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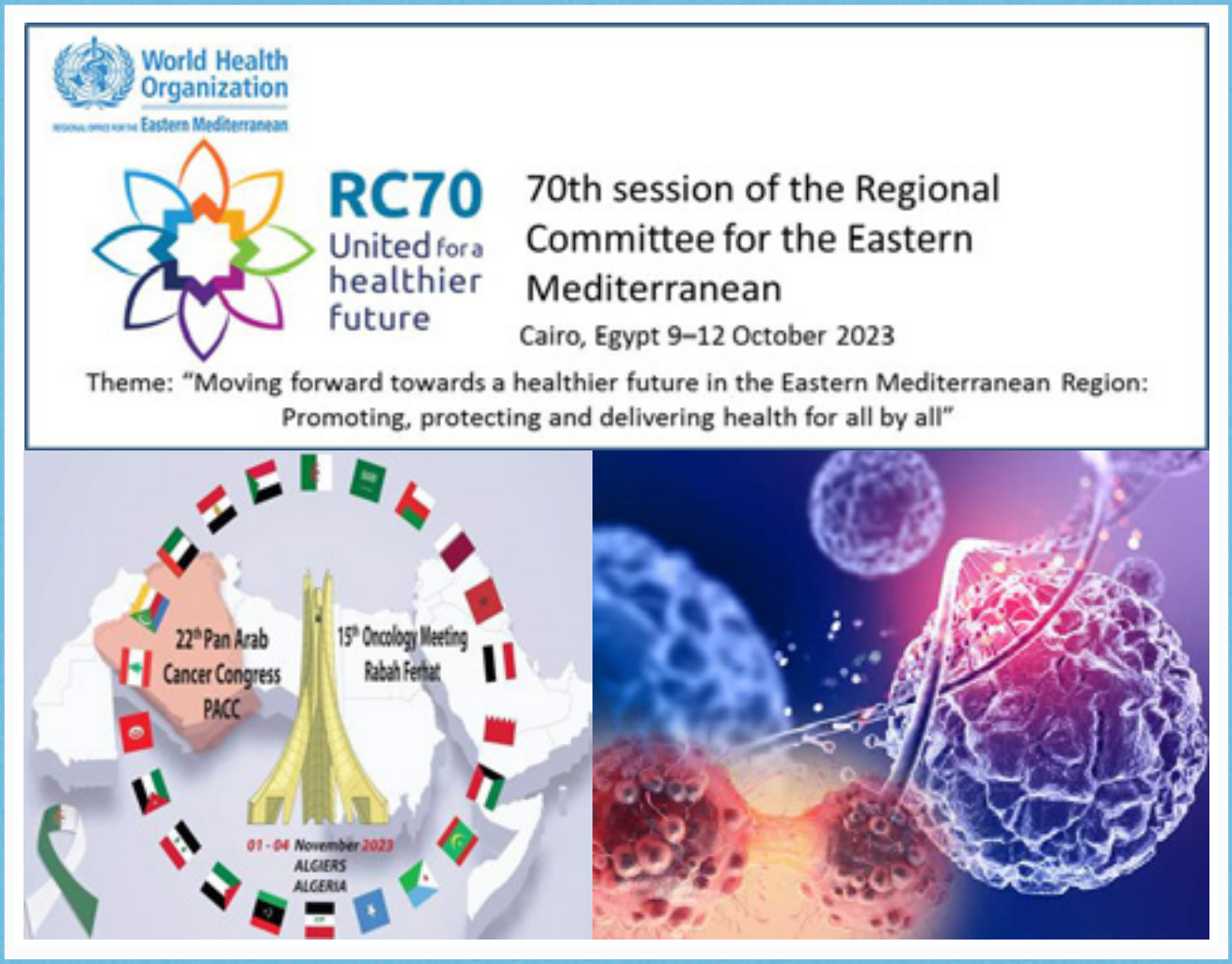

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Case Report

Glioblastoma with Primitive Neuroectodermal Tumor like Component: Rare and Enigmatic.

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Abstract

Glioblastoma (GBM) with Primitive Neuroectodermal tumor (PNET) like features is an extremely rare tumor showing dual features of malignant glioma and primitive neuroectodermal tumour occurring mostly in adults. It poses diagnostics dilemma to the neuropathologist and treating oncologist team because of its rarity, tendency to spread to cerebrospinal fluid and dismal prognosis. We have described this tumor in a 11 years old male child in this case report.

Keywords: glioma,glioblastoma,primitive neuroectodermal tumor, variant, pediatric

Introduction

Glioblastoma (GBM) with Primitive Neuroectodermal tumor (PNET) like component is rare, emerging tumor entity recently recognized and defined by WHO in 2016 classification of Central Nervous System (CNS) tumor. [1] This high grade tumor is defined by the presence of astrocytoma of any grade with zones of primitive cells displaying neuronal differentiation.[2]. Because of two different high grade entities occurring together in the same tumor, it became one of the most challenging situation for the neuropathologist to diagnose and later for the treating clinicians due to dismal prognosis. Recent studies have suggested that Glioblastoma multiforme with PNET like features as potent variant of Glioblastoma multiforme usually occuring in older adults.[3]The incidence of Glioblastoma multiforme with PNET like features is extremely rare in pediatrics cases with few cases described in the world literature so far.

Case history

An 11 years old male child and unknown case of any medical illness, was referred to our hospital with a history of confusion and headache and had two episodes of loss of consciousness over the period of 9 weeks. The physical examination showed that the patient was fully conscious and oriented for place, time and person with a Glasgow coma scale of 15/15. MRI showed a well–defined intra–axial hemorrhagic space occupying lesion seen in the right temporal region measuring 29 x 28 x 26 mm associated with grade II vasogenic edema and mild mass effect. [Fig 1] The differential diagnosis considered were Cavernoma and benign hemorrhagic mass lesion. Subsequently the patient had undergone first craniotomy procedures for debulking of the tumor followed by the second craniotomy procedure for excision of the tumor. Histopathological examination reveals high grade cellular tumor showing large cells with abundant eosinophilic cytoplasm and hyperchromatic pleomorphic nuclei. [Fig 2]. Foci of microvascular proliferation and atypical mitotic figures were also seen. Also seen foci showing sheets of small round cells having scanty cytoplasm and round hyperchromatic pleomorphic nuclei.[Fig 3].Because of the young age of the patient and relatively short duration of the symptoms and site of the lesion, we initially thought of first Primitive neuroectodermal tumour with glial differentiation (GBM) and the second and rare possibility of Glioblastoma Multiforme with PNET like features. On immunohistochemistry, GFAP

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[Fig 4] and Vimentin were positive and Synaptophysin was negative in the astrocytic component whereas the primitive neuronal areas were positive for Synaptophysin [Fig 5] and negative for GFAP. Ki67 showed increases proliferative index 50%. Also olig2 and p53 were diffusely positive. INI1 and ATRX were retained. H3G34R, BRAFV600E and IDH1R132H were negative. MLH1, MSH2, MSH6 and PMS2 are retained. On molecular testing, Nanostring was negative for RELA fusions. The patient had started with chemotherapy and is under follow up.

Discussion

Glioblastoma multiforme (GBM), classified as grade IV in the World health organization (WHO) system, is the most common high grade and aggressive primary tumor of the brain in adults.[4] The incidence of GBM in the pediatric age group is 0.8 per 10000 children.[5]. Supratentorial Primitive neuroetodermal tumors (sPNET) are high grade (IV) embryonal tumors which account for 2.3% of pediatric brain tumors, with a mean age of presentation of 5.5 years.[6] GBM with PNET–like features is a new emerging variant of GBM combining the features of GBM and sPNET, posing utmost challenges to the pathologist applying diagnostic modalities, and to the oncologist team while managing the patient.[7].It is defined as a tumor displaying two distinct architectural, indicating a high grade glioma mostly GBM and hypercellular, PNET–like area with minimal fibrillary background, small multinucleated cell with scant cytoplasm, oval or round hyperchromatic nuclei and Homer–Wright rosettes.[8]. GBM with PNET–like features is a very rare, newly purposed entity and rarely reported in the literature, especially in the pediatric age group.[9] The mean age of presentation of GBM with PNET like feature is 4.3 +/– 2.9 years, with M:F ration being 1:1.4. Whereas the mean age of pediatric GBM is 8.3 +/– 4.8 (M:F:1:2) as described in a study comparing GBM and GBM with PNET–like features in the pediatric age group.[10] GBM with PNET–like features is mostly described as isolated cases with a few case series. Perry *et al* had published the largest series of 53 cases describing the clinico–pathological and genetic aspects mostly in adults with only two pediatric cases, age 12 and 17 year. [7]

GBM with PNET–like features is most commonly see in the temporal lobe, as described by Perry et al. [7] Majority of cases of that study presented with a short duration (less than 6 months) of symptoms as described in the index case.[9]

On imaging: GBM with PNET–like features revealed a well–circumscribed tumor with significant mass effect, diffuse perilesional edema, and rarely intra–lesional hemorrhage, necrosis and cystic spaces.[7,9]. Our patient revealed similar features.

Several theories have been proposed describing the origin of this high grade lesion. The most commonly accepted hypothesis is that both GBM and sPNET develop from the (i) same stem cell, which show different differentiation. [1] The other hypotheses are the (ii) neuronal metaplasia phenomenon, or de–differentiation of the anterior compartment, resulting in neuronal cells.[1] (iii) Collision tumor with two distinct clonal expression.[11] (iv) Development of differentiated glial tumor from pre–existing neuronal cells [9]. However, the exact pathogenesis remains controversial due the small number of cases and case

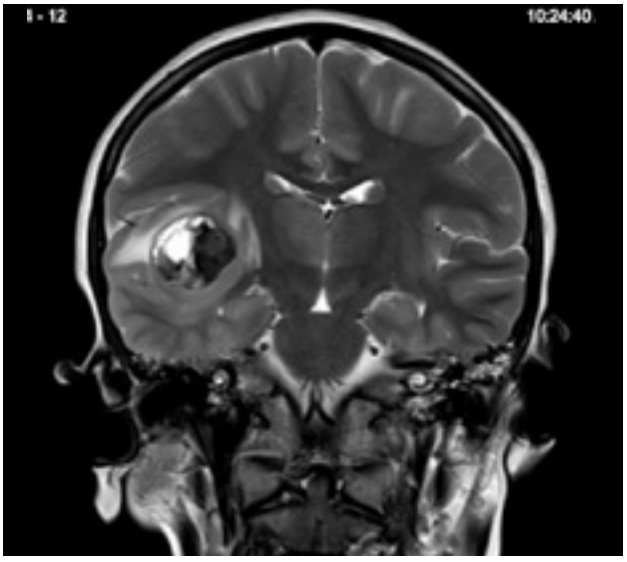

Fig 1: MRI showed a well–defined intra–axial hemorrhagic space occupying lesion seen in the right temporal region measuring 29 x 28 x 26 mm associated with grade II vasogenic edema and mild mass

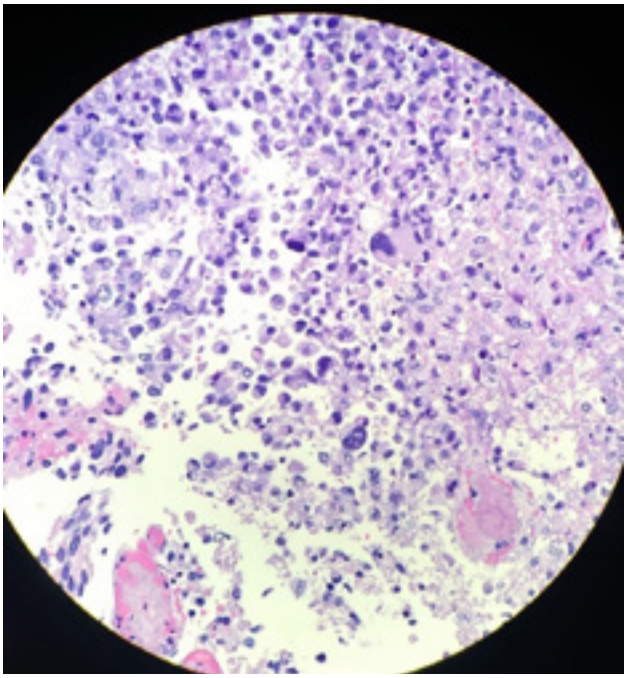

Fig 2: Histopathological examination reveals high grade cellular tumor with showing cells with abundant eosinophilic cytoplasm and hyperchromatic pleomorphic nuclei against fibrillary background. (H&E,20x)

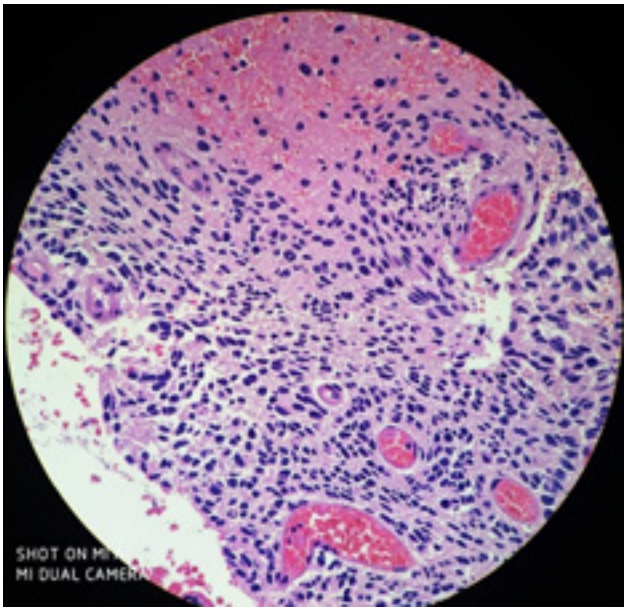

Fig 3 : Histopathological examination showing sheets of small round cells having scanty cytoplasm and round hyperchromatic pleomorphic nuclei were seen. .(H&E,20x)

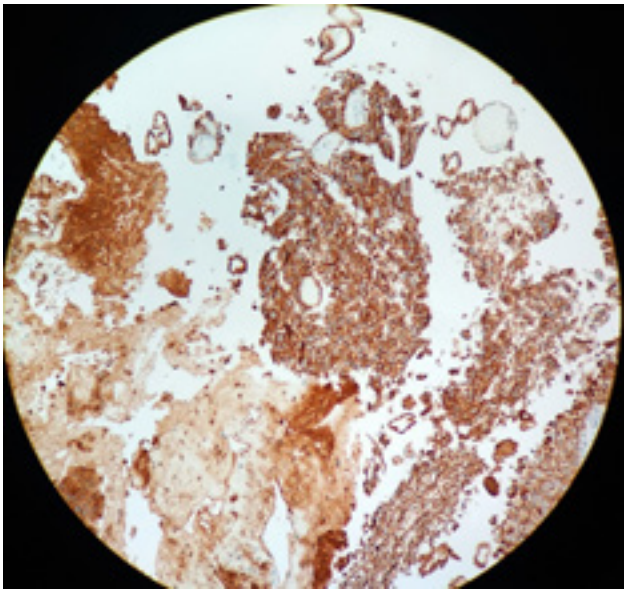

Fig 4: On immunohistochemistry, GFAP positivity in the astrocytic component.

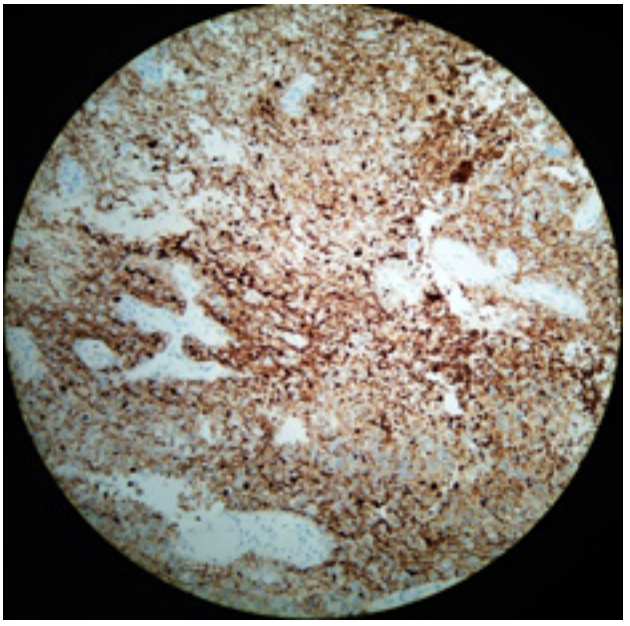

Fig 5: On immunohistochemistry, Synaptophysin positivity in the primitive neuronal areas.

series in the world literature. On squash cytology, it reveals features of high grade glioma, i.e. large glial cells occurring singly or in clusters against a fibrillary background, along with the small round cells that are hyperchromatic, pleomorphic, round–to–oval or carrot shaped, with nuclei often molded to each other and scanty cytoplasm.[12] Unfortunately intraoperative squash cytology and frozen section were not done in this described case. Gross examination shows necrotic soft friable tan white tissue. [1,3]Microscopic examination reveals predominantly high grade glioma component resembling GBM, gliosarcoma(GS) or anaplastic oligodendroglioma along with minority component comprising of hypercellular nodules, showing tumor cell with increased N:C ratio, hyperchromasia, oval to carrot shaped nuclei, high mitotic activity, high karryorhectic indices, Homer–Wright rosettes.[1,2,3,8,9,] The differential diagnosis considered are small cell Glioblastoma (GBM) and Atypical teratoid rhabdoid tumor (ATRT) [1,7]. Small cell GBM shows diffuse parenchymal infiltrate of monomorphic bland oval cells with intervening diffuse numerous thin GFAP pushing processes, and lack hypercellular nodules, marked hyperchromasia, Homer–Wright rosettes. [7] Immunohistochemistry(IHC) aids in arriving at the diagnosis along with the molecular diagnostic testing. On IHC, high grade glial tumor area shows diffuse GFAP +ve, S100 +ve, Vimentin +ve, olig 2 +, p53+ and negative for synaptophysin, whereas the primitive component is positive for synaptophysin, CD99 and NSE.[1,3,4,] INI–1 also helps in ruling out the possibility of Atypical Teratoid Rhabdoid tumor (ATRT) [1,7]. Ki–67 index ranges from 30 to 100% in PNET like component.[1,3] On Flourescent in situ (FISH), GBM with PNET–like features show either glioma like 10q deletion, EGFR amplification and/or 1p/19q deletions, or PNET like, i.e *n–myc* or *c–myc* amplification genetic alterations, or it can show a combination of the two entities .[7]GBM with PNET–like features has poor median survival time. It has been reported as 9.1 months in a largest case series reported by Perry et al [7]. It also has tendency to show a cranio–spinal dissemination feature associated mostly with primitive neuronal component rendering poor prognosis for the patient. [1,3,] GBM with PNET–like features is usually managed by surgical resection, radiotherapy and platinum–based chemotherapy.[1,3,4,5,6,] However, further studies are to be undertaken on the newly described entity to confirm and develop standard treatment modalities.

Conflict of Interest:

NIL

Acknowledgement:

NIL.

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