Case Report

Synchronous multicentric glioblastoma with PNET and O subtypes: Possible pathogenesis

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Abstract

Background: Glioblastomas (GBM) are highly infiltrative, cellular and mitotically active tumors with large histologic variations within and between tumors. Several subtypes have been described including the GBM with oligodendroglial differentiation (GBM-O) and primitive neuroectodermal tumour components (GBM-PNET). We report the first described case of a patient with synchronous multi-centric GBM-O and GBM-PNET components.

Case Description: A patient, who presented with a short history of progressive headache and difficulty with memory recall, was found on MRI imaging to have two intracranial lesions. These showed heterogeneous enhancement and were found in the left frontal and left temporal regions. The patient underwent gross total resection of these two lesions which were found to show GBM-O and GBM-PNET differentiations.

Conclusion: Although tumour cell migration in the context of GBM is a well-recognized phenomenon, the traditional hypothesis is not able to satisfactorily explain this case of multicentric GBM whereby the two lesions demonstrate different cell origins. More current understanding of the migratory pathways from the subventricular zone provide an alternate and plausible pathway that fits our patient’s unusual diagnosis.

Key Words: Glioblastoma, migration, oligodendroglial differentiation, primitive neuroectodermal tumour, pathogenesis, subventricular zone

INTRODUCTION

Neuroglial tumours account for approximately 30% of all primary intracranial and 80% of all malignant brain tumours.[3] They are classified in the WHO system based on their histological cell types.[1,19] The most devastating and common of these tumours is the WHO Grade IV glioblastomamultiforme (GBM). Despite the implementation of the concomitant temozolomide with radiation therapy post-tumour resection, the prognosis generally remains dismal with a median survival period between 12 to 15 months.[30] In the GBM group, several specific subtypes based on histopathology have been described including GBM with oligodendroglial
differentiation (GBM-O), gliosarcoma, giant cell GBM and GBM with primitive neuroectodermal tumour components (GBM-PNET).

The commonly held view of GBM, in spite of its subtype variances, is that the tumour is a monoclonal neoplasm, derived from the clonal expansion of a single transformed astrocyte that has undergone genetic alteration. Although there are notable cell differences between these subtypes, the standard approach to their management remains the same.

In this paper, we report the case of a patient with a GBM having both GBM-O and GBM-PNET subtypes at two different locations with synchronous presentation. Owing to the uniqueness of his diagnosis, we discuss the literature and present our hypothesis for this unusual occurrence.

CASE REPORT

A 47-year-old Caucasian male with no past medical history, presented with a four week history of episodic frontal headache and easy fatiguability. He also noted to have progressive difficulty with recall which was associated with occasional dizziness and an unsteady gait. On examination, there were no cranial nerve abnormalities and other focal neurologic findings. The rest of his clinical examination was unremarkable.

Magnetic resonance imaging (MRI) brain scan was performed which revealed two intra-axial lesions with similar imaging characteristics [Figure 1]. The first lesion approximated 70 × 48 mm and was located at the left temporal lobe while the second lesion was at the left frontal parasagittal region and approximated 34 × 31 mm. Both lesions had solid and necrotic-cystic areas with areas of T1 hypointensity, T2 hyperintensity, with heterogeneous enhancement post-gadolinium contrast. Susceptibility within the masses suggested intra-lesional haemorrhage and/or calcification. Both lesions were associated with significant perilesional oedema causing mass effect and midline shift to the right. The radiological diagnosis was multi-centric glioblastomamultiforme, with differential diagnosis of metastasis.

Additional imaging workup included computed tomography scans of his thorax, abdomen and pelvis and MRI of his whole spine, which did not demonstrate any further lesions.

The patient underwent an awake craniotomy for gross total resection of the left frontal and parieto-temporal tumours. Intraoperative frozen section was reported as suggestive of a high grade glioma. The patient recovered well postoperatively with no new focal neurological deficits. Post-operative MRI brain scan was performed 48 hours after surgery and showed no gross evidence of residual tumor. He was subsequently referred to the medical and radiation oncology teams for adjuvant therapy, and has since commenced on both chemotherapy (temozolamide) and radiotherapy to both cranium and spine.

The resection specimen from the left temporal lobe tumour showed two histologically distinct components. In some areas, the tumour resembled a glioblastoma (WHO grade IV) [Figure 2a]. These areas consisted of a cellular proliferation of astrocytes with markedly enlarged, irregular, pleomorphic nuclei and moderate to abundant quantities of fibrillary cytoplasm. Neoplastic gemistocytic astrocytes and multinucleated astrocytes were seen. There was brisk mitotic activity, microvascular proliferation and pseudopalisading necrosis. In other areas, the tumour resembled a central nervous system primitive neuroectodermal tumour (CNS PNET, WHO grade IV) [Figure 2b]. These latter areas consisted of densely packed cells with hyperchromatic oval to elongated nuclei, high nuclear cytoplasmic ratios, brisk mitotic activity and karyorrhexis. There were also areas where cells from both tumour types were closely intermingled. The lesion included large confluent areas of coagulative tumour necrosis. Immunoperoxidase staining for glial fibrillary acid protein (GFAP) was positive in the glioblastoma component [Figure 2c] and negative in the CNS PNET areas, while synaptophysin was positive in the CNS PNET areas [Figure 2d] and negative in the glioblastoma cells. The features were compatible with a malignant glioma with a PNET-like component. [26]
The resection specimen from the left frontal lobe tumour showed features of a glioblastoma with an oligodendroglial component (WHO grade IV). The glioblastoma consisted of a cellular proliferation of astrocytes with irregular, hyperchromatic, pleomorphic nuclei and fibrillary cytoplasm. There was brisk mitotic activity, microvascular proliferation and pseudopalisading necrosis [Figure 3a]. Focally, there was a proliferation of cells resembling oligodendrocytes with round regular nuclei, clear cytoplasm and distinct cytoplasmic borders. The oligodendroglial population was associated with a branching capillary network [Figure 3b].

**DISCUSSION**

Glioblastoma multiforme (GBM) is one of the most common and devastating adult primary brain tumours. An unusual variant of this disease that heralds even poorer prognosis is the multi-lesion GBM (MLGBM) whose exact underlying mechanisms are still uncertain.[1] MLGBM can be further categorized as firstly, multifocal tumours (MFGBM) where multiple areas of the parenchyma are involved, with a clear path of spread from one lesion to another.[31] Here, the lesion starts as synchronous foci, in which a microscopic connection is presumed, and dissemination is along an established pathway.[10,24] Next, multicentric tumours (MCGBM) are multiple separate lesions without any clear microscopic or macroscopic connection.[25,31] The incidence of MLGBM has a wide range from 0.5% to 20%,[1,4,9,14,17,24,32] and most of them are found in the supratentorial component, especially in the frontal and parietal lobes.[1] Overall, it is difficult to differentiate between MFGBM and MCGBM with available imaging technology or their histological features.[21] Furthermore, the clinical relevance of this distinction between MLGBM subtype has yet to be fully elucidated.[1,10,24] Based on current criteria, true MCGBMs need to have similar histological appearances.[21]

The early traditionally held view of the pathogenesis of MLGBMs is by three possible pathways. First, a previously known primary high-grade glioma spreads through the cerebrospinal fluid or white matter tracts to other locations. Second, multiple areas of high-grade glioma arise de novo from initially non-neoplastic cells that are influenced by genetic defect. Third and last, initially diffuse low-grade glioma develops separate from separate areas of malignant transformation within itself, hence giving rise to MFGBM.[28] However, this ‘3-pathway criteria’ would not satisfactorily explain our case.

The uniqueness of his diagnosis lies in the different subtypes of the initial cells that transforms into eventual GBM at 2 separate locations. Here, the patient has a rare primitive neuroectodermal tumour (CNS-PNET) in the left frontal lobe. This is a tumour composed of undifferentiated or poorly differentiated neuroepithelial cells which display divergent differentiation along neuronal, astrocytic, muscular and, or melanocytic lines. At present, CNS neoplasms that demonstrate combined areas of GBM and CNS-PNET is not a codified entity in the WHO Classification. Such cases multi-lesion are still not well-characterized.[26] They are considered to be highly malignant tumors owing to the high risk of dissemination to the entire neuroaxis[16,23,26] and surgical resection is difficult due to poor brain-tumour interface.[18,22] Next, the left parieto-temporal tumour was found to be a separate GBM with an oligodendroglial component (GBM-O). This subtype of GBM represents about 5-18% of all malignant gliomas.[15,27] Their molecular alterations include EGFR, p53, IDH1, MGMT, loss of chromosome 1p, 9p21, 10, 19q, and gain of chromosome 7. GBM-Os may resemble GBMs
The existence of a...to undergo unsupervised proliferation and differentiation, and due to aberrancy in growth regulatory pathways, tumor formation. In the context of our patient, we hypothesize that different transformed progenitor cells or their parental GSCs migrate out from SVZ to their final destinations and once in the cortex, they interact with parenchyma and draw on micro-environmental cues to undergo unsupervised proliferation as part of tumorigenesis. Figure 4 illustrates our hypothesis for the migratory pathway of the 2 separate GBM subtypes in our patient. In general, GBMs are highly infiltrative, cellular and mitotically active tumors with large histologic variations within and between tumors. Although tumor cell migration in the context of GBM is a well-recognized phenomenon, traditional hypothesis is not able to satisfactorily explain this first reported case of MCCBM whereby the 2 lesions demonstrate different cell origins. More current understanding of the migratory pathways from the SVZ provide an alternate and plausible pathway that fits our patient’s unusual diagnosis.

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Figure 4: The likely migratory pathway of transformed GSCs and, or their progenitors from the stem-cell enriched subventricular zone (SVZ) to the subcortical region.

on histology, but at the same time, they contain areas resembling oligodendrogliomas. Studies have shown that patients with GBM-O tend to be younger, and the tumors are more chemosensitive, conferring a favorable prognosis. In view of the inter-tumoral differences within the same patient and, based on our current understanding of GBM, we postulate that the key to our patient’s MCCBM lies in the origin of the cells responsible for malignant gliomas. Although tumour cell migration in the context of GBM is a well-recognized
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