EPIDEMIOLOGICAL, CLINICAL, HISTOLOGICAL AND IMMUNO-HISTOCHEMICAL CHARACTERISTICS OF SUBEPENDYMAL GIANT CELL ASTROCYTOMA : ABOUT THREE CASES AND A LITERATURE REVIEW.

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ABSTRACT

Background: Subependymal giant cell astrocytoma (SEGA) is a rare benign tumor, which typically occurs in the lateral ventricle. Its histogenesis is poorly understood.

Cases presentation: We reviewed the clinical, histological and immuno-histochemistrical characteristics of three cases of subependymal giant cell astrocytoma. The age ranged between 6 years old and 10 years old. Two of patients were male. All patients show symptoms in relation to intracranial hypertension with seizures in one case. All the tumors were located in the lateral ventricle. One patient showed tuberous sclerosis complex signs (subcortical tubers). A tumor resection was performed in all cases and microscopic examination revealed a tumor composed of ganglion-like cells, spindle cells, gemistocytic-like cells and multinucleated cells. Immunohistochemistry showed focal Glial fibrillary acid protein (GFAP) positivity and neurofilament, synaptophysin and S100 protein negativity in all cases. Ki-67 labeling index ranged from 1% to 10%.

Conclusion: Astrocytoma subependymal giant cell is a rare benign tumor that affects children and young adults. Its association with tuberous sclerosis complex is well known. Most patients tend to present with convulsions and symptoms related to intracranial hypertension. Radiologically, CT scan and Magnetic Resonance Imaging don't show specific signs. Microscopically, this tumor is conventionally composed of a proliferation of three cell types: ganglion-like cells; fibrillar spindle cells; and gemistocytic-like cells. Immunohistochemistry reveals that both glial and neuronal proteins are expressed. If the histological diagnosis of this tumor is enough easy, the main problem remains in its histogenesis. SEGA is a low-grade tumor with excellent prognosis if surgically removed.

Keywords: Histogenesis, Brain neoplasm; Subependymal giant cell astrocytoma, Tuberous sclerosis complex, Immunohistochemistry.

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BACKGROUND

Subependymal giant cell astrocytoma (SEGA) is a rare benign slowly growing tumor, which typically occurs in the lateral ventricle near the foramen of Monro and rarely in the third ventricle [1-4]. It is pathologically classified as grade I glioma by the World Health Organization (WHO) [2; 3]. Its histogenesis is poorly understood. Previous studies have reported glial (astrocytic or rarely ependymal), neuronal or mixed glial-neuronal differentiation. These hypotheses are based upon studies of small numbers of cases, except for a few reports that studied a slightly larger number of cases [1; 2; 4]. The association of SEGA with tuberous sclerosis (Bourneville disease) is common (5 to 14%) and the SEGA is the one of the major features in the diagnostic criteria for the tuberous sclerosis complex (TSC) [3], but cases in its absence are also reported in literature [1; 2; 4]. We review three cases of subependymal giant cell astrocytoma, we discuss clinical, radiological, histological and immuno-histochemical characteristics and histogenesis of this tumor, with review of the literature.

CASES PRESENTATION

Case 1: A 10-year-old Moroccan girl reported symptoms in relation to intracranial hypertension like headache and vomiting over a period of 15 days. On cranial MRI, there was a lobulated, intense and heterogeneous contrast-enhanced mass in the left lateral ventricle, measuring 58x50x34mm, with hydrocephalus and subependymal calcifications (**Figure 1**).
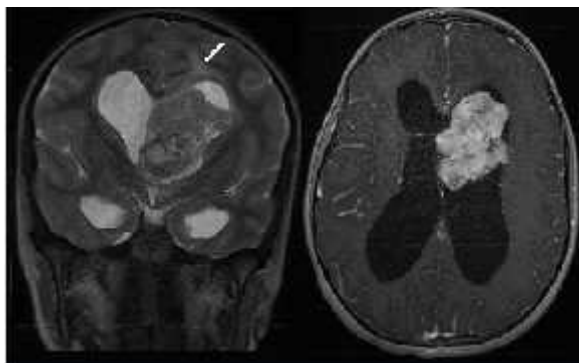

Figure 1: Cranial magnetic resonance imaging (MRI) revealing, in the left lateral ventricle, a voluminous and irregular mass, hypointense heterogenous on T2-weighted images with a strong contrast enhancement, with hydrocephalus (arrow).

These findings suggested the diagnosis of Subependymal Giant Cell Astrocytoma or ependymoma. Histological study of the resection specimen showed a proliferation of multinucleated eosinophilic tumor cells with abundant cytoplasm, ganglion-like cells, and elongated tumor cells (**figures 2 , 3),** without nuclear pleomorphism or mitotic activity. Necrosis and endothelial proliferation were also seen. Tumor matrix was fibrillated. An immunohistochemical analysis showed focal positive staining for **GFAP**. The cells were negative for neurofilament, synaptophysin and S100 protein. Ki-67 labeling index was of approximately 1%. The diagnosis of Subependymal Giant Cell Astrocytoma was then confirmed.
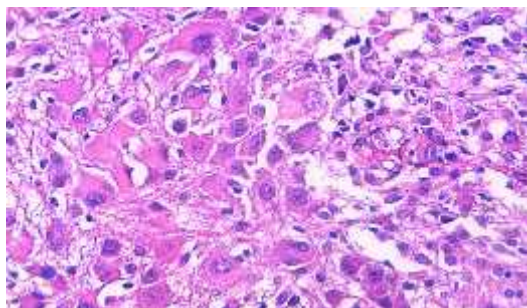

Figure 2: Microscopic appearance: proliferation of ganglion-like cells and multinucleated eosinophilic tumor cells with abundant cytoplasm (Hematoxylin and eosin stain; original magnification ×200).

Case 2: A 7-year-old Moroccan boy was admitted for a 6 years history of seizures with, during the last six months, headaches and vomiting. Cranial MRI revealed multiple lesions in the sub-cortical white matter, with bilateral and asymmetric distribution, with hypersignal intensity on T2-weighted and Flair images, without contrast enhancement, associated with a large, 4cm-sized subependymal nodule, adjacent to the right foramen of Monro, with intense enhancement after contrast injection. These findings suggested the diagnosis of tuberous sclerosis complex with sub-cortical tubers and subependymal nodule. A tumor resection was performed and microscopic examination showed a proliferation of multinucleated eosinophilic tumor cells with abundant cytoplasm, elongated tumor cells, gemistocytic-like cells (figure 4) and ganglion-like cells, without nuclear pleomorphism or mitotic activity (**Figure 3**).
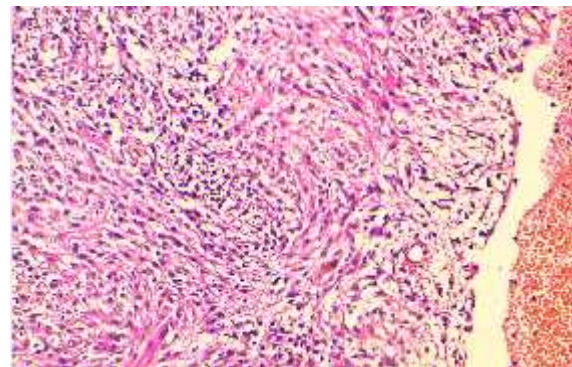

Figure 3: Microscopic appearance: proliferation of elongated tumor cells (Hematoxylin and eosin stain; original magnification ×100).

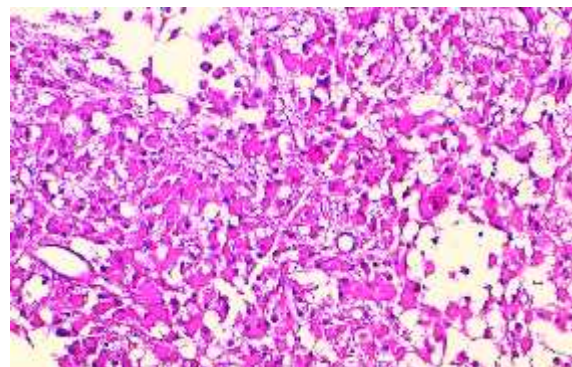**Figure 4:** Microscopic appearance: proliferation of gemistocytic-like cells (Hematoxylin and eosin stain; original magnification ×100).

Tumor matrix was fibrillated and contained **lymphocytes**. Focal areas of necrosis were seen (**Figure 5**). Immunohistochemical analysis showed focal positive staining for **GFAP** (**Figure 6**). The

cells were negative for neurofilament (NF), S100 protein and synaptophysin. Ki-67 labeling index was of approximately 10%.
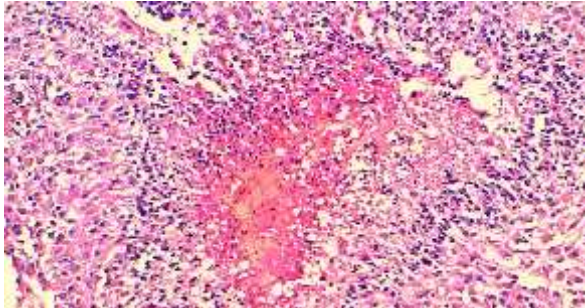

Figure 5: Microscopic appearance: Focal areas of necrosis (Hematoxylin and eosin stain; original magnification ×100).
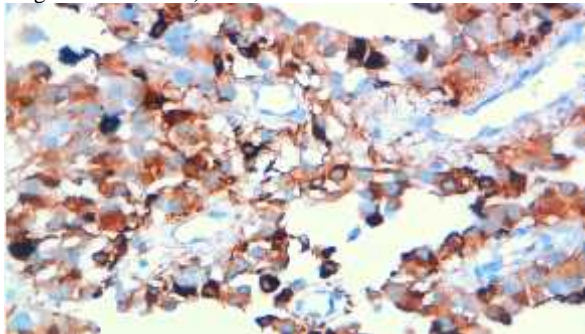

Figure 6: focal positive immunostaining for Glial fibrillary acid protein (Original magnification ×400).

Case 3: A 6-year-old Moroccan boy presented with a 6 months history of headache and vomiting. Cranial magnetic resonance imaging (MRI) revealed a solido-cystic mass located in the right lateral ventricle, with intense enhancement after contrast injection and hydrocephalus, measuring 54 x 45 x 41mm, suggesting the diagnosis of central neurocytoma or ependymoma. A complete tumor resection was performed and microscopic examination revealed a tumor composed of a proliferation of ganglion-like cells, spindle cells, gémistocytic-like cells and multinucleated cells, with large eosinophilic cytoplasm, without nuclear pleomorphism or mitotic activity. Tumor matrix was fibrillated and contained inflammatory elements such as lymphocyts and siderophages. Necrosis was also seen. On immunohistochemistry, Glial fibrillary acid protein (GFAP) was focally positive. Immunostaining for neurofilament, synaptophysin and S100 protein was negative. Ki-67 labeling index was of approximately 2%. Based on these data, the diagnosis of Subependymal Giant Cell Astrocytoma was confirmed.

Table I summarizes epidemiological, clinical, and pathological characteristics of these cases

Table I: Epidemiological, clinical, histological and immuno-histochemical characteristics of our cases

	Age ; gender	Location	Symptoms	TSC signs	Histology	Immunohistochemistry				
						GFAP	NF	SYN	S100	Ki67
Case 1	6y; M	RLV	Headaches, vomiting	Absent	-ganglion-like cells -spindle cells -gémistocytic-like cells -multinucleated cells - necrosis	+F	-	-	-	2%
Case 2	10y ; F	LLV	Headache, vomiting	Absent	ganglion-like cells -spindle cells -multinucleated cells -necrosis	+F	-	-	-	1%
Case 3	7y ; M	foramen of Monro	seizures, headaches, vomiting	Present (subcortical tubers)	-ganglion-like cells -spindle cells - gémistocytic-like cells -multinucleated cells -necrosis	+F	-	-	-	10%

+F: focally positive; -: negative; F: femal; GFAP: Glial fibrillary acid protein; LLV: left lateral ventricule; M: male; NF: neurofilament; RLV: right lateral ventricle; SYN: synaptophysin; TSC: tuberous sclerosis complex; y: years

DISCUSSION

Astrocytoma subependymal giant cell is a rare benign tumor that typically arises at the caudo-thalamic groove adjacent to the foramen of Monro, in the lateral ventricle [1-3]. Exceptions to the typical intra-ventricular location may occur, and extra-ventricular lesions have been described [5]. SEGAs may appear bilaterally or at different locations; invasive lesions invading the fornix, hypothalamus, basal ganglia, and genu of the internal capsule have been reported in literature[3]. Usually, SEGAs **affect** children and young adults (1st and 2nd decade) [1]. Most patients show clinicopathological symptoms between 8 and 19 years and the mean age is 9.7 years [6; 7]. Rarely these tumors **are** present in the neonatal period or in fetuses [8-11]. None of the cases in our series presented in this period. The association of this tumor with tuberous sclerosis complex (TSC) is well known. Tuberous sclerosis is a rare autosomal dominant disease resulting from inactivating mutations in either of two tumor suppressor genes: TSC1 (located on 9q34) or TSC2 (located on 16p13). Protein products of the TSC1 and TSC2 genes form a heterodimer that suppresses the mammalian target of rapamycin (mTOR), a major cell growth and proliferation controller [2-4; 12]. In TSC, these mutations cause hyperactivation of mTOR pathway; that leads to the disorganized cellular overgrowth, abnormal differentiation, more protein translation, and development of tumors [2; 7]. TSC is characterized by hamartomatous tumors in multiple organs, including brain, kidneys, heart, eyes, lungs, and skin [1; 2; 12]. Rare malignant tumors that occur in TSC are renal cell carcinoma, malignant angiomyolipoma, and glioblastoma multiforme [4] The involvement of the central nervous system (CNS) was first described by Bourneville in 1880, and is mainly characterized by the presence of cortical tubers, white matter lesions, subependymal nodules and SEGA [1; 2; 7; 12]. The latter is the most common intracranial tumor found in TSC [4]. In the Mayo Clinic series comprising 345 patients, Shepherd et al reported 6.1% incidence of this tumor in TSC [13]. In a series of 22 cases of SEGA reported by Bonnin et al, only 5 cases (22.7%) were associated with tuberous sclerosis [14]. In contrast, 9 of 23 patients with SEGA (39.1%), reported by Sharma et al were associated with tuberous sclerosis [4].

In relation to clinical, neurological manifestations vary from mild symptoms to extremely severe. Most patients tend to present with convulsions and symptoms related to intracranial hypertension due to obstructive hydrocephalus, like headache, vomiting and visual disturbances. However, other manifestations such as psychomotor retardation in varying degrees and focusing signs like hemiparesis and paralysis of cranial nerves are possible [1; 12; 15-18]. As the combination of SEGA and the STB is common, symptoms characteristics of this condition are often present. In some cases, SEGA may inaugurate the clinical manifestations in the absence of STB signs [1] like in case 3 reported herein. In our cases, all patients were symptomatic, with seizures and symptoms of raised intracranial pressure, like headache and vomiting.

Radiologically, CT scan and brain MRI don't show specific signs; the intensity and the signal of this lesion vary from one case to another. On RMI, it appears as a heterogeneous tumor with low signal intensity on T1, high signal on T2-weighted images and heterogeneous enhancement after gadolinium

injection. Hydrocephalus is frequent. Areas of intratumoral calcifications are sometimes seen [1; 6; 12].

Microscopically, SEGAs have varied morphology ranging from a monomorphic to a highly polymorphic proliferation. They are conventionally composed of a proliferation of three cell types, in varying proportions, in a fibrillar background: globular or rounded ganglion-like cells, with large, eosinophilic and finely granular cytoplasm and eccentric, round or oval, large and irregular nuclei; fibrillar spindle cells; and gemistocytic-like cells. The capillaries are numerous and tumor cells tend to form peri-vascular palissading [1; 4; 19]. Peri-vascular inflammatory component is highly characteristic. It usually contains mast cells and T lymphocytes. Calcifications are also seen. Presence of mitosis, necrosis and occasionally endothelial proliferation is not sign of tumor malignancy[1; 4]. Rarely SEGAs with frank features of malignancy have been reported in the literature [20]. In our reported cases, the histological appearance reveals all cellular types (ganglion-like cells, gemistocytic-like cells, spindle cells and multinucleated cells). Necrosis was also seen in all cases.

Immuno-histochemical staining for glial and neuronal markers reveals that both glial and neuronal proteins are expressed in SEGAs. The difference in degree of GFAP positivity between the tumors with and without TSC is variable. Sharma et al showed no difference and GFAP positivity was expressed in all three components at variable intensity [4], in contrast to the observation made by Bonnin et al, reporting GFAP negativity in the tumors associated with TS [14]. Neuronal markers (NF and NSE) were positive in 15/23 cases (65.2%) in Sharma et al series. The positivity for synaptophysin in the ganglion-like cells in the same series was observed in 3 cases (12.1%). This positivity was not observed in spindle cells and gemistocyte- like cells [4]. In the present cases, GFAP was focally expressed and S100 protein, neurofilament and synaptophysin were negative in the 03 cases.

If the histological diagnosis of this tumor is enough easy, the main problem remains in its histogenesis. Indeed, many hypotheses raised glial, neuronal or mixed (neuro-glial) origin. The astrocytic nature is based on reactivity for GFAP and S-100 protein, as well as ultra-structural demonstration of intermediate filaments, Rosenthal fibers and junctional complexes with capillary basement membrane. Secondly neurosecretory granules and synapses, presence of large ganglion-like cells and their immunoreactivity for neuron-specific enolase (NSE) and NF indicate a neuronal origin [1]. Some authors have suggested that the cell giving rise to this tumor would result from a genetic defect causing a double, astrocytic and neuronal, differentiation, especially when the TSC signs are present [21; 22].

Treatment of SEGAs has been solely surgical because of a lack of responsiveness to other strategies such as chemotherapy or radiation [2; 3]. For a long time, surgery was indicated only in symptomatic patients. Currently, we admit that a precoce surgery, even in asymptomatic cases, decreases morbidity and mortality [1]. Recently, an mTOR inhibitor, everolimus, was approved by EMA and FDA for medical treatment of SEGA associated with TSC, from the age of 12 months [23-26]. In the recent clinical studies, this treatment significantly decreases the volume over 50% of SEGAs in 35% to 42% at six months of the treatment [23; 25]. Moreover, the cessation of the treatment may result in tumor re-growth [27]. But mTOR inhibitor does not lead to total disappearance. It is not, therefore, an alternative to surgery [1]. It is favored in the cases of multiple tumors, in the rare cases of bilateral lesions of the Fornix, in lesions for which gross total resection in unlikely and growing residual tumors [1], and in patients with contraindication for general anesthesia. [2; 28]

SEGA is a low-grade tumor with favorable outcome, and excellent prognosis if surgically removed. Small tumors are usually less invasive and associated with excellent clinical outcomes with low morbidity and mortality. However, when diagnosed at a later stage, the tumor more often affects and invades neighboring structures such as the fornix, hypothalamus, basal ganglia, and genu of internal capsule, and resection is associated with higher surgical morbidity and mortality [2-4]. Although they are benign in nature and grow slowly, they represent the major cause of death in patients with tuberous sclerosis [2; 17; 29]. Tumors resulted in death in 50% of the patients after the age of 10 years in the Mayo Clinic series [29; 30]. Death occurs because of increased intracranial pressure after misdiagnosed tumour growth, or less commonly after **intra-tumoral** hemorrhage [17]. Use Ki-67, whose expression varies generally between 1.5% and 7.4%, does not allow prediction of the prognosis [19; 31].

CONCLUSION

Astrocytoma subependymal giant cell is a rare benign tumor. In the present cases, as reported in the literature, **it** affects children and arises in the lateral ventricle. Symptoms in these cases are in relation to intracranial hypertension. One case occurs in the background of TSC. If the histological

diagnosis of this tumor is enough easy, the main problem remains in its histogenesis.

Abbreviations

GFAP: Glial fibrillary acid protein; LLV: left lateral ventricule; MRI: magnetic resonance imaging ; NF: neurofilament ; NSE: neuron-specific enolase ; RLV: right lateral ventricle; SEGA: Subependymal giant cell astrocytoma; SYN: synaptophysin ; TSC: tuberous sclerosis complex ; WHO: World Health Organization

There is no conflict of interest.

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