

Subependymal giant cell astrocytoma with atypical clinical and pathological features: a diagnostic pitfall

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SUMMARY

Subependymal giant cell astrocytoma (SEGA) is benign, slowly growing tumor linked to the tuberous sclerosis complex. It almost always occurs near the foramen of Monro. Parenchymal extension and worrisome histological features, such as necrosis, mitoses, microvascular proliferation and pleomorphism are unusual in these tumors, but can occur rarely. A case of SEGA is presented, in a patient with no signs of tuberous sclerosis so far, with atypical imaging findings and areas of necrosis found microscopically. These worrisome features initially led to the false diagnosis of glioblastoma. The differential diagnosis of SEGA is discussed.

Keywords: subependymal giant cell astrocytoma – atypical – necrosis

Subependymálny obrovskobunkový astrocytóm s atypickými klinickými a patologickými črtami: diagnostická pasca

SÚHRN

Subependymálny obrovskobunkový astrocytóm (SEGA) je benígny pomaly rastúci tumor asociovaný so syndrómom tuberóznej sklerózy. Vyskytuje sa takmer výlučne v oblasti foramen Monro. Šírenie do parenchýmu hemisféry a znepokojujúce histologické črty ako sú nekrózy, mitózy, mikrovaskulárna proliferácia a pleomorfia sú nezvyčajné, ale vzácne môžu byť prítomné. Prezentujeme prípad SEGA u pacienta, u ktorého zatiaľ nie sú prítomné ďalšie známky syndrómu tuberóznej sklerózy, s atypickým radiologickým nálezom a mikroskopicky prítomnými nekrozami. Tieto znepokojujúce črty iniciálne viedli k nesprávnej diagnóze glioblastómu. Je diskutovaná diferenciálna diagnóza SEGA.

Kľúčové slová: subependymálny obrovskobunkový astrocytóm – atypický – nekroza

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Subependymal giant cell astrocytoma (SEGA) is benign, WHO grade 1, slowly growing tumor linked to the tuberous sclerosis complex (TSC), which forms an expansive mass in the wall of the lateral or third ventricle, almost always near the foramen of Monro (1–3). Parenchymal extension and worrisome histological features, such as necrosis, mitoses, microvascular proliferation or pleomorphism, are unusual in these tumors, but can occur (4). We present an unusual case of SEGA in a patient with no signs of TSC so far, which formed a large solid and cystic parenchymal mass, with a shift of the midline structures and microscopically showed areas of necrosis. These worrisome features led to the false diagnosis of glioblastoma.

CASE REPORT

1.5-year-old girl was admitted to the hospital in June 2008 because of walking difficulties and febrility. At admission, signs of intracranial hypertension were found. Computed tomography (CT)

and magnetic resonance imaging (MRI) showed a large expansive tumor in the left fronto-parieto-temporal region, with a shift of the midline structures and hydrocephalus. Gadolinium enhanced MRI showed non-homogenous, predominantly peripheral (“ring”) contrast enhancement of the tumor (Fig. 1). Partial resection of the tumor was performed (Fig. 2).

Microscopically, the tumor was composed of large gemistocyte-like cells with prominent excentric nuclei, some with prominent nucleoli. Binucleated cells resembling dysplastic ganglion cells could also be seen. The cytoplasm was fibrillary to glassy and the growth of the tumor was solid and expansive. Mitoses were hard to find and microvascular proliferation was not present. However, large areas of geographic necrosis without pseudopalisading were found (Fig. 3).

By immunohistochemistry, most of the neoplastic cells were GFAP positive (clone 6F2, DiagnosticBioSystems), with patchy neurofilament protein expression (clone 2F11, DiagnosticBioSystems) (Fig. 4). Neural filaments were not stained in the background, confirming the non-infiltrative growth pattern. The Ki-67 labeling index (clone MIB-1, DAKO) was very low, approximately 1 %. P53 (clone DO-7, Neomarkers) focally and faintly stained some of the nuclei (< 2 %, not shown).

At the time of sign-out, no further clinical data, including the results of imaging were available to the pathologist. Despite the presence of necrosis, the case was signed-out as SEGA, WHO grade 1.

After the sign-out, clinicians asked for a second look opinion, because of atypical and worrisome imaging characteristics of the tumor and the presence of the necrosis, not quite consistent with

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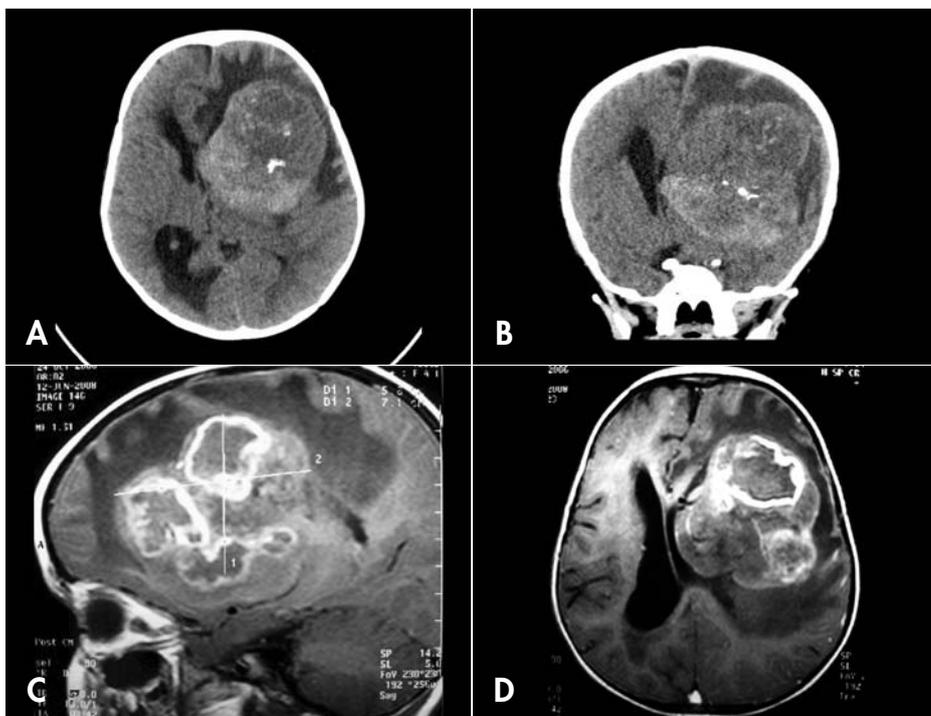


Fig. 1. Preoperative CT imaging showed large expansive fronto-parieto-temporal lesion with shift of the midline structures and hydrocephalus. Intratumoral calcification could be seen. Although the tumor was subependymal and near the foramen of Monro, such extensive involvement of the hemisphere was unusual for SEGA (A, B). T1 MRI with gadolinium showed non-homogenous, predominantly peripheral (“ring”) contrast enhancement of the tumor (C, D).

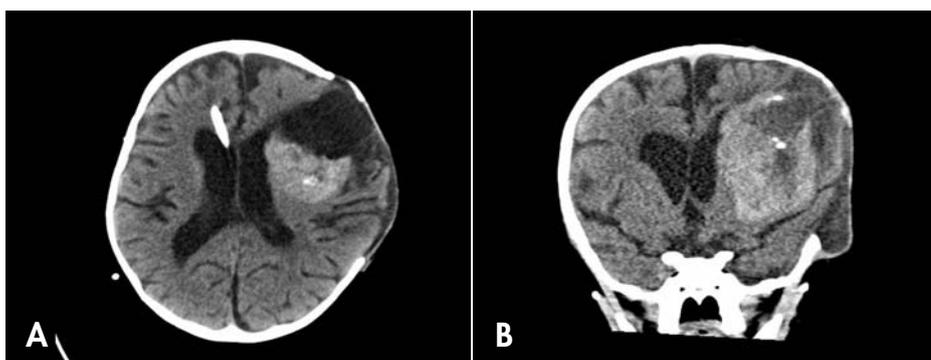


Fig. 2. Postoperative CT showing the result of partial resection of the tumor.

SEGA. A second look was done at a prominent international academic institution. Two neuropathology experts agreed on the diagnosis of glioblastoma, WHO grade 4, despite lack of mitoses and very low proliferation index (the Ki-67 immunohistochemistry was repeated at that institution).

In August 2008, a second partial resection was done and chemotherapy was initiated (POG protocol 9233/34). After initial clinical response, residual tumor size remained stable from the 11th month after beginning chemotherapy. In January 2010 chemotherapy was finished and in March 2010 gross total resection of the residual tumor was performed at another hospital (Fig. 5). Pathological diagnosis at that institution was SEGA again, and planned radiotherapy was canceled. Histomorphology of the resected tumor after the chemotherapy was identical with the previous biopsies. At the time of writing this report (November 2012), i.e. more than four years after initial diagnosis, the patient is in very good clinical condition, with no evidence of the disease. So far, no signs of TSC are evident in the patient. Despite that, we have changed the final diagnosis back to SEGA. Results of the molecular genetics are pending.

DISCUSSION

SEGA is one of the major criteria for the diagnosis of TSC (1–3). In most patients with SEGA, the diagnosis of TSC has already be-

en established, but in some cases it seems to be sporadic or precede other signs of the syndrome (5–8). Whether these cases are truly sporadic or represent *forme fruste* of TSC remains a controversial and unsolved issue at this time. Testing for the mutation of TSC1 and TSC2 genes may be helpful, when a patient does not fulfill criteria for the definite diagnosis. SEGA occurs during the first two decades of life (mean age is 13 years), but rare infant and even congenital cases have been described (4, 9, 10). Patients usually show symptoms of increased intracranial pressure or a worsening of epilepsy.

By imaging, SEGAs are well circumscribed, hyperdense relative to the cortex by CT, with frequent calcifications, mixed intensities on T1 and T2-weighted MRI images and contrast enhancement on both CT and MRI (11). A spontaneous hemorrhage can occur rarely (5). Although the location near the foramen of Monro is characteristic, extraventricular examples have been reported (12,13).

Microscopically, SEGA shows a non-infiltrating growth pattern and is composed of large polygonal gemistocyte-like cells with eosinophilic and sometimes glassy cytoplasm, excentric nuclei and prominent nucleoli. Bi- and multinucleation is quite common and some tumor cells strongly resemble normal and dysplastic ganglion cells. A streaming spindle cell pattern and perivascular pseudorosettes reminiscent of an ependymoma can also be present. Focal inflammatory infiltrates composed of T-cells and mastocytes are common (2,8).

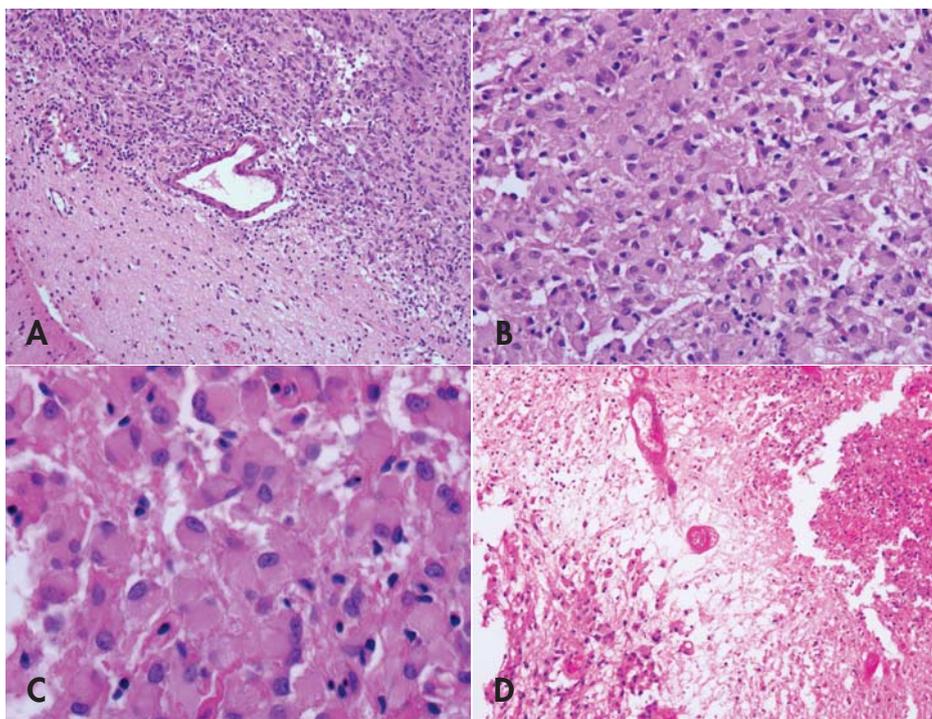


Fig. 3. Expansive growth of the tumor. Note sharp interface with normal parenchyma (A). Gemistocyte-like cells with prominent excentric nuclei and prominent nucleoli, some binucleated cells are also present (B, C). Geographic infarct-like necrosis without pseudopalisading (D). Hematoxylin-eosin, original magnification 100x (A), 200x (B), 400x (C) and 100x (D).

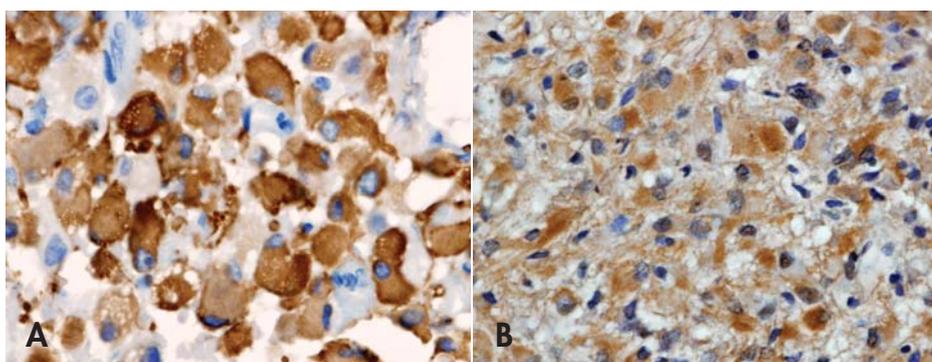


Fig. 4. GFAP expression (A) and patchy neurofilament protein expression (B) by the neoplastic cells. Immunohistochemistry, original magnification 400x (A) and 200x (B).

Immunohistochemically, tumor cells are variably GFAP and S100 positive, and they can consistently but focally also express neuronal markers (neurofilament protein, class III beta-tubulin, synaptophysin, Neu-N). The Ki-67 labeling index is very low and focal P53 immunopositivity (mean labeling index 2.4 %) was described in 60 % of cases in one study (8,14–16).

In some of the tumors nuclear pleomorphism, mitoses, necroses, microvascular proliferation and increased Ki-67 labeling can be found (2,4,8,17). There is a very unusual case report of a 17-year-old male patient with TSC and spinal cord metastasis of SEGA

(18). Traditionally, these “high grade” features are declared not to impact the diagnosis or prognosis. However, some of these “atypical” SEGAs are larger and are symptomatic in younger children, indicating more rapid growth and the possibility of a more aggressive course than usual SEGAs (4). However, more studies on this topic are needed.

Gemistocytic astrocytoma (GA), with high propensity to progress to glioblastoma (although this still remains controversial), is clearly the most important differential diagnosis, as demonstrated in our case. GA is defined as a diffuse astrocytoma variant, characteri-

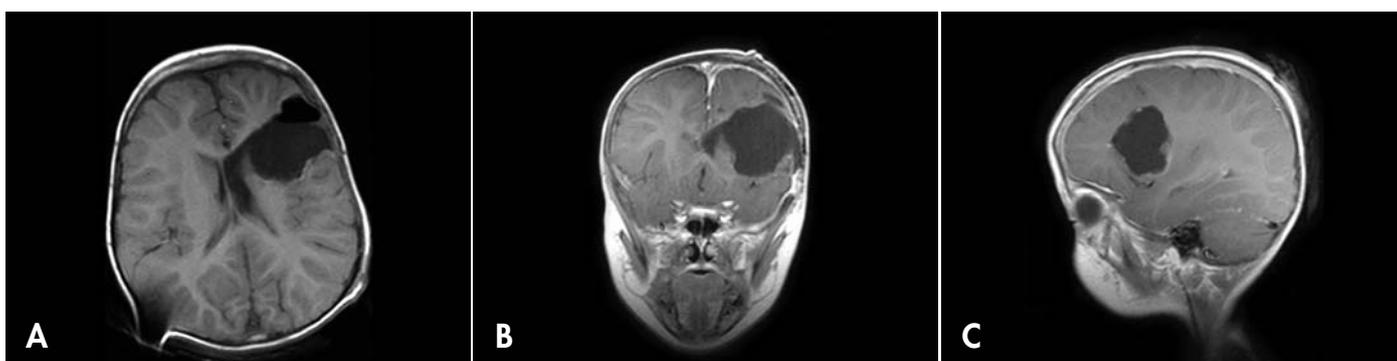


Fig. 5. T1 MRI with gadolinium enhancement after gross total resection.

zed by the presence of an arbitrary set fraction of at least 20 % of gemistocytic astrocytes in a diffuse infiltrating astrocytoma (19,20). Highly cellular regions of GA, composed of gemistocytes with plump, glassy cytoplasm and entrapped neurons can resemble SEGA. Binucleated cells and lymphocytic infiltrates are also common. However, an admixture of smaller, atypical, non-gemistocytic neoplastic astrocytes is typical for GA. GFAP often stains the periphery of the cytoplasm of gemistocytes in GA and neurofilament protein will highlight entrapped neural processes in the background. Staining for neuronal markers in the neoplastic cells is not expected in GA. P53 gene mutations and more diffuse immunohistochemical P53 expression are typical of GA (19-21). Cytological features of SEGA in smear preparations are described as high-

ly characteristic, and also can help to separate it from GA (22), although, in our opinion, in a case of an "atypical" SEGA, smear cytology probably will not clearly distinguish these two tumors.

In conclusion, in some cases SEGA and high grade GA or glioblastoma are lookalikes, and even experts in neuropathology can misdiagnose them. Low mitotic count and Ki-67 labeling index, expansive growth pattern (without entrapped neurofilaments) and absence of atypical small cells are probably the best discriminating features. P53 immunohistochemistry and/or genetics can help in difficult cases. Unusual imaging and microscopic features rarely occur in SEGAs, but careful histological and immunohistochemical examination should lead to the correct diagnosis. Whether these "atypical" SEGAs do show a more aggressive course still remains in question.

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