Revista Chilena de Neurocirugía 43: 2017

Spinal Pleomorphic Xanthoastrocytoma: Case Report and literature review

Xantoastrocitoma pleomórfico espinal: Reporte de caso y revisión de la literatura

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Rev. Chil. Neurocirugía 43: 37-41, 2017

Resumen

El Xantoastrocitoma Pleomórfico Espinal (XAPE) es una neoplasia primaria infrecuente del sistema nervioso central, descrita por primer vez en 1979. De estirpe astrocítica y aunque clasificada como grado II por la OMS, pueden existir variantes anaplásicas o malignas. Con localización usualmente temporal, pocos casos espinales se han descrito a la fecha, debido probablemente a un subdiagnóstico o un subregistro. El pronóstico es generalmente bueno y depende en gran medida del tipo histológico y extensión de la resección quirurgica. Describimos el caso de un hombre de 30 años de edad con dorsalgia y paresia del miembro inferior izquierdo. Se encontró en imágenes de resonancia magnética una lesión aparentemente intradural, extraaxial en los segmentos T8-T9 que se llevó a resección. Se confirmó por histopatología la presencia de un XAPE primario. En la presente publicación realizamos una revisión de la literatura disponible.

Palabras clave: Astrocitoma, Médula espinal, Neoplasia, Proteína fibrilar glial ácida.

Abstract

Spinal Pleomorphic Xanthoastrocytoma (SPXA) is a rare CNS primary neoplasm, first described in 1979. Although of astrocytic lineage and classified as a grade II neoplasm by the WHO, it may be have anaplastic or malignant variants. Usually located in the temporal lobe, few spinal cases have been described to date, probably due to underdiagnosis and underreporting. It usually has a good prognosis, but it depends on its histological type and extent of surgical resection. In this article, we describe the case of a 30-year old male who complained of low back pain and left lower limb paresis. The MRI showed an apparently intradural, extraaxial lesion at T8-T9 segments. The diagnosis of a primary SPXA was confirmed by histopathological studies. In this article, a review of the available literature is presented.

Key words: Astrocytoma, Spinal Cord, Neoplasm, Glial fibrillary acidic protein.

Introduction

Pleomorphic Xanthoastrocytoma (PXA) is a rare tumor in children and young adults. It was initially considered a tumor of mesenchymal origin, but it was redefined by Kepes et al., in 1979. They described a type of tumor, found in twelve patients, expressing great pleomorphism, to which it owes its name. At that time, it was considered a tumor of astrocytic lineage in young patients, mostly, with temporal lobe involvement[1]. It is now known that it can involve other regions in a smaller percentage, such as the cerebellum, retina, pineal region and spinal cord[2,3].

The PXA affects individuals of both sexes and its etiology is unknown and most of the cases arise sporadically without evidence of a specific genetic susceptibility[4,5].

Even though its pleomorphism implies the possibility of malignancy, it carries a

good 5-year prognosis when compared with diffuse infiltrative astrocytomas. A 30% recurrence rate and an overall survival rate of 75-80% after primary resection is accepted[9,10,11,12].

Its histopathologic features, particularly the abundance of reticular fibers, lead to the assumption that it stems from superficially located astrocytes, affecting the leptomeninges but not the dura mater.

Since it was demonstrated that these tumors express glial fibrillary acidic protein (GFAP), these tumors were considered to be astrocytomas[1]. Recently, with the aid of immunohistochemistry and electron microscopy it has been suggested that these tumors may have a neuronal phenotype, thus favoring a ganglioneural differentiation, over an astrocytic differentiation. Despite this controversy, PXA has been listed as a tumor of astrocytic lineage in the last edition of the WHO classification of tumors[14].

It is known that a mitotic index (MI) ≥ 5/10 high power fields (HPF) is associated with decreased recurrence-free time and overall survival[11]. It has therefore been proposed that PXA with MI ≥ 5/10 HPF with or without necrosis be known as "PXA with anaplastic features", because of the greater possibility of being more aggressive than those without such histological findings[9].

Within WHO grade III tumors group, there are tumors with different natural histories and survival rates (e.g., anaplastic ependymoma, anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic meningioma). Therefore, it seems reasonable to consider that PXA with anaplastic features would fit in this heterogeneous "anaplastic" WHO grade III group.

When supratentorial, patients may present with ictal episodes and intracranial hypertension[6,7,13]. In this review, as shown below, those of spinal location can produce motor and sensory symptoms.

Histologically, PXA has lipidized pleomorphic giant cells, fascicles of spindled cells in a reticulin rich stroma, eosinophilic granular bodies (EGBs) and a lymphocytic infiltrate. It often displays a population of highly ramifying CD34-positive cells. If anaplastic, it reveals ≥ 5/10 CAP and/or necrosis. Recent genetic advances have uncovered that approximately 2/3 of PXAs harbor a *BRAF* V600E mutation[13,16,17].

Giannini et al., report that the mitotic index and the extent of primary resection may be the two most important predictors of recurrence and survival in these patients[11].

Das et al., conducted a mutational analysis in spinal pleomorphic xanthoastrocytomas (SPXA) that failed to reveal the V600E *BRAF* mutation that is commonly present in cerebral PX. It is apparent that 1/3 to 1/2 of all PXAs will not bear a V600E mutation, and as such the absence of a mutation cannot be used to refute the diagnosis of PXA[13].

Case description

We report the case of a previously healthy, 30-year old male patient, who presented with progressive back pain, who developed lower left monoparesis. On physical examination, the presence of pain in the lower back was evident, becoming more intense with flexion-extension movements; muscle strength was found at 4/5 in the lower left limb, as well as a positive Babinski sign and hyperreflexia.

MRI revealed an intraspinal, intradural, extraaxial mass at T8-T9, with a polar cyst. Ependymoma and meningioma were considered as first diagnostic possibilities (Figure 1).

The patient was taken to a biopsy that was initially interpreted as a medullar glioblastoma. During hospital stay, the patient's pain increased. The histopathological samples were reviewed, revealing the presence of a PXA. The patient was then taken to tumor resection through a costotransversectomy, gaining direct access to the affected region. The tumor was apparently involving the T8 root, but during its complete dissection, it was found to be unaffected (Figure 2). It was thought to be thoroughly extraaxial but the mass turned out to be attached to a deeper

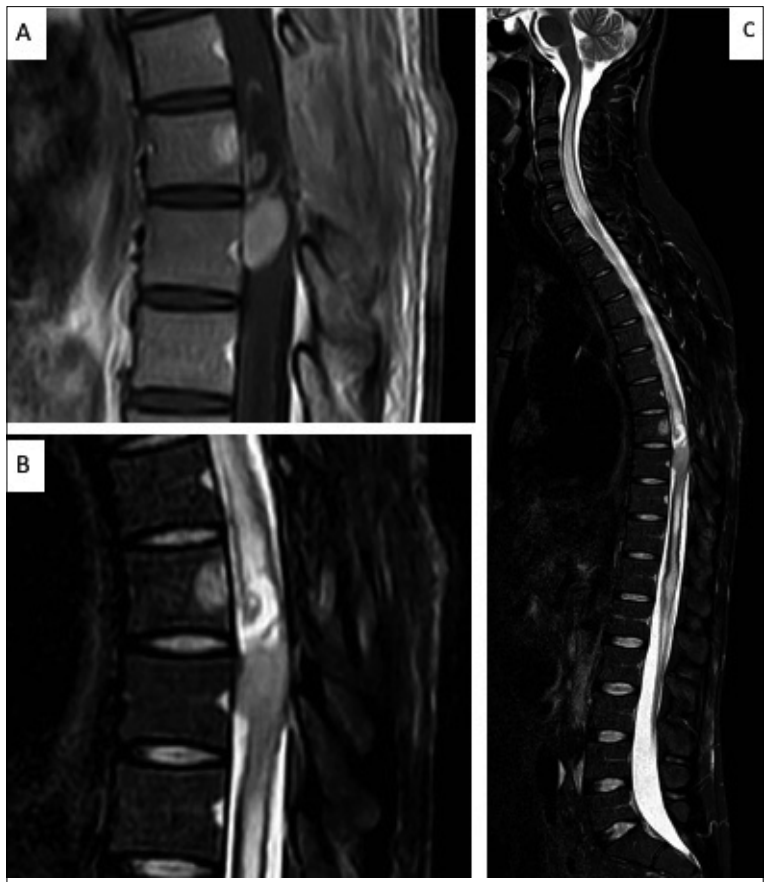

Figure 1. Magnetic resonance imaging. A. MRI-T1, sagittal. Dorsal spine; B. MRI T2-Stir, sagittal. Dorsal spine; C. MRI T2-Stir, Sagittal. Total spine. Apparently intradural, extraaxial tumor with a polar cyst. Extensive syringomyelia from C1 to L2.

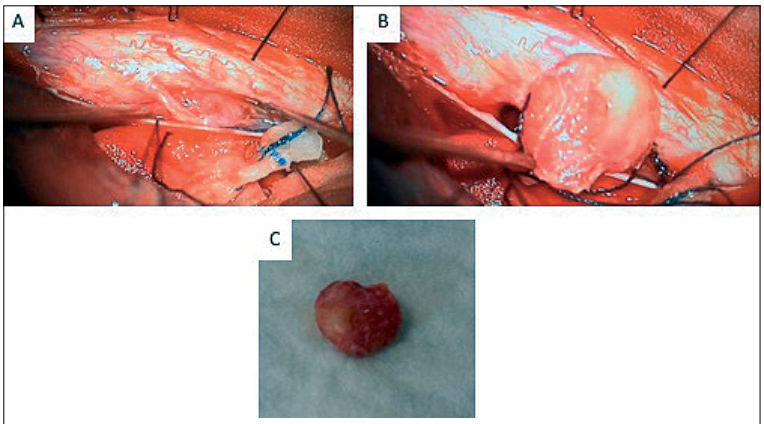

Figure 2. Intraoperative images. A. Dural opening at T8-T9; B. Complete tumor resection. There are clear adhesions to leptomeninges; C. Specimen. Apparent involvement of T8 nerve root. Finally, complete resection is achieved without section of the root.

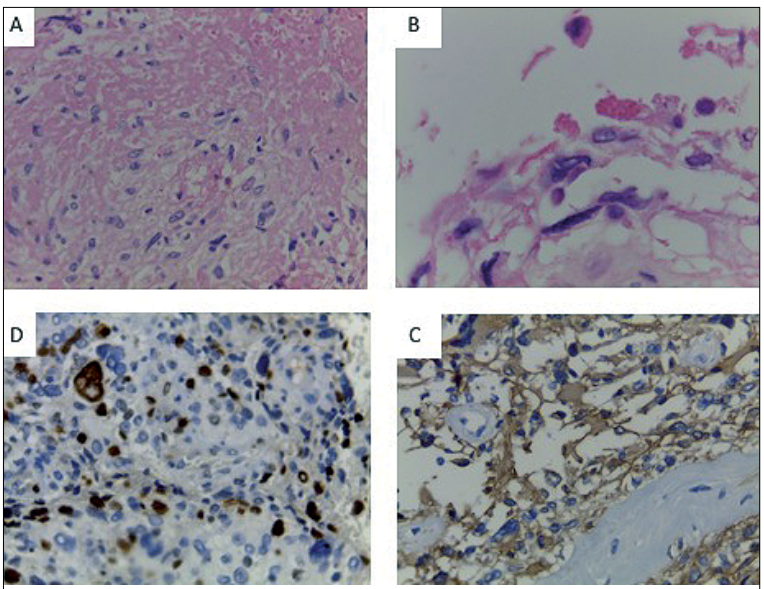

Figure 3. Histopathology. A. Neoplasm constituted of glial cells with nuclear pleomorphism and eosinophilic cytoplasm arranged in sheets; B. Eosinophilic granular bodies were focally observed; C. Glial fibrillary acidic protein (GFAP) revealing its astrocityc nature; D. Ki 67 approx. 20%.

medullary plane, making its resection more difficult. Complete resection was obtained with a short-term favorable evolution. Transpedicular screws were inserted as well as lateral bars to stabilize this spinal segment.

Histochemical studies showed a neoplasm made up of glial cells with nuclear pleomorphism and eosinophilic cytoplasm arranged in sheets. Only small areas of necrosis were found and occasional mitotic activity within the tumor tissue was identified. Eosinophilic granular bodies were focally observed. Reticulum stain was positive revealing abundant fibers delineating small cell groups.

A high Ki 67 index of approximately 20% was found suggesting an aggressive biological behavior. Glial fibrillary acidic protein (GFAP) revealed the astrocytic nature of the mass. Hence, the diagnosis of ganglioglioma was considered, the synaptophysin stain was carried out with no neuronal elements identified. Negative result for EMA immunohistochemical study was also obtained, which ruled out the diagnosis of meningioma. The final diagnosis was PXA.

Discussion

Supratentorial location for PXA is far more common than the spinal one, and that is why that PXA reports are much more abundant in the literature than those of SPXA. To date, few cases have been reported (Table 1).

With our report, there are now seven cases in the literature (Table 1). Despite the lack of data, we have found, from previous reports and from our own, a very subtle preference of SPXA for female gender, cervical spine and less commonly, dorsal and lumbar spine. The average age of diagnosis was 34 years, with a ranging from 12 to 66 years. The usual presenting symptoms was motor deficits and sensory disturbance. Total resections were achieved in most cases which was associated with a good prognosis.

Zhao et al., reported the case of a lumbar PXA at L2-L3[15]. Postoperative dizziness was followed by CT scan of the head which showed a left periventricular hypodense lesion. The MRI, supported the diagnosis of tumor and it was concluded that it was a multi-PXA. However, histological confirmation of the last finding was lacking.

Of the cases presented above, few have been extensively studied to rule out the case of a supratentorial lesion which extends into the spinal cord, as pointed out by Simal et al[6,15].

Radiologically, the differential diagnoses to be considered include diffuse astrocytomas and ependymomas, since they are the most frequent intramedullary lesions and usually have a cystic component[6]. Nevertheless, the most typical feature of PXA tumors is their close contact and attachment to leptomeninges and most of them have syringomyelic cavities, with no wall enhancement[1,6].

Histologically, PXA is characterized by marked cellular pleomorphism including spindle cells, mononuclear or multinucleated giant tumor cells with bizarre nuclei, prominent lipid droplets in cytoplasm, frequent perivascular lymphocytic infiltration, and eosinophilic granular bodies together with a dense reticulin network. The presence of eosinophilic granular bodies is considered necessary for this diagnosis. Necrosis is usually not present. Necrotic PXAs differ from glioblastoma because of the lack of vascular endothelial proliferation, their superficial location and less

Table 1.
Published cases of spinal pleomorphic xanthoastrocytoma

Case	Sex	Age	Clinical presentation	Locat.	Resection	Adyuvantradio ther.	Recurrence	Outcome
Herpes 1994	F	66	Hypoesthesia T1-T12	T2-T4	Total	Yes, after second surgery	Yes, local after 8 months of surgery	Hypoesthesia paraparesis
Fouladi 2001	M	12	Headache	-	Total	Yes	Yes, local metastasis	Death
Nakamura 2006	F	33	Hypoesthesia	C5-T1	Total	No	No, 3 years after surgery	Hypoesthesia at 11
Simal 2010	F	60	Paresis	C4-C5	Total	No	No, 3 years after surgery	Proprioceptive disturbance
Gill 2010	F	23	Paraplegia	T11-L2	Subtotal		Yes, 7 months after surgery	
Das 2014	M	15	Pain, paresis	C5-C6	Subtotal		Yes, 2 years after surgery	
Our report	M	30	Pain, paresis	T8-T9	Total	Yes	No	

aggressive clinical behavior[5]. Although, the presence of necrosis is associated with a less favorable outcome, the prognosis of PXAs is often more favorable and less precipitous than other astrocytomas with the same histopathological feature[5].

Electron microscopy reveals presence of abundant intermediate filaments admixed with abundant cytoplasmic organelles, lipid droplets, lysosomes and presence of surface basement membranes which are characteristic of astrocytic differentiation. However, a few may show evidence of microtubules, dense core granules and/or clear vesicles suggestive of neuronal differentiation. GFAP expression is mandatory for definitive diagnosis of PXA and effectively segregates it from mesenchymal tumors[5,19]. Immunoreactivity for synaptophysin and neurofilament proteins in various studies have ranged from 38% to 100% and from 8% to 71%, respectively. S-100 protein immunoreactivity is usually diffusely and strongly present in all tumors[4,20,21,22,23,24,25].

The molecular pathogenesis of PXA is unclear. Few molecular and cytogenetic studies have been reported, of which the majority have failed to link a specific genetic aberration to these rare tumors. Weber et al., studied chromosomal imbalances in 50 PXAs and reported the loss of chromosome 9 as the most common chromosomal alteration in PXAs, which occurred in as many as half of the patients[26].

Although rare, it is clear that more SPXAs need to be interrogated for the *BRAF* V600E mutation, not only from a diagnostic perspective, but also from a therapeutic point of view[13].

The first line treatment is the gross total resection, although adjuvant chemotherapy and radiation therapy may play role(s) in recurrent and/or aggressive cases. Estimates of overall survival have been reported as 81% for 5-year survival and 70% for 10-year survival[1,13,18].

Early and total removal will be achieved more easily in the less infiltrative masses. Herpers et al., report that PXA exhibits a more aggressive biological behavior than those in other locations[3].

Data to support the role of adjuvant treatment are scanty and sparse[5]. Despite the absence of specific studies in SPXA, several management protocols have been extrapolated from supratentorial lesions. Macaulay et al.[27], addressed the role of adjuvant radiation therapy and reported a trend towards better recurrence-free survival with use of adjuvant radiation. However, the difference in overall survival was not statistically significant despite a long follow-up period of fifteen years. With the retrospective nature of these studies, there could be an element of selection bias with the less favorable prognostic subset of PXAs (comprising either subtotal excised or those having adverse histopathological features) being subjected to adjuvant radiotherapy while those with gross total excision and favorable histopathological features were kept on observation[5].

Adjuvant radiation therapy should be offered to all unfavorable PXAs and the role of radiation in the favorable prognostic group is less clear and more studies are needed to resolve this issue[5,6].

Conclusions

The study and report of more cases of SPXA is necessary to issue clear management guidelines that allow the best outcome for patients. We share the conclusions of several publications concerning the shortage of literature about this matter[2,13].

Recibido: 20 de agosto de 2016
Aceptado: 25 de septiembre de 2016

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