Sudden death due to a complicated subependymal giant cell astrocytoma

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Abstract: Astrocytic tumors in children, especially subependymal giant cell astrocytoma (SEGA) are slow growing, rare and exotic tumors, with histological similarities, but with distinct evolution. We report a case of a 14 years old female with neurologic deficiency from birth, which developed an intracranial hypertension syndrome and died suddenly at the hospital. During the autopsy an ill-defined, irregular tumor, with invasion into the 3rd and the 4th ventricles was found incidentally, without any associated anomalies. Histologically, the tumor was composed of large, plump, macro-gemistocytic like cells, proliferating in well delineated solid sheets, with small areas of necrobiosis and hemorrhage. The cells had abundant cytoplasm with ground glass aspect and peripherally located nuclei. The nuclear anomalies were minimal and no atypical mitoses were noticed. GFAP, S-100 and vimentin were diffusely positive with strong IHC reaction. Ki-67 was positive in less than 5% of tumor cell nuclei. The underlying cause of death was considered the subependymal giant cell astrocytoma that caused neurological deficits favoring the lung aspiration of gastric contents complicated finally with bronchopneumonia.

Key Words: subependymal giant cell astrocytoma, sudden death, aspiration pneumonia.

Subependymal giant cell astrocytomas (SEGAs) are rare neurological tumors, usually but not always [1] associated with tuberous sclerosis [2]. Recent guidelines suggest the use of the term subependymal giant cell tumor instead of SEGA as the tumor has a glioneuronal origin, distinct from astrocytomas [3], but most researchers still used the older term. Nowadays most patients with SEGA are identified early by using MRI, and dramatic cases, as the one presented in this article, are rarely identified [4]. A proper identification of SEGA allows the surgical resection of the tumor and/or the use of radio/chemotherapy or as of recent biological therapies including mTOR inhibitors like Everolimus [5] or Rapamycin [6]. Sudden death associated with SEGAs has usually been considered as a sudden unexpected death in epilepsy [7-10]. Due to its location within the brain, it can lead to intracranial hypertension, obstructive hydrocephalus and even sudden death [11].

We present the case of a 14 years old girl who died suddenly due to SEGA complications.

CASE REPORT

A 14 years old girl, known with neurological
sudden death due to a complicated subependymal giant cell astrocytoma

During the autopsy external examination proved unremarkable. Internal examination revealed a tumor in the right lateral ventricle, compressive on the right basal nucleus, thalamus, and hypothalamus, and degenerative changes within the corpus callosum and under it, with increased width of the lateral and IV ventricles (Fig. 1).

No foci of hemorrhage or necrosis were noticed, but a variable area of an old ischemic cerebral infarct was surrounding the tumor. The patient also presented asphyxial petechiae, hemorrhagic pneumopathy, bronchopneumonia, mild myocardial fibrosis, and kidney and liver dystrophy.

Pathology investigation

Tissue sampling and stains:
Tissue specimens from brain, lung, heart, liver and kidney were taken for histopathology investigation. The cerebral fragments were harvested from the right lateral ventricular wall and corpus callosum.

The selected tissue samples were fixed in 10% neutral buffered formalin (pH - 7) for 24–48 hours and embedded in paraffin. Sections were cut at 5 μm and stained with standard HE, van Gieson and Nissl.

Immunohistochemistry:

Immunohistochemical analysis (IHC) was done using sections displayed on slides treated first with poly-L-lysine. IHC was performed on 3 μm thick sections from formalin-fixed paraffin-embedded specimens.

The method used was an indirect tristoidal Avidin-Biotin-Complex technique, with a NovoLink Polymer detection system which utilizes a novel control polymerization technology to prepare polymeric HRP-linker antibody conjugates, according to the manufacturer’s specifications (Novocastra, UK).

Briefly, the procedure comprised: deparaffination in toluene and rehydration in alcohol series, washing in phosphate buffer saline (PBS), blocking with normal serum, for 5 min., incubation with primary antibody 60 min., incubation with post-primary block 30 min., then with NovoLink Polymer 30 min. Sections are further incubated with the substrate / chromogen 3,3’-DAB and counterstained with Meyers’ hematoxylin.

The antibodies used for IHC were: GFAP, S-100, vimentin, Ki-67 (for details, see Table 1).

Antigen retrieval techniques (thermal or enzymatic pretreatment) for some of the aforementioned antibodies were done, according to the producer’s specifications. Both positive and negative controls were used.

Negative control was made by using a primary irrelevant antibody or by replacing the secondary antibody with phosphate buffered-saline (PBS). Positive control was made comparatively with the expression of antibody investigated in the peritumoral normal tissue structures (positive internal control on slides).

To ensure the reliability of the experimental study, internal quality control of histopathologic and IHC techniques were performed as a part of an implemented and certified quality assurance system (ISO 9001/2008).

All slides were examined and photographed on a Zeiss Axio Imager microscope (Gottingen, Germany). Digital images acquired with Zeiss Axio Vision program have been processed and analyzed with ACDSee Pro Photo Manager (Washington DC), running under Windows Vista.

The distribution of markers-positivity has been assessed using the modified Quick score method [12], which takes into account the intensity and distribution of the IHC reaction: negative (no staining) = 0; weak (only visible at high magnification)= 1; moderate (readily visible at low magnification)= 2; strong (strikingly positive at low magnification)= 3.

RESULTS

Histologically, the tumor was composed of large, plump, macro-gemistocytic like cells, proliferating in well delineated solid sheets, with small areas of necrobiosis and hemorrhage(Figs 2, 3).

The cells had abundant cytoplasm with ground glass aspect and peripherally located nuclei. The nuclear
anomalies were minimal and no atypical mitoses were noticed.

GFAP (Fig. 4) was diffusely positive in the cytoplasm of tumor cells with strong IHC reaction, S-100 stained also positive in the gemistocytic cells (Fig. 5) and vimentin was positive in tumor cells and the surrounding stroma (Fig. 6). Ki-67 was positive in less than 5% of tumor cell nuclei.

Other associated lesions were: a peritumoral old ischemic infarct with cystic residual change, foci of haemorrhages, vascular thrombosis and cerebral edema.

The lung examination showed bronchopneumonia, with pulmonary abcesses, lung hemorrhages, areas of atelectasis, and gastric aspirate in the bronchi and alveolae.

The underlying cause of death was considered the subependymal giant cell astrocytoma that caused neurological deficits favoring the lung aspiration of gastric contents complicated finally with bronchopneumonia.

**DISCUSSIONS**

Subependymal giant cell astrocytoma is a benign tumor usually identified in the area of the foramen of Monro, the third ventricle or on the wall of the lateral ventricle over the basal ganglia, characterized by the
presence of cells with nuclear characteristics superficially similar to those of the neurons [13]. Astrocytic tumors in children, especially subependimal giant cell astrocytoma (SEGA) are slow growing, rare and exotic tumors, with histopathologic similarities, but with distinct evolution. A particularity of the case resides in the difficulty of making the differential diagnosis between SEGA, diffuse giant cell astrocytoma (DGA) and gangliocytoma due to the presence of necrobiosis and the macro-gemistocytic tumor cells.

In our case the patient had neurological deficits since birth, and was not further investigated. Moreover, the patient did not present signs suggestive for a diagnosis of tuberous sclerosis. The presence of an isolated SEGA, without being associated with tuberous sclerosis extremely rare. Isolated SEGA is a rare WHO grade I tumor, which must be differentiated from DGA (a WHO grade II tumor), that has an intrinsic tendency for malignant progression and ultimately to glioblastoma.

The most frequent complications causing the death of the patients with SEGA are convulsions (sudden unexpected death in epilepsy), or increased intracranial pressure secondary to the blockage of the Monro orifice caused by the tumor[7-11]. In our case the immediate cause of death was different, and related to complications arising from the neurological deficits secondary to the mass effect of the tumor. Based on its location we hypothesized neurological motor deficits able to impede with the normal motor function of the upper digestive and respiratory systems. This in turn caused aspiration of the gastric contents without the possibility to efficiently expel it from the respiratory system.

Normally this is not a typical case of sudden death; however, as the neurological deficits were not considered initially life threatening, and the death was sudden, we were able to include it in this category.

In conclusion, we presented here a case of isolated SEGA in a minor, causing sudden death through a mechanism distinct of those already published in the scientific literature.

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