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Case Report

Giant Cell Glioblastoma in a Child with Clinical and Family History of Neurofibromatosis

Abstract

We report a case of giant cell glioblastoma (GCG) in a 13-year-old child with clinical features and family history of neurofibromatosis type 1 (NF1). To the best of our knowledge, only two cases of GCG have been reported in a scenario of NF1, and only one of that was in a pediatric age group. A report on our case is presented here along with a review of literature.

Keywords: *Giant cell glioblastoma, neurofibromatosis, pediatric tumors*

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Introduction

The term giant cell glioblastoma (GCG) was first introduced in the World Health Organization (WHO) classification in 2000 as a histological variant of glioblastoma to define a neoplasm that contains abundant bizarre multinucleated giant cells with prominent reticulin stroma and a high frequency of p53 mutations.[1] GCG is a rare entity accounting for 0.8% of all central nervous system tumors up to 5% of glioblastoma and is extremely rare in pediatric age group.[2] The authors report a case of GCG in a 13-year-old girl with clinical features and family history of neurofibromatosis (NF). Case reports of GCG in children are sparse in literature. To the best of our knowledge, this is the third case report of GCG associated with clinical features of NF, and the second case report in a child in a scenario of NF type 1 (NF1).[3,4] In this case report, we discuss GCG with a review of the relevant literature.

Case Report

A 13-year-old girl presented with a short history of brief spells of sharp shooting headaches for 2 months, bouts of vomiting for 1 month followed by a single episode of seizure 15 days back. On examination, she had multiple café-au-lait spots [Figure 1a-c] and few small subcutaneous neurofibromas. No neurological deficit was noted. The other family members had clinical features that were strongly suggestive of NF1 as all her siblings had similar café-au-lait spots [Figure 1d]. One of her siblings also had small subcutaneous neurofibromas while her elder brother had been diagnosed as having osteosarcoma. Computed tomography scan showed a left parietal isodense lesion with a small contrast enhancing area with perilesional edema [Figure 2a]. The magnetic resonance imaging (MRI) revealed an ill-defined, large, multilobulated heterogeneous predominantly solid mass involving the left frontoparietotemporal lobe [Figure 2b]. The mass exhibited diffuse intense heterogeneous contrast enhancement [Figure 2c]. MR spectroscopy showed a high choline level with significantly reduced N-acetylaspartate [Figure 2d]. A differential diagnosis of high-grade glioma and primitive neuroectodermal tumor was made. The lesion was approached by a left parietal craniotomy, exposing a tense and bulging dura. Durotomy revealed an intraparenchymal mass in the left parietal lobe which was lobulated, grayish yellow, firm, nonsuckable, and moderately vascular with occasional calcified areas [Figure 3]. A clear plane was identifiable between the tumor and the brain tissue. Gross total tumor removal was done. The per-operative specimen sent to the histopathology laboratory was subjected to squash smear preparation and frozen sections. Squash smears and frozen sections revealed prominent necrotic foci, chronic inflammatory infiltrate and scattered epithelioid cells. No tumor cells were seen [Figure 4a]. Based on the above findings, a per-operative diagnosis of an

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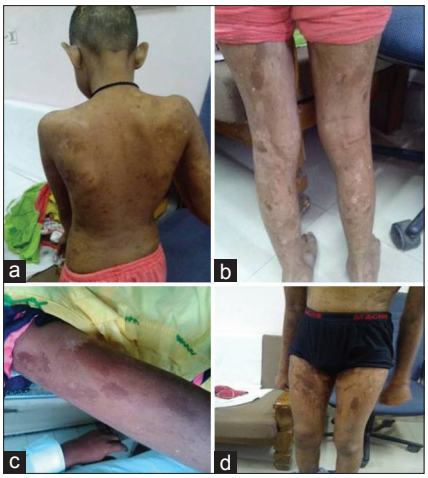

Figure 1: (a-c) Patient exhibiting multiple café-au-lait spots; (d) sibling showing similar café-au-lait spots

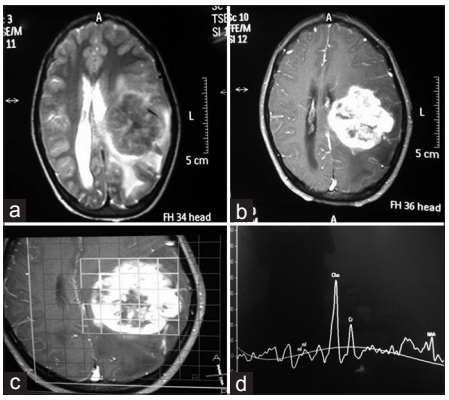

Figure 2: (a) Computed tomography scan showing isodense lesion with minimal enhancement and perilesional edema; (b) magnetic resonance imaging showing an ill-defined large, multilobulated heterogeneous predominantly solid mass involving the left frontoparietotemporal lobe; (c) mass exhibiting diffuse intense heterogeneous contrast enhancement; and (d) magnetic resonance spectroscopy showing high choline level with significantly reduced N-acetylaspartate

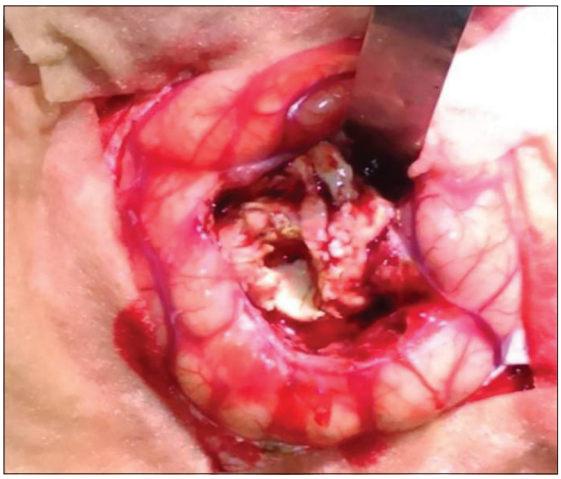

Figure 3: Microphotograph showing a firm, nonsuckable, lobulated, grayish yellow mass with moderate vascularity, and few calcified areas

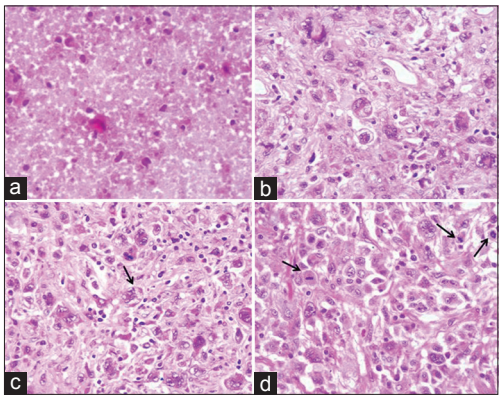

Figure 4: (a) Squash smear showing epithelioid cells, inflammatory infiltrate against a necrotic background (H and E, ×400); (b and c) histopathology showing bizarre neoplastic and heavily lipidized giant cells (H and E, ×400); and (d) brisk mitosis (H and E, ×400)

inflammatory lesion was suggested. The latter specimen received in formalin for paraffin sections showed a cellular pleomorphic astrocytic tumor with numerous multinucleated giant cells and large areas of geographic necrosis with occasional epithelioid cells [Figure 4b]. The giant cells had extremely bizarre appearance; some cells were heavily lipidized [Figure 4c]. Atypical mitosis was frequent [Figure 4d]. Marked stromal reaction was evident on reticulin and Masson's trichrome stain [Figure 5a]. Giant cells showed immunopositivity for S100, vimentin, and p53; however, glial fibrillary acidic protein (GFAP) was positive in most of the giant cells. All neuronal antigens were immunonegative. Tumor overall showed a high proliferative activity as high labeling index determined by Ki 67 antibody [Figure 5b-f]. This case was reported as GCG (WHO Grade IV). Large areas of necrosis, chronic inflammatory cell infiltrate, and occasional epithelioid cells in the paraffin sections explains the squash smear being reported as inflammatory lesion as probably this was the area that was picked up in the squash smears. This also highlights the importance and role of adequate sampling during per-operative squash smears and frozen sections preparation.

The postoperative course was uneventful; postoperative MRI revealed no residual tumor. The patient underwent radiotherapy. She was well for 6 months when she had recurrent episodes of seizures and died 1 day later.

Discussion

GCG was first described in 1979 by Zulch as "monstrocellular sarcoma" because of the prominent giant cells and the stromal reticulin network.[5] However, the astrocytic nature of this tumor was firmly established in 1993 because of the consistent expression of GFAP in the giant cells.[6] Later in 2000, the term GCG was introduced in the WHO classification to define a histological variant of glioblastoma that contains abundant bizarre multinucleated giant cells with prominent reticulin stroma and a high frequency of p53 mutations.[1] GCG is a rare entity,

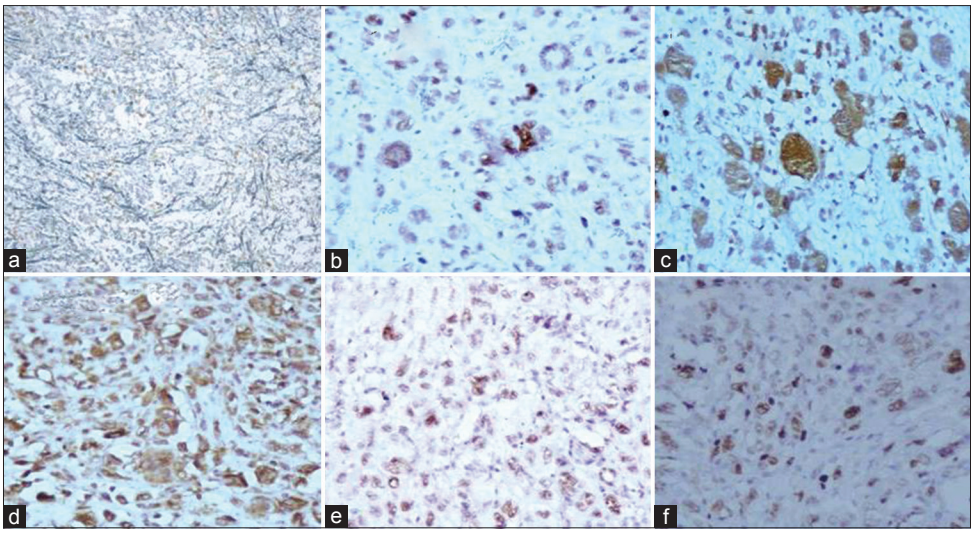

Figure 5: (a) Reticulin stain showing marked stromal reaction (×200); (b) p53 immunopositivity in tumor cells (×400); (c) immunopositivity for S100 in tumor cells (×400); (d) tumor cells showing strong immunopositivity for vimentin (×400); (e) glial fibrillary acidic protein positive tumor cells (×400); and (f) high Ki 67 proliferation index (×400)

manifesting in adults.[7] The mean age at diagnosis is 41 years with a wide range of age presentation, may occur in children, however, is extremely rare in pediatric age group.[8] This tumor is usually located subcortically in the temporal and parietal lobes.[1] Other less common locations include the cerebellum, lateral ventricles, optic chiasm, and spinal cord.[9,10] Rarely, it is multifocal.[11]

Radiological features are distinctive exhibiting a well-demarcated mass. However, it may progress from well-circumscribed and homogeneous to infiltrative and heterogeneous mass in a short span as described by Can *et al*. in their case report.[12] In addition to MRI, MR spectroscopy, diffusion-weighted imaging, and perfusion imaging often offer clues for specific diagnosis of GCG.

GCGs have clinical features similar to glioblastoma, although GCGs manifest with a shorter preoperative history. This case when compared to the existing literature presented with the usual clinical history at a usual location. However, GCGs with a clinical and family history of NF are extremely rare. To the best of our knowledge, only two cases of GCG with NF1 have been reported in the literature to date. The first case was reported by Kroh *et al*. in 2004 in an 8-year-old child,[3] and the second case was reported by Taraszewska *et al*. in a 29-year-old female in 2013.[4]

Histopathologically, GCGs correspond to WHO Grade IV. The key histopathological features are a predominance of giant cells and necrosis with abundant reticulin stroma. Molecular genetic analysis of these tumors indicates that these occupy a hybrid position between primary (*de novo*) glioblastomas and secondary glioblastomas.[13] Features in common with primary GBM include a short clinical history, absence of a less malignant precursor lesion, and frequent PTEN mutations while features in common with secondary GBM are a younger age of clinical manifestation and a high frequency of TP53 mutations.[13] The prognosis of patients with GCG is better than for patients with ordinary glioblastoma.[14] As far as treatment is concerned, the standard treatment of GCG is a complete surgical excision, followed by radiotherapy and chemotherapy.

Pleomorphic xanthoastrocytoma (PXA) is an important differential diagnosis of GCG in children. The common features shared by GCG and PXA include numerous giant cells, prominent reticulin stroma, lymphocytic infiltrates, and evident circumscription. Points favoring GCG include, clinically a short history with quicker evolution of seizures, histopathology showing numerous bizarre giant cells, frequent atypical mitoses, pseudopalisading necrosis, with immunopositivity for p53 and GFAP, and immunonegative for neuronal markers.

Conclusion

To conclude, GCGs remains an extremely rare entity in the pediatric age group, especially so with the clinical background strongly indicative of NF. Though these are rare in childhood, diagnosis is important as they have longer survival than classical glioblastoma in pediatric cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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