CASE REPORT

CLINICO-PATHOLOGICAL FEATURES OF GRANULAR CELL ASTROCYTOMA

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We report a rare case of Granular cell astrocytoma (GCA) in a 59 years old male and the dilemma related to its histopathological diagnosis. As Granular cell Astrocytoma cells resemble macrophages this case is important in the pitfalls in its diagnosis and this report emphasizes on the issues related to it. This particular patient had neurological complaints for 7 months and was not investigated. Later he had a CT scan followed by a contrast-enhanced MRI of the Brain that showed multiple focal lesions with surrounding oedema. After metastatic workup with PET/CT scan which was negative; he underwent craniotomy and biopsy of the lesion, which at first was reported as benign. Later his blocks were sent abroad and on further immunohistochemical markers it was finally reported as Granular Cell Astrocytoma (Granular cell Astrocytoma). Granular cell Astrocytoma is a very rare subtype of glioblastoma, which was first described by Markesbery *et al* in 1973 as a granular cell tumour (GCT) in the brain/central nervous system. GCAs are rare and highly aggressive brain tumours. The cells of GCA are distinguished from macrophages by their expression of glial immune-stains, including glial fibrillary acidic protein (GFAP). The perplexity in diagnosing GCA in this case and its similar characteristics as other benign conditions; makes it a unique rare brain tumour on which we should keep an eye on when we have a fix in diagnosis of similar brain lesions.

Keywords: Granular cell astrocytoma; Granular cell tumour of brain; Rare brain tumours; Astrocytoma; Aggressive brain tumours

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INTRODUCTION

Granular cell astrocytoma (GCA) is a very rare subtype of glioblastoma with distinct morphologic features. It is characterized by the presence of sometimes surprisingly bland looking granular cells that may mimic macrophages. Markesbery *et al* first described it in 1973 as a granular cell tumour (GCT) in the central nervous system.[1] Granular cell tumours in other parts of the body look cytologically similar, but are benign, in contrast to GCAs, which are highly aggressive brain tumours. The cells of GCA are distinguished from macrophages by their expression of glial immune-stains, including glial fibrillary acidic protein (GFAP). However, GCAs often have associated lymphocytic infiltrate and the tumour cells look like lipid-laden macrophages; these features make diagnosis of this rare entity difficult and it therefore a problem to distinguish it from non-neoplastic lesions like infarction or demyelination, especially on frozen section samples. The clinical course of GCAs shows that they have an aggressive behaviour comparable to GBMs with a low median survival despite maximizing surgery, radiation, and chemotherapy.

CASE PRESENTATION

We present a case of a 59 years old man with no known co-morbidities, who was seen in the Oncology clinic at Ziauddin University Hospital. He had a previous history of incoordination of the left foot for 7 months, for which he was assessed elsewhere, including a brain CT reportedly showing a few hypodense areas in the frontal lobe. These were interpreted as representing brain oedema due to ischemic injury. A subsequent MRI showed multiple focal lesions of abnormal signal with surrounding oedema involving the genu and rostrum of the corpus callosum, the left insular cortex and the claustrum on left side (Figure-1). A PET/CT scan had also been done to rule out any extracranial primary lesion since the diagnosis was not conclusive. This study revealed increased FDG uptake in the white matter of the right frontal lobe measuring 1.7×1.9 cm with SUV 8.28 and also in the corpus callosum measuring 2.1×2.7 cm with SUV 4.58; the rest of the exam was negative. The differential diagnosis included primary CNS lymphoma and multifocal glioma/gliomatosis. A biopsy was performed and histopathology revealed no convincing evidence of malignancy.

A repeat MRI performed one month later additionally showed multiple abnormal signal intensity areas in both cerebellar hemispheres and bilateral basal ganglia. Mild peri-lesional oedema was also present. A post-contrast study showed nodular and ring enhancing lesions, the largest measuring 3×3 cm in the right frontal lobe. The previous blocks of histopathology, which were initially reported as negative for tumour were sent for second opinion and a diagnosis of GCA was

rendered. On microscopic examination it demonstrated an infiltrative glial neoplasm composed of mostly cytologically bland large cells with cytoplasm ranging from eosinophilic to granular to clear and foamy, similar to that of macrophages. Focally however, there were occasional intervening tumour cells resembling fibrillary astrocytoma. No microvascular proliferation or necrosis was identified. Mitotic figures were inconspicuous. Immunohistochemistry revealed strong CD68 positivity in small macrophages with weaker staining in the large atypical tumour cells; a more specific macrophage marker CD163 was strongly positive in macrophages whereas the tumour cells were negative. Clustered atypical cells were positive for OLIG2 confirming their glial neoplastic nature. More of the atypical cells were also positive for SOX2. GFAP was positive in a small subset of tumour cells and the IDH1 R132H mutant protein stain was negative. The ATRX stain was non-contributory due to suboptimal staining quality. There was scattered staining for p53 protein and the proliferative index Ki-67 was estimated at 7%. A diagnosis of granular cell astrocytoma was established (Figure-2). Although by standard grading criteria, it would have only qualified as WHO grade II, many studies show that this subtype behaves as a grade IV astrocytoma (GBM) even in the absence of high-grade histologic features.[2]

A repeat MRI Brain was done post-surgery which once again showed an ill-defined diffusely infiltrating abnormal signal intensity mass lesion seen involving the white matter of the frontal lobe with extension into basal ganglia, as well as the genu and body of the corpus callosum. Multiple variable sized nodular lesions were seen involving bilateral frontal lobes more on left side. As compared to the previous MRI, there was evidence of progressive disease as the size and number of nodular lesions had increased. The patient was treated with concurrent temozolomide and external beam whole brain radiation therapy (WBRT) to a dose of 3600 cGy followed by a boost to the large lesion with Cyber-knife treatment.

After completion of his treatment, he presented in the clinic two days later with complaints of altered consciousness and drowsiness, eventually becoming bedridden completely. On detailed examination his GCS was 6/15 and he was opening his eyes only to painful stimuli. He was admitted to the hospital, but his condition further worsened, with GCS dropping to 4/15. A differential diagnosis of post-radiation necrosis was made and he was started on steroids, antibiotics (Moxifloxacin and Co-trimoxazole), as well as anti-viral (Acyclovir) and anti-fungal (Fluconazole) agents after blood and urine cultures. During the course of his admission, he developed tonic-clonic seizures and was started on anti-epileptic (Valproic acid) treatment. A repeat MRI showed multiple rings enhancing lesions in both frontal and temporal lobes, bilateral basal ganglia, thalamus and cerebellum with associated vasogenic oedema, suggestive of diffuse brain metastasis (Figure-1).

The patient was later discharged home for hospice care only and subsequently expired.

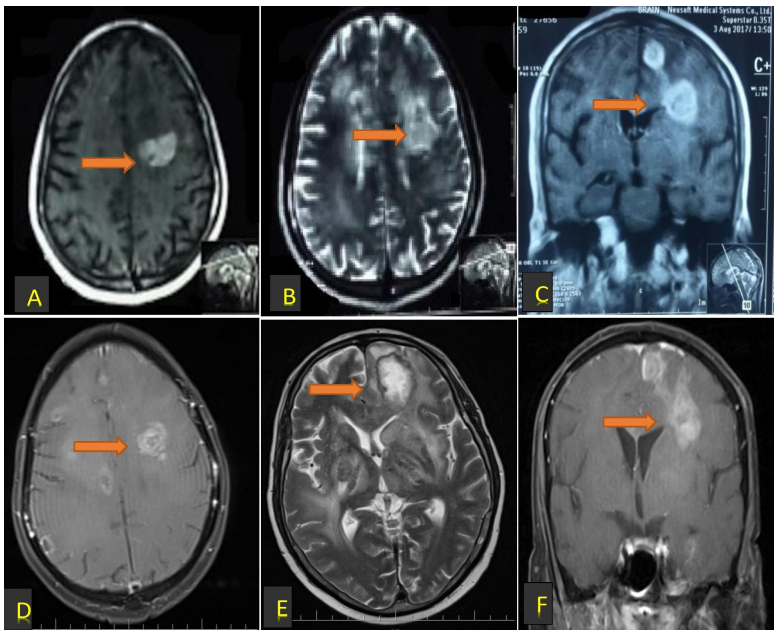

Figure-1: A, B and C: Pre-operative Contrast enhanced MRI images with an arrow showing the focal lesions. A: Axial T1 post-contrast images, B: Axial T2 images, C: Sagittal T1 post-contrast images.
D, E and F: Post-operative Contrast enhanced MRI images with an arrow showing the focal lesions. D: Axial T1 post-contrast images, B: Axial T2 images, C: Sagittal T1 post-contrast images.

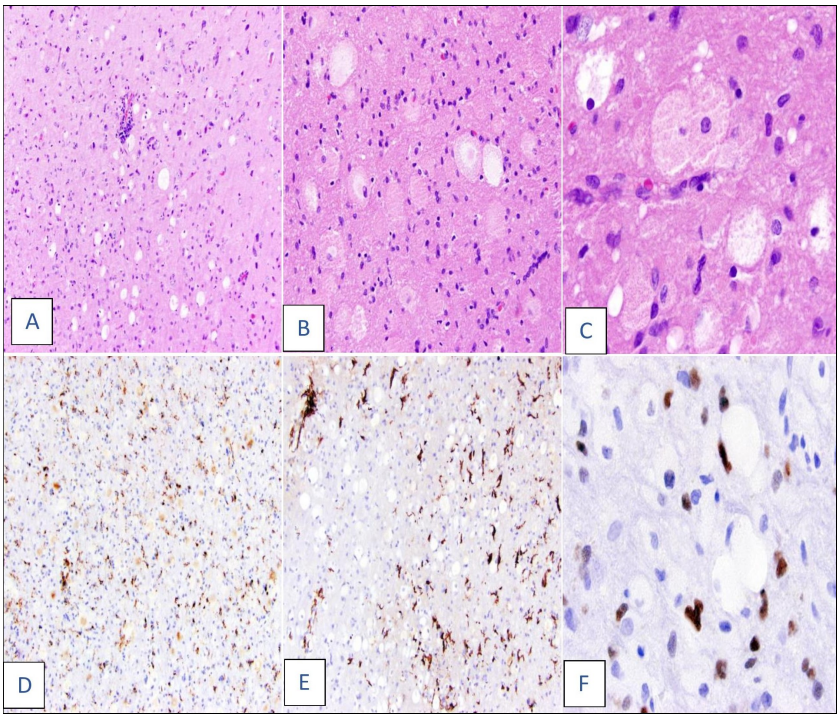

Figure-2: A, B and C: Hematoxylin and Eosin (H & E) slides of histopathology slides with increasing toxicity. A: 20x Magnification, B: 40x Magnification, C: 100 x Magnification. D: CD 68 Immuno-stain, E: CD 163 Immuno-stain, F: OLIG-2 Immuno-stain.

DISCUSSION AND CONCLUSION

Granular cell tumour (GCT) was first described by Abrikossoff in 1926. It is now generally accepted that the origin is from the Schwann cell.[1] GCT has been reported in different locations mostly in the skin of the head and neck and especially inside the mouth (70% of cases), the tongue being the most common site. The tumour cells are large and the cytoplasm is highly granular. Most of these tumours pursue a benign clinical course.

In contrast, granular Cell Astrocytoma (GCA) is a primary neoplasm of the central nervous system. These are rare infiltrative astrocytomas that are characterized by large PAS-positive astrocytic cells with granular cytoplasm. William Markesbery first described granular cell tumours in 1973 in a paper published in Journal of Neuropathology and Experimental Neurology. He reported 2 cases; one in the cerebrum and other was located in the leptomeninges. An extensive literature search was done to further explore the biological nature of this disease and it was concluded that GCA is a highly aggressive tumour, which is contrary to the benign nature of GCT in other parts of the body.[1] However, GCA is a distinctive morphologic variant of infiltrative astrocytoma associated with granular cytoplasm due to lysosomal accumulation.[3–5] Previous reports suggest that the patient age ranges from 27–83 years with a mean of 57 years. These patients generally present with new onset seizures, headache, vomiting, blurred vision, confusion, aphasia and hemiparesis.

Diagnosis of GCA is challenging on intraoperative frozen section because the cells may mimic lipid-laden macrophages. Limited studies are done on the cytological features of GCA.[6] A study by Kang M. in 2012 reported some features of cytology in one of a patient of GCA. The crush smears of that patient had singly-scattered, large eosinophilic cells with eccentrically located nuclei as well as plump, finely granular cytoplasm with distinct borders. There was mild cellular atypia and also absent mitotic activity. These cells were also admixed with small mature lymphoid cells.[7]

These histological features make the diagnosis of GCA a challenging process, raising differential diagnoses that may include tumefactive inflammatory demyelinating process, infarction, and rarely histiocytosis or sarcoidosis [8,9]. This differentiation is critical because GCA is treated by maximal safe resection, whereas these other diseases are primarily treated medically. Tumour cells in GCA closely resemble macrophages because of their granular cytoplasm. Both GCA cells and macrophages can show limited cytologic atypia and mitoses, but certain histologic clues can aid in the diagnosis of GCA. These include: large cells ranging

from 60 to 100 µm in diameter, mainly eosinophilic granular cytoplasm, and distinct cell borders in contrast to the ruffled membrane of macrophages. Other supportive evidence in the diagnosis of GCA includes immunohistochemical evidence of glial differentiation, such as GFAP, S-100, OLIG2, and/or SOX10 positivity. In this particular case, the initial challenge was in reaching an accurate diagnosis. Due to its rare nature, it resemblance to non-neoplastic diseases and the unavailability of specific immunohistochemical studies, it was initially missed.

Although GCA's have a histological appearance that is unique from other astrocytomas and malignant brain tumours, they still behave as aggressively as other high-grade gliomas, particularly GBM.[10,11] In a large study of 22 cases in 2002, by WHO criteria, four GCAs were grade II, seven were grade III, and eleven were grade IV. Nevertheless, the mean survival was only 7.6 months regardless of WHO grade, suggesting that they should all be considered grade IV clinically.[12]

Because of its aggressive nature GCA is treated just like other high-grade brain tumours. Keeping in view this high-grade behaviour, this patient was treated similarly. Post-surgery he was started with chemo-radiation followed by a boost with Cyber-knife radiation technology; unfortunately, he developed complications and treatment failures, eventually succumbing to his disease roughly 9 months after presentation.

In conclusion, we report a case of granular cell astrocytoma, which is to our knowledge, the first such case reported from Pakistan. This case also is important because it shows the complexity in diagnosing GCA in common brain tumour scenarios. However, it resembles GBM and Astrocytoma still it was difficult to diagnose which led to delayed treatment.

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