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Mysterious Case of Anaplastic Astrocytoma; A Diagnostic Dilemma Due to Unusual Morphology

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Abstract

Background-Anaplastic astrocytoma with unusual clear cell morphology is extremely rare. Although gliomas are the most common primary central nervous system tumours, literature to demonstrate their clear cell cytology is scarce.

Material and Method-A 31-year-old man presented with neurological symptoms and a large well defined left frontoparietal lesion.

Result-Histopathological examination and immunohistochemistry work up revealed sheets of clear cells with negative reactivity for EMA, PANCK, CK7, CK20, TTF1, CD10, CD43 and diffuse strong positivity for GFAP, IDH 1, and S100 with Ki67 index 10 to 12% which suggested a high-grade glial tumour (Anaplastic Astrocytoma-IDH Mutant type).

Conclusion-The case is presented to understand the uncustomary morphologies of anaplastic astrocytoma and prepare a layout to solve the mysteries using immunohistochemistry and special stains.

Keywords: Clear cell, Anaplastic Astrocytoma, Immunohistochemistry, CNS tumour

INTRODUCTION

Gliomas are the most common primary brain tumours in humans, which are divided into four grades by WHO classification: Grades I and II are diffuse and non-infiltrative, whereas Grades III (anaplastic astrocytoma) and IV (glioblastoma) are the infiltrative. Anaplastic astrocytoma has a better prognosis than glioblastomas and responds better to treatment.[1] Here, we are presenting one such case of Anaplastic astrocytoma which presented with an unusual cytomorphology on squash cytology and histopathology leading to diagnostic challenge which was resolved only by an algorithm of extensive immunohistochemistry panel.

Case History:

A thirty-one-year-old man presented with neurological symptom of giddiness for one month followed by five episodes of seizures each lasting for about fifteen to twenty seconds for three days associated with right upper and lower limb weakness, altered sensorium and aphasia. There was no significant medical, family, personal and past history. General and systemic examination revealed no significant abnormalities. Serum chemistries were unremarkable.

Radiological investigation (Non Contrast Computerized Tomography) showed large well defined round intra axial soft tissue mass lesion of size approximately 64 x 69 x 59 mm involving left

frontoparietal lobe involving both grey matter, sub-cortical and deep white matter, causing mass effect with raised intracranial tension, suggestive of neoplastic etiology possibly metastatic.(Fig. 1. A) The patient underwent craniotomy and we received sampled tissue from the mass lesion for frozen section and squash cytology which was followed by tissue for histopathological examination.

Intra operative Squash Cytology showed neoplastic cells arranged singly and were loosely cohesive, having high N:C ratio, hyperchromatic nuclei, pleomorphism and vacuolated cytoplasm. The background resembled tigroid appearance and haemorrhage with lymphocytic infiltrate, suggestive of metastatic deposits. (Fig. 1. B)

Histopathology sections studied showed neoplasm composed of cells with vacuolated clear cytoplasm with eccentrically placed hyperchromatic nuclei. Few cells showed multinucleation and prominent nucleoli. Small areas of necrosis were noted. However, there was no endovascular proliferation. Histopathology examination was suggestive of Clear Cell Tumour of CNS. (Fig. 1. C and D)

Special stains used were PAS, Mucicarmine and Alcian blue were negative which ruled out secondaries from seminoma and GIT. Immunohistochemistry panel was done. EMA and PANCK were negative ruling out carcinoma; CK7, CK20 and TTF1 were negative ruling out secondaries from lung and colorectal carcinoma; EMA and CD10 were negative ruling out secondaries from Renal Cell Carcinoma. GFAP and S100 were positive which suggested a high-grade glial tumor. For further classification, ATRX, IDH1 and Ki67 were done. IDH1 was positive. Loss of ATRX favored astrocytoma over oligodendroglioma. High Ki67 index of 10-12 % suggested high grade astrocytoma. (Fig 2. A, B, C, D, E and F) Absence of large area of necrosis and endovascular proliferation ruled out glioblastoma. Hence, Final diagnosis of Anaplastic Astrocytoma – IDH mutant type (WHO Gr III).

Informed patient consent was taken.

Discussion:

CNS space occupying lesions may assume a clear cell appearance which are diverse in nature and challenging to diagnose. Primary CNS clear cell tumours include oligodendroglioma (OG), neurocytoma, chordoid meningioma, hemangioblastoma, clear cell ependymoma (CCE), germinoma, pleomorphic xantho-astrocytoma (PXA), and lipid-rich glioblastoma. They can be identified by giving attention to clinical presentation, location, radiographic findings, and histopathology features with special stains, immunohistochemistry, and electron microscopic analysis. Recommended panel of antibodies used for differentiation of clear cell CNS tumours are GFAP, S-100, EMA, vimentin and synaptophysin. Most frequently seen clear cell neoplasms in CNS are oligodendroglioma (OG), central neurocytoma (CN), and clear cell ependymoma (CCE) which can be differentiated by a panel of antibodies.[2]

In our case, clinic radiological findings were suggestive of metastasis. Intraoperative squash smear cytology and frozen section revealed a cellular and vascular tissue against a tigroid background with round and foamy cells, resembling metastatic tumor. Large areas of necrosis, mitotic activities and endovascular proliferation was not seen. Young male with clear vacuolated cells, tigroid background and few lymphocytes made us think of secondaries probably from testis. However, histopathological examination showing pools of clear cells led to diagnostic dilemma of primary versus secondary clear cell neoplasm. Immunohistochemical algorithm to navigate through the complex features that characterize clear cell tumours of the CNS was followed. Positive reaction to GFAP is seen in astrocytoma, ependymoma, and astrocytic cells of mixed gliomas, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, astroblastoma, and gliosarcoma.[3] IDH1 gene mutations have been identified in a large proportion of diffuse and infiltrative gliomas and are considered significant for genetic alterations in gliomagenesis.[4] *ATRX* mutations are very common in diffuse astrocytoma and anaplastic astrocytoma while they are rare in glioblastoma.[5] Though IDH1 is positive in both high grade astrocytoma and oligodendrogliomas, immunohistochemistry showed lost ATRX in our case that helped us to rule out oligodendrogliomas. S-100 positivity was also seen which is positive in astrocytoma.[6] Immunohistochemistry work up revealed negative

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reactivity in EMA, PANCK, CK7, CK20, TTF1, CD10, CD43 and diffuse strong positivity for GFAP, IDH1, and S100 with Ki67 – 10 to 12 % which suggested a high-grade glial tumour (Anaplastic Astrocytoma- IDH Mutant type).

IDH-mutant gliomas have longer overall survival and better response to alkylating agents, while, IDH-wildtype gliomas show much poorer prognosis when compared to IDH-mutant counterparts. They are also least chemo-sensitive. However, radiotherapy is used as adjuvant treatment in anaplastic gliomas is (59.4–60 Gray in 1.8–2.0 Gray/fraction), singly or along with chemotherapy after surgical removal.[7]

Conclusion:

Clear cells in Central nervous system were a diagnostic challenge. This case is being presented to highlight a comprehensive approach to solve diagnostic dilemma of clear cells with unusual cytology in central nervous system based on histopathology and immunohistochemistry.

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Figures and Legends –

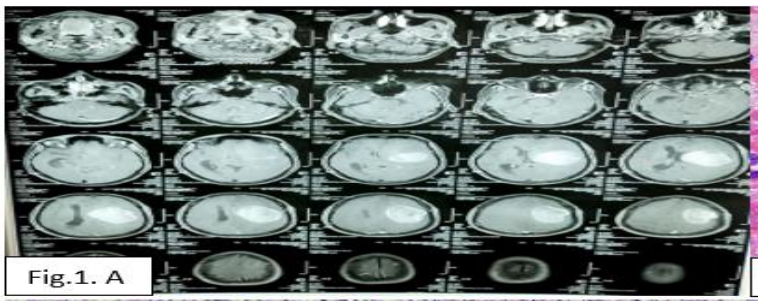
Fig.1. A

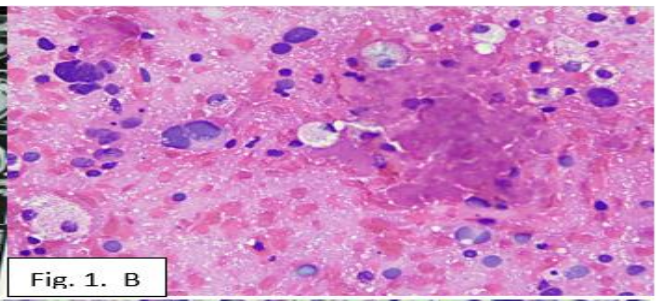
Fig. 1. B

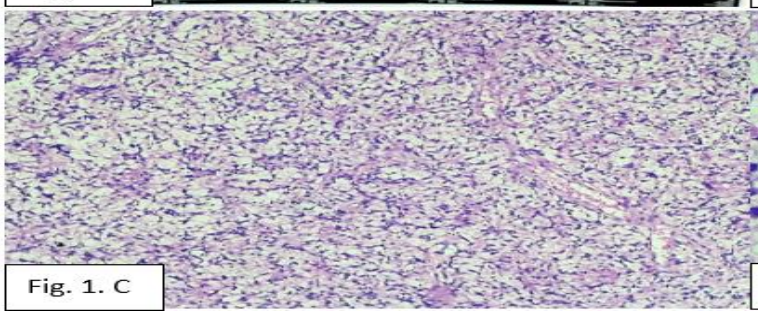
Fig. 1. C

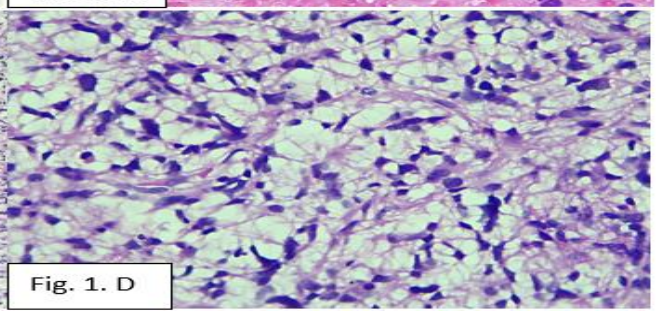
Fig. 1. D

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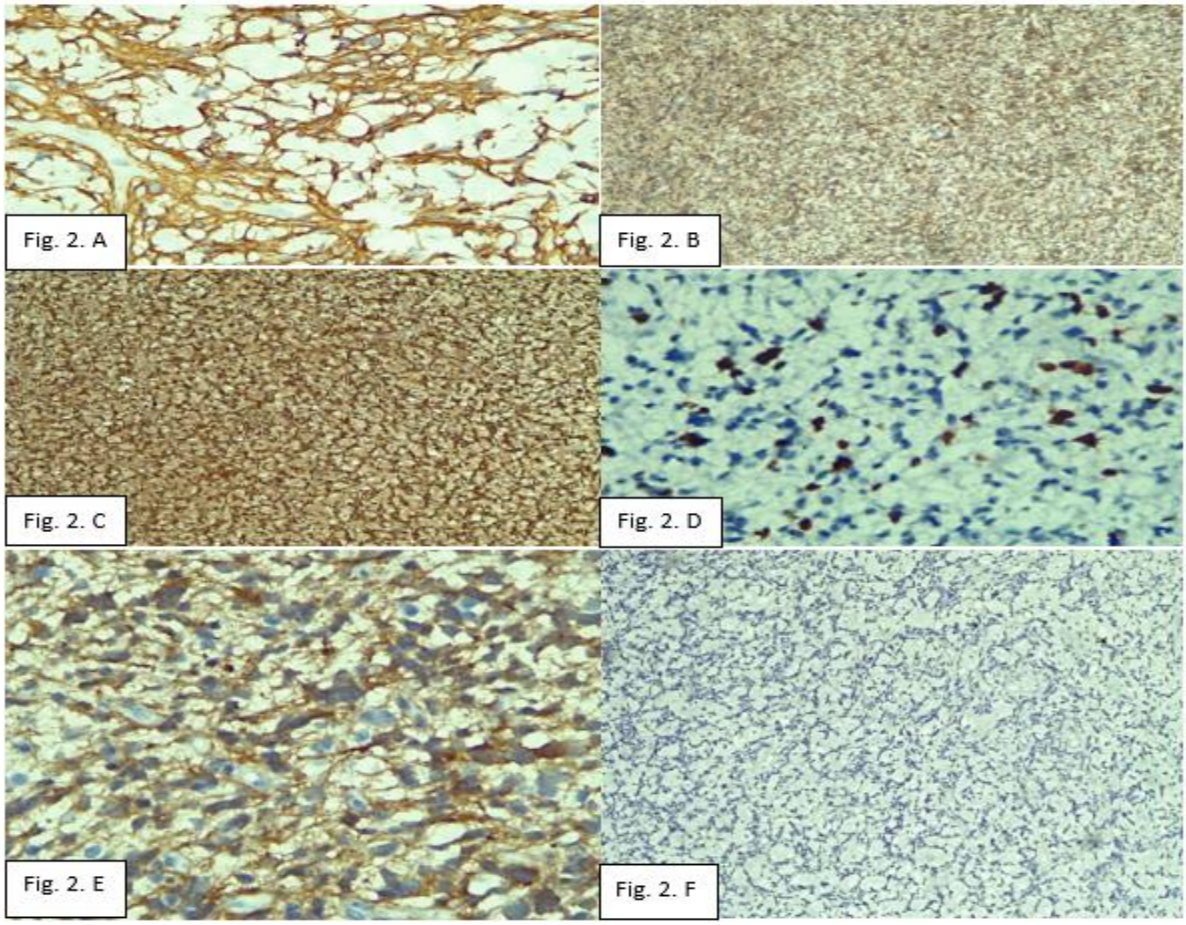

Legends to figure –

Fig. 1. A: NCCT of the brain with lesion,

B: Squash Cytology showing vacuolated cells (H&E, x400)

C: Histopathology showing clear cells (H&E X100)

D: clear cells with hyperchromatic nuclei (H&E X400)

Fig. 2. A: Cytoplasmic strong positivity for GFAP (IHC X400)

B: Strong cytoplasmic positivity for IDH1 (IHC X100)

C: Strong cytoplasmic positivity for S100 (IHC X100)

D: Nuclear positivity in Ki67 (IHC X400)

E: Lost ATRX (IHC X400)

F: Negative PANCYTOKERATIN (IHC X100)

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