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Case Report

Granular cell astrocytoma: Case report

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ABSTRACT

Granular Cell Astrocytoma (GCA) is a rare astrocytic brain tumor histologically composed of plump astrocytic cells with abundant eosinophilic granular cytoplasm that exhibits immunoreactivity for GFAP and S100 proteins. It is associated with poor outcome often akin to glioblastoma despite its bland histologic appearance. We report a case of GCA in which neoplastic cells resembled macrophages on intra-operative frozen section and smear. Paraffin sections showed features of a granular cell astrocytoma, WHO grade IV, with diffuse immunohistochemical coexpression of GFAP and S100. No mutation of IDH1 or P53 was identified by immunohistochemistry; however, ATRX loss indicating mutation supported an astrocytic lineage. Additionally, sporadic weak cytoplasmic staining for CD68 and EMA and negative staining for CD163 is likely non-specific due to increased lysosomal activity and does not indicate true histiocytic or epithelial differentiation. We recommend that in the absence of overt high-grade features or admixture with conventional diffuse astrocytoma on intra-operative smear and frozen section, it may be advisable to wait to confirm the diagnosis on paraffin section histology and immunohistochemical stains before proceeding with definitive tumor resection. This diagnostic approach will prevent over-treatment by resection of non-neoplastic mimics of GCA.

1. Introduction

Granular Cell Astrocytoma (GCA) is a rare aggressive astrocytic brain tumor that generally arises supratentorially within the cerebral hemispheres and very rarely infratentorially within the cerebellum or spinal cord. Histologically, it is an infiltrative astrocytoma that is composed predominantly of plump astrocytic cells with abundant eosinophilic granular cytoplasm, with gradual transition into conventional diffuse astrocytoma mostly at the tumor periphery [1–3]. This tumor was first described by Markesbery, et al. in 1973 as a granular cell tumor (GCT) of the central nervous system [4], and later reclassified as GCA by Brat et al. in 2002 [5]. Although tumor cells of GCA closely resemble those of generally benign granular cell tumors (GCT) on morphology, their immunopositivity for glial fibrillary acidic protein (GFAP) establishes their astrocytic differentiation [5]. However, GCAs often have associated lymphocytic infiltrate and the tumor cells resemble lipid-laden macrophages, which can make their diagnosis difficult to distinguish from non-neoplastic diseases such as infarction or tumefactive demyelination, especially on frozen section [1, 2, 5–7]. It is important to differentiate GCA from these differential diagnoses, as GCA typically displays aggressive behavior with poor outcome [2, 8]. We report a case of GCA in an 81-year-old female and aim to clarify some of its morphologic and biologic ambiguity.

2. Case

81-year-old female with multiple medical comorbidities presented with an acute episode of seizure and left-sided hemiparesis. Outside CT scan had demonstrated an area of hypodensity in the right temporal lobe without significant associated mass effect or acute intracranial hemorrhage. Contrast-enhanced MRI was performed at admission, which demonstrated a thick-walled rim-enhancing right temporal occipital region mass within the subcortical white matter (See Fig. 1). The lesion showed a thick rim of enhancement measuring 22.2 mm. Localized mass effect with partial effacement of the atrium of the right lateral ventricle was demonstrated. No midline shift or additional areas of enhancement or FLAIR signal abnormality were identified.

Intraoperative smear and frozen section on initial stereotactic biopsy demonstrated a mildly to moderately hypercellular and relatively monomorphic proliferation of mostly large rounded to polygonal and loosely cohesive to discohesive cells with occasional mitoses. Differential diagnosis included reactive histiocytic proliferation (e.g. unusual demyelination) with a significant concern for anaplastic granular cell astrocytoma. Pathologic findings were discussed with the

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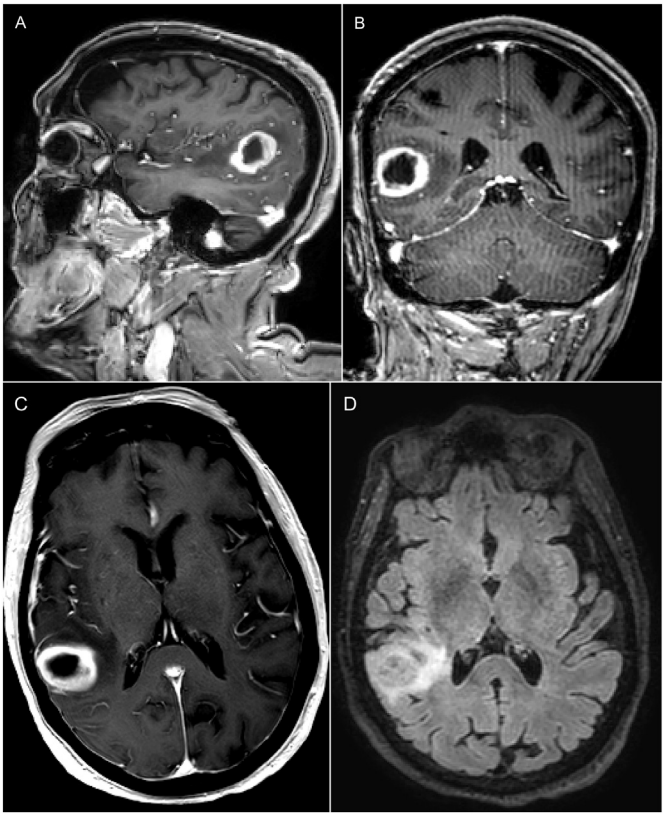

Fig. 1. MRI: Post-contrast T1-weighted sagittal (1A), coronal (1B), and axial (1C) sections demonstrate a well-defined thick-walled ring-enhancing mass-centered in right temporo-occipital subcortical white matter. Axial FLAIR section (1D) showed intrinsic FLAIR intense signal with associated vasogenic edema and mass effect with effacement of adjacent sulci reaching up to right lateral ventricle without midline shift.

neurosurgeon and it was decided to wait to confirm the diagnosis on paraffin sections the following day before proceeding with a definitive resection. Paraffin sections demonstrated a mildly to moderately hypercellular and relatively monomorphic proliferation of mostly large rounded to polygonal and loosely cohesive to discohesive cells characterized by well-defined cell outlines, abundant granular cytoplasm with bland vesicular nuclei, a low nuclear/cytoplasmic ratio, and mildly to moderately pleomorphic and irregular nuclei with few detectable prominent nucleoli. The tumor lacked features of a conventional astrocytoma as the cells demonstrated very scant fibrillary processes and sparse infiltration of scant adjacent brain. A few mitotic figures were present including occasionally two mitoses per high-power field. Additionally, there was evidence of mild to moderate microvascular proliferation and a small focus of necrosis without any pseudopalisading (See Fig. 2). The tumor cells were diffusely positive for GFAP and S100. Although there was sporadic weak cytoplasmic staining for CD68 and EMA (without any membranous staining), CD163 staining was negative in tumor cells with reactivity of only interspersed microglial cells. Ki-67 labeling index was elevated to 22% with P53 staining a small subset of tumor cells in a wild-type sporadic pattern. Additionally, immunostaining for IDH1 was negative indicating absence of the mutation while on the contrary, loss of nuclear staining for ATRX indicated presence of the mutation (See Fig. 3). Although the tumor was unusual in lacking many of the conventional cytologic features of glioblastoma (GBM) on intra-operative smear and frozen section, the overall histopathologic findings on paraffin sections were diagnostic of the very rare entity of high-grade granular cell astrocytoma (WHO grade IV) known for aggressive growth comparable to that of GBM. About 48 h following biopsy, the patient was taken back to the operating room and a definitive tumor resection circumferentially around the original biopsy site was performed. The patient tolerated the procedure well and at 5-month follow-up, she had completed radiotherapy with a 6000 cGy tumor dose in 30 fractions using 6MV X-rays IMRT/IGRT and was scheduled to receive temozolomide.

3. Discussion

GCAs are rare infiltrative astrocytomas that are characterized by large PAS-positive astrocytic cells with granular cytoplasm, closely resembling GCTs that occur in the pituitary stalk. However, in contrast to GCTs, which are generally benign [9], GCAs typically demonstrate aggressive glioblastoma-like clinical behavior even when histologic appearance is that of WHO grade II or III with a median survival of 9 to 11 months in published series [2, 5, 8, 10]. The majority of the cases occur in the cerebral hemispheres with rare cases reported in the pineal gland, cerebellum, and spinal cord. Among hemispheric examples, most cases involve the parietal lobe, followed by the frontal, temporal, and occipital in that order with most cases involving more than one lobe as well. Additionally, reported patient age ranges from 27 to 83 years with a mean of 57 years and most common clinical features include new onset seizures, headache, vomiting, blurred vision, confusion, aphasia, and hemiparesis [7, 8].

Diagnosis of GCA can be challenging on intraoperative frozen section and smears of the brain mass when granular astrocytes form the dominant or exclusive population, mimic lipid-laden macrophages, and are not associated with conventional diffuse astrocytoma or significant nuclear atypia. These findings create a challenge in distinguishing GCA from a tumefactive inflammatory demyelinating process, infarction, and rarely histiocytosis [11] and sarcoidosis [12]. This differentiation is critical because GCA is treated by maximal safe resection, whereas surgery in tumefactive inflammatory demyelination, infarction, and sarcoidosis is typically limited to a biopsy and definitive treatment is primarily medical. Additionally, there is generally significant lymphocytic infiltrate and the tumor cells closely resemble macrophages because of their granular cytoplasm, which most likely represents maturing lysosomes [1, 3, 5–7]. Both GCA cells and macrophages can show a small amount of atypia and mitoses, but certain histologic characteristics can aid in the diagnosis of GCA. These include: large cells ranging from 60 to 100 μm in diameter, mainly eosinophilic granular cytoplasm (rather than the conspicuous foamy or bubbly cytoplasm associated with macrophages or renal cell carcinomas), and distinct cell borders in contrast to the ruffled membrane of macrophages [1, 13]. Nonetheless, the most important histological characteristics that support the diagnosis of GCA are its admixture of conventional diffuse astrocytoma and high-grade neoplastic features. In the absence of the latter features, paraffin sections with immunopositivity for GFAP and S100 are often needed to establish the diagnosis [1, 2, 5, 6].

Our patient initially underwent surgery for resection of the mass, but intraoperative frozen section showed only granular cells without associated conventional astrocytoma. Although the diagnosis of GCA was favored based on morphology and patient age, in the absence of admixture with features of conventional diffuse astrocytoma there was a small possibility of tumefactive demyelination. Therefore, it was decided to hold definitive resection until the diagnosis of GCA could be confirmed on the basis of paraffin sections, GFAP, and Ki67 and then bring the patient back about 48 h later for a planned maximal safe resection. Histologic appearance on FFPE sections indicated a diagnosis of GCA, WHO grade IV, and the tumor cells were diffusely immunopositive for GFAP and S100 with an elevated Ki-67 labeling index up to 22%. Additionally, ATRX loss on immunohistochemistry indicating mutation further supported astrocytic lineage. Once the histologic diagnosis of GCA was confirmed, surgical resection was performed. Of note, there is inconsistency in the literature regarding CD68 and EMA staining in GCAs as some authors have shown positive staining for both CD68 and EMA in neoplastic cells while others have