoma

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Summary

Pilocytic astrocytoma (PA) is a circumscribed neoplasia considered as a grade I astrocytoma by the World Health Organization. Its most common location is the cerebellum and it develops during the first two decades of the life. Prognosis is mostly excellent if gross-total resection can be achieved, with 10-year survival rates of up to 80%. Anaplastic or malignant transformation (MT) can rarely occur and is usually related to previous radiation. Spontaneous MT has exceptionally been reported. Histological criteria for diagnosis of MT are unclear, so no consensus exists. We present an atypical case of MT of a frontal PA without previous radiotherapy in a 28 years old patient. Also, we review the literature about prognostic factors of PA and discuss histological features that are considered as anaplastic or malignant in the PA.

KEY WORDS: Pilocytic astrocytoma. Malignant transformation. Radiotherapy. Prognosis

Introduction

Pilocytic astrocytoma (PA) is a slowly growing, relatively circumscribed neoplasia that is classified by the World Health Organization (WHO) as grade I tumour37. It usually develops during the first two decades of life and it represents the most common cerebral tumour (18%) in the paediatric age36. PA arises throughout the central nervous system but its most common locations are the cerebellum (80%) and hypothalamic/optical pathways12, 37.

Histologically, PA is characterized by a biphasic pattern: in one, there are compact zones constituted by strongly glial fibrillary acidic protein (GFAP) immunopositive bipolar cells with Rosenthal fibers, and, on the other, microcystic areas that contain weakly GFAP-positive multipolar cells with eosinophilic granular bodies37. Occasional mitoses, hyperchromatic and pleomorphic nuclei and glomeruloid vascular proliferation may appear, but they are not considered signs of malignancy37, 47. Proliferative markers are generally low, with bromodeoxyuridine (BUdR) index less than 1% and MIB-1 labelling index ranging from 0 to 3.9%37.

On MRI PA is generally a well-demarcated, either oval or round mass that is constituted by a cyst and mural nodule. Solid component is hypointense relative to gray

matter in T1-weighted images and hyperintense relative to gray matter in T2-weighted images. After gadolinium administration the mural nodule intensely, heterogeneously enhances\(^{25,31}\) while most cyst walls do not\(^{25}\). On magnetic resonance spectroscopy, PA has an aggressive-appearing metabolite pattern, with elevated choline (Cho), reduced N-acetylaspartate (NAA), elevated Cho/NAA ratio and high lactate\(^{25,31}\).

Overall, prognosis for patients with PA is excellent, with 10-year survival rate of up 80% and a 20-year survival rate of 79\%\(^{15,25}\). One of the main prognostic factors related to outcome is the degree of resection\(^{15,22,40}\). Those tumours undergoing a gross-total resection have a significantly better prognosis than those with subtotal resection\(^{15,22,40}\). Radiotherapy has a limited therapeutic role and is indicated when tumours are surgically inaccessible, in multicentric PAs, anaplastic recurrence or significant residual postoperative tumour\(^{15,26,40}\).

Sometimes an unfavourable evolution can occur. This feature is characterized by phenomena such as local recurrence, multicentric disease, leptomeningeal dissemination or malignant transformation (MT)\(^{15,16,40}\). Anaplastic or malignant transformation of PA is a rare event described in the literature\(^{12}\). Radiation therapy may be related with this anaplastic change because most of such tumours had been previously irradiated\(^{14,33,37}\). However, pathological criteria for classifying PAs with atypical features are unclear\(^{33,45}\).

We describe a case of MT of a PA located in frontal lobe without previous radiotherapy. We review the literature about prognostic factors related with PA and the evolution of this tumour. Lastly, we discuss features that are related with anaplastic transformation in PA.

**Case report and literature search strategy**

This 25 year old patient was first admitted to our service referring lancinating pain in the left side of his neck for two weeks and double vision on left lateral gaze since 5 days before his admission. He did not refer headache or other neurological symptoms. Neurological examination only evidenced a left VI cranial nerve palsy. Cranial computed tomography and MRI with and without contrast enhancement, showed a voluminous right frontal cystic tumour with nodule and mural enhancement (Figure 1). He was operated through a right pterional approach and a complete excision of the tumour was achieved without complications. He was discharged asymptomatic. The tumour was pathologically diagnosed as PA, with some necrotic and brain infiltration areas, but no mitosis nor atypical features were found (Figures 2 and 3).

He was followed on an ambulatory basis for the next 3 years, with no evidence of persistence or recurrence of the tumour on imaging. 3 years after the operation and 3 months after a normal imaging control study, the patient was readmitted because of an epileptic seizure. The MRI disclosed a rapidly growing recurrent cystic tumour on the right frontal region (Figure 4). He was operated again through the same previous right pterional craniotomy and a complete excision could be achieved although this time, the sylvian artery branches were surrounded and involved by tumour, making resection less straightforward but without complications. The patient was discharged neurologically asymptomatic on anticonvulsants. The pathological diagnosis of the tumour was PA with MT (Figures 5 and 6). He was submitted to the Radiotherapy Service where he was complementary treated with whole brain radiation therapy.

He was followed for the next 30 months, with no remarkable events but some scarce epileptic seizures and imaging studies remained without visible recurrence but some small enhancing punctuate lesions scattered in both cerebral hemispheres and brainstem that progressively appeared and were interpreted as reactive radiotherapy changes.

At this time the patient suffered a new rapid neurological deterioration and was readmitted presenting right hemiplegia and aphasia secondary to a frontoparietal parasagittal subcortical expansive lesion affecting the corpus callosum. The tumour was operated through a right pterional approach and a complete excision was achieved without complications. The patient was discharged neurologically asymptomatic on anticonvulsants. The pathological diagnosis of the tumour was PA with MT (Figures 7 and 8). He was submitted to the Radiotherapy Service where he was complementary treated with whole brain radiation therapy.
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callosum, which enhanced homogeneously on MRI. The MR spectroscopy was compatible with radionecrosis. No amelioration was obtained with dexamethasone. He was operated through a frontoparietal left craniotomy, excising the necrotic tissue and the pathological diagnosis confirmed radio-necrosis. He recovered partially from his hemiplegia and aphasia, and was discharged with sequelae, that persist

Figure 2. Air dried smears stained with Diff Quick (20x) (Romanowsky type stains). Bipolar neoplastic cells with elongated hair-like processes. The nuclei are round to oval with open chromatin and indistinct nucleoli. Lack of substantial pleomorphism.

Figure 3. Obtained material smeared on slide, alcohol-fixed and stained with Hematoxylin-Eosin (20x). Observe multiple nuclei within large or giant cells. There is no mitosis nor necrosis nor vascular proliferation.

Figure 4. Axial contrast enhanced MRI displays cystic tumor with nodule at the same location.

Figure 5. Hematoxylin-Eosin stained biopsy material (10x) showing malignant degeneration with hypercellularity, higher cellular pleomorphism and mitotic figures.

Figure 6. Hematoxylin-Eosin stained biopsy material (20x) of the malignant degeneration tumour showing hypercellularity, endothelial proliferation and focal necrosis.
2 years after his third operation.

The patient is still alive, 33 years old by now, but neurologically severely disabled. He is ambulatory controlled every 6 months. He developed progressive ventriculomegaly finally requiring a ventriculoperitoneal shunt this year. In the last MR controls no recurrence of the original tumour is seen but there is evidence of leptomeningeal spread of his tumour and a new cerebellar vermian solid tumour that enhances brightly and is compatible with an astrocytic tumour by spectrometry. This tumour has not yet been biopsied.

To review the literature, a computerized search of the National Library of Medicine database of the literature published from 1985 to 2009 was undertaken. The following medical subject headings were used in combination with ‘pilocytic astrocytoma’: ‘anaplastic’, ‘malignant’, ‘outcome’ and ‘prognosis’. Non-English language citations were excluded.

**Discussion**

PA is a low-grade, slowly growing tumour, generally considered to have a benign course. It is classified as a grade I tumour by the WHO grading system, which means a neoplasm with low proliferative potential and the possibility of cure following surgical resection alone. Although PA is regarded as a circumscribed neoplasm, infiltration of the surrounding parenchyma might be demonstrated histologically. Coakley et al observed that 64% of PAs showed infiltration into the surrounding brain parenchyma at pathological review despite well-demarcated appearance on MRI (96%), but the significance of this infiltration is unknown.

The main localizations of PAs are the cerebellum, optic nerve, optic chiasm/hypothalamus, thalamus/basal ganglia and brainstem. Dirven et al reported that 80% of PAs have a cerebellar localization. In a retrospective study of 80 cases in paediatric patients, the cerebellum was the most common affected site (33 of 80 PAs), followed by opticochiasmatic region (18/80) and brainstem (16/80). Malik et al reported that 61.8% of 120 PAs included in their study were located in posterior fossa, whereas other affected areas were the supratentorial region (10.8%), optic nerve (6.7%), brainstem (5.8%) and sellar/suprasellar area (5.8%). Supratentorial hemispheric PAs, as the presented case in this report, are relatively uncommon and little information has been reported on incidence and behaviour of this location. In one retrospective, single institution study of 20 recurrent PAs in children, only 3 lesions were described in the cerebral hemispheres. In their series of 107 PAs, Tibbetts et al reported that 23% (25/107) of these tumours were located in supratentorial region.

Long-term prognosis for PA is generally considered excellent, with 10-year survival rate of up to 80%. In the Childhood Brain Tumour Consortium database, 5-year survival among 481 patients with infratentorial PAs was 95% over the 50 years of the study. Long-term disease-free survival rates have also been reported. In a retrospective study of 80 PAs, the 5-year progression-free survival was 75%. In a series of one hundred thirty-two astrocytomas of the cerebellum, Hayostek et al reported that the 5, 10, and 20-year survival rates of the 105 PAs in the series were 85%, 81% and 79%, respectively, and 5-year, 10-year, and 20-year disease-free survival rates were 85%, 81%, and 78%. Respect to supratentorial PAs, in a retrospective study about 51 patients, Forsyth et al reported that survival percentages at 5, 10, and 20 years were 86%, 82%, and 82%, respectively. In Brown’s cohort of 20 supratentorial PAs in adults, the 5-year progression-free and overall survival rates were both 95%.

Various features have been considered to correlate with prognosis. One of the main prognostic factors is the grade of surgical resection. Complete resection generally implies better prognosis than partial resection. Fernandez showed that 5-year survival rate was 100% and 92% after total and partial removal, respectively. Hayostek found that gross total resection was related with improved survival and disease-free survival. In their study, Forsyth et al estimated that 10-year survival percentages were 100% for the patients who underwent gross total or radical subtotal resection, 84% for the patients which underwent subtotal resection and 44% for the patients who underwent biopsy only. In their cohort of 20 supratentorial PAs, Brown et al showed that 5-year survival rate was 100% in the resected group (partial and total resection) and 67% in the biopsied group. However, in their series of 171 benign cerebellar astrocytomas (pilocytic and nonpilocytic) in children, Pencalet et al reported that extent of surgical excision was not related with survival, although this feature significantly determined the risk of tumour recurrence. Tumour location also has been related with outcome, but this may be a result of the strong correlation between the extent of resection and tumour location. Fernandez et al reported that optochiasmatic PAs carried the worst prognosis (28% 5-year progression-free survival), and they noted that complete surgical removal was never achieved in this location. The best survival rates were observed in the cerebellum located PAs. Likewise, Tibbetts et al found that the optic pathway was the only location statistically associated with worse outcome (p=0.0296). Pencalet et al showed that if cerebellar PAs extended towards the brainstem (“transitional forms” according to the authors), survival was lower. In their series of ninety-seven patients with cerebellar astrocytomas, Sgouros et al concluded that...
the main negative prognostic factor was the brain stem involvement. There is some controversy over biologic behaviour of PAs in adults. Some authors like Brown et al\textsuperscript{45} did not find differences in the prognosis of these tumours in adults. However, in reviewing their 44 cases of PAs, Stüer et al\textsuperscript{43} noted a recurrence rate of 30\% and a MT rate of 50\% for those patients who underwent second surgery for tumour recurrence. Moreover, in the Ellis study of 20 adult patients with PAs found a recurrence rate of 30\% and observed MT in three of the four tumors that required a second resection\textsuperscript{14}. Respect to cystic tumours, solid PAs have not been generally associated with shorter survival times\textsuperscript{15,19,34,42}. However, Klein et al\textsuperscript{24} observed that cyst-nodule type of PAs were more amenable to total resection because they did not frequently affect the brainstem structures since they usually settled in a lateral cerebellar position.

No association has been generally found between proliferation indices such as MIB-1 labelling or BUdR index and outcome\textsuperscript{20,23,28,35,46}. The reported mean values of the MIB-1 labelling range from 0.9\% to 6\%\textsuperscript{13}. However, in a report of 39 PAs, Dirven et al\textsuperscript{13} observed that there was a tendency towards fewer tumour progression in the group of PAs with MIB-1 negative indexes than PAs with MIB-1 positive indices (p=0.15). In another report of 141 PAs in children, Bowers et al\textsuperscript{4} found that a MIB-1 labelling index of more than 2.0 was associated with shortened progression-free survival. Nevertheless, when evaluation of MIB-1 labelling indexes was restricted to partially resected tumours, there was only an insignificant trend of MIB-1 labelling higher than 2.0 having a shortened progression-free survival.

The evolution of patients treated for PAs is occasionally unfavourable since recurrence, LD and MT might occur. Some PAs seed throughout the neural axis. Reported prevalence of LD ranges from 2\% to 12\%\textsuperscript{25}. Incidence of LD appears increased when PAs are located in the hypothalamus. Mamelak et al\textsuperscript{30} concluded that hypothalamic PA was 23 times more likely to show dissemination than cerebellar one. This feature might be due to their proximity to the ventricular system. LD tends to occur within 3 years of initial diagnosis. Outcome of patients with LD is unknown\textsuperscript{16}. However, this phenomenon does not necessarily imply poor prognosis, because of metastatic implants tend to grow slowly\textsuperscript{37}.

Anaplastic or malignant transformation is an uncommon event. In the review of Parsa and Girrad\textsuperscript{33}, they found 24 reported cases of PA undergoing anaplastic transformation that had been confirmed. They excluded 22 reported tumours initially considered as PAs with MT, because they did not match the criteria for PA. Since most patients with MT of PA had undergone previous radiotherapy and the malignant form developed 5-45 years after the first treatment, radiation therapy might be a factor related with this malignant change\textsuperscript{7,11,12,14,26,27,33,34,44,48}. Spontaneous MT has been reported (see Table 1). Tomlinson et al\textsuperscript{47} estimated that the incidence of spontaneous histological malignancy of PAs was 0.9\% whereas radiation-induced malignancy incidence was 1.8\%. However, after a review of these cases, Parsa et al\textsuperscript{33} think that these tumours might not initially correspond to PA but to diffuse astrocytoma (WHO grade II)\textsuperscript{24}, reactive piloid gliosis\textsuperscript{8} or pilomyxoid astrocytoma (frontoparietal tumour in Krieger’s series)\textsuperscript{26}.

<table>
<thead>
<tr>
<th>Report</th>
<th>Age at initial presentation</th>
<th>Location</th>
<th>Surgery</th>
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<tr>
<td>Steinberg\textsuperscript{35}</td>
<td>50 years</td>
<td>Cerebellum</td>
<td>Subtotal resection</td>
<td>51 years</td>
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<tr>
<td>Casadei\textsuperscript{5}</td>
<td>6 years</td>
<td>Cerebellar hemisphere</td>
<td>Subtotal resection</td>
<td>41 years</td>
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<tr>
<td>Claus\textsuperscript{6}</td>
<td>41 years</td>
<td>Conus medullaris</td>
<td>Resection</td>
<td>43 years</td>
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<tr>
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<td>3 years</td>
<td>Cerebellar hemisphere</td>
<td>Subtotal resection</td>
<td>4 years</td>
</tr>
<tr>
<td>Krieger\textsuperscript{21}</td>
<td>14 years</td>
<td>Cerebellar hemisphere</td>
<td>Subtotal resection</td>
<td>14 years 4 months</td>
</tr>
<tr>
<td>Krieger\textsuperscript{21}</td>
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<td>IV ventricular floor</td>
<td>Partial resection</td>
<td>9 years</td>
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<tr>
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<td>15 months</td>
<td>Frontoparietal</td>
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<td>Stüer*</td>
<td>NA</td>
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<td>NA</td>
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<td>Our case</td>
<td>25 years</td>
<td>Frontal</td>
<td>Total resection</td>
<td>28 years</td>
</tr>
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* 4 cases. Non-described features. NA: not available.
Moreover, anaplasia criteria reported by Krieger et al\textsuperscript{26} such as increased cellularity and nuclear atypia mismatch with nowadays accepted criteria for anaplasia (see below). Furthermore, Stüer et al describe 4 cases of malignant transformation, but do not specify the location of these tumors\textsuperscript{26,37,47,49}. Considering this discussion, we believe that our case is one of the first supratentorial PAs which has undergone MT. As resection was total, we consider MT might have been originated in tumour cells that infiltrate into surrounding brain.

No consensus exists about histological features for diagnosis of anaplastic or malignant variant of PA\textsuperscript{26,33,37}. Hyperchromasia, nuclear atypia, endothelial proliferation, increased cellularity, mitotic activity, necrosis or multinucleated giant cells have been described as signs of malignancy; however, they have been accepted only by some neuropathologists\textsuperscript{6,11,26,29,33,38,47,49}. Some features such as hyperchromatic nuclei, multinucleated giant cells and endothelial proliferation are usually considered as degenerative changes\textsuperscript{26,29}. Other authors consider that nuclear atypia, increased cellularity, mitotic activity, endothelial activity or necrosis do not correlate with prognosis and have an uncertain prognostic value\textsuperscript{29,37,47}. Considering Tomilsen’s report\textsuperscript{47}, the 2007 WHO classification remarks that PAs which undergo MT often show multiple mitoses per high-power microscopic field, endothelial proliferation and palisading necrosis\textsuperscript{37}. Our case shows hypercellularity, necrosis, endothelial proliferation and mitotic figures (Figures 2 and 3), which do not appear in the first description (Figures 2 and 3). Lastly, prognosis of PAs that undergo MT is not necessarily dismal as confirmed by our case. Thus, they must not be designated as multiformal glioblastomas\textsuperscript{37}.

References


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