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Pictorial Essay

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The many faces of glioblastoma: Pictorial review of atypical imaging features

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Abstract

Glioblastoma is an aggressive primary central nervous system tumour that usually has a poor prognosis. Generally, the typical imaging features are easily recognisable, but the behaviour of glioblastoma multiforme (GBM) can often be unusual. Several variations and heterogeneity in GBM appearance have been known to occur. In this pictorial essay, we present cases of pathologically confirmed GBM that illustrate unusual locations and atypical features on neuroimaging, and review the relevant literature. Even innocuous-looking foci, cystic lesions, meningeal-based pathology, intraventricular and infratentorial masses, multifocal/multicentric lesions and spinal cord abnormalities may represent GBM. We aim to highlight the atypical characteristics of glioblastoma, clarify their importance and list the potential mimickers. Although a definitive diagnosis in these rare cases of GBM warrants histopathological confirmation, an overview of the many imaging aspects may help make an early diagnosis.

Keywords

Glioblastoma, magnetic resonance imaging, atypical, neuroradiology, neuroimaging, CNS tumours

Introduction

Glioblastoma multiforme (GBM) is an aggressive primary brain neoplasm. It accounts for up to 50–60% of primary gliomas and 16% of all brain tumours.[1] It is classified by the World Health Organization (WHO) as a highly malignant (grade IV) astrocytoma, histologically characterised by a pleomorphism of cells, nuclear atypia, micro-haemorrhage and necrosis.[2] Headaches, vomiting, seizures and cognitive impairment are the most common presentations, with most patients presenting in the fifth or sixth decades with a mean age of 55 years and median age of 64 years.[3] It is more common in Caucasians and is also slightly more frequent in males than females.[4] It has a predilection for the cerebral hemispheres, basal ganglia and commissural pathways, with infiltration occurring along white-matter tracts and peri-vascular spaces. GBM has a rapid doubling time that accounts for its poor prognosis, with a median survival time of approximately 15 months in most cases.[3]

According to the updated 2016 WHO classification of central nervous system tumors,[2] GBM is divided into the following molecular subtypes:

- GBM, isocitrate dehydrogenase (IDH)-wild type (roughly 90% of cases), representing primary or de novo GBM and common in patients >55 years of age;
- GBM, IDH-mutant (about 10% of cases), representing secondary GBM in patients with a history of prior low-grade glioma, and commonly occurring in younger patients; and
- GBM, not otherwise specified (NOS) – a diagnosis reserved for those tumours for which full IDH analysis cannot be done.

Often, the behaviour of GBMs is unusual with regards to the heterogeneity of its appearance on imaging. In approximately 13% of cases, GBM may present as multifocal or multicentric masses (more than two lesions, including leptomeningeal dissemination), distant (second lesion non-contiguous with primary lesion) or diffuse disease.[4] Infra-tentorial GBMs are infrequent, and the behaviour of the tumour is different in this region.[5] In this pictorial essay, we review the unusual locations and atypical neuroimaging features of pathologically proven GBMs, with a primary focus on adult cases. However, of note, there are also other atypical presentations such as early-stage GBM and exclusive paediatric GBM, which unfortunately go beyond the scope of this review article.

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Intraventricular glioblastoma

Intraventricular GBM is a rare secondary intraventricular tumour. Unlike primary intraventricular tumours that arise from the ventricular wall and its lining, or from structures within the ventricles, secondary tumours are those that arise from structures adjacent to the ventricle (primarily from cerebral tissue) and gradually enlarge so that more than two thirds of them are present within the ventricle. Therefore, they occur secondary to trans-ependymal development. Primary intraventricular tumours include ependymoma, choroid plexus papilloma, choroid plexus carcinoma and meningioma. Astrocytomas, subependymal giant cell astrocytomas, choroid glioma, GBM and mixed glial neuronal tumours are rare secondary intraventricular tumours.[6]

Intraventricular GBMs, even though their location is not very typical, can have general imaging features of high-grade gliomas, including irregular heterogeneous contrast enhancement and infiltrative irregular margins and areas of necrosis (Figure 1). However, the lesions may also be well defined, with either homogeneous or minimal enhancement.[7,8] There have been reports on intraventricular GBM appearing benign enough to mimic a meningioma.[7]

In adults, meningiomas, astrocytomas and ependymomas most commonly occur at the trigone of the lateral ventricles. Often, the more benign lateral ventricular tumours enlarge slowly, and typically patients are asymptomatic until the lesions are large enough to cause obstructive hydrocephalus or compression of surrounding eloquent structures.[8,9] Intraventricular GBM, on the other hand, can show more aggressive growth, and may be associated with cerebrospinal fluid (CSF) seeding and sub-ependymal metastasis (Figure 2).

Ben Nsir et al. conducted a case series on intraventricular GBMs. Their study sample was of eight patients who had a mean age of 29 years, with a male-to-female ratio of 5:3 and a median survival time of 32 months. All of them had isocitrate dehydrogenase–mutated tumours. The tumour was located within the lateral ventricle in six cases and the anterior third ventricle in the two remaining cases.[10] Lateral

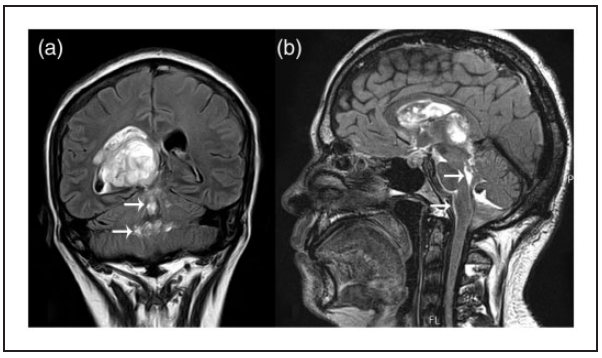

Figure 2. Diffuse leptomeningeal enhancement in the right lateral ventricle, third and fourth ventricles and pre-pontine cistern on coronal (a) and sagittal (b) post-contrast FLAIR sequences, indicating cerebrospinal fluid seeding and sub-ependymal spread (arrows) in the same patient from Figure 1.

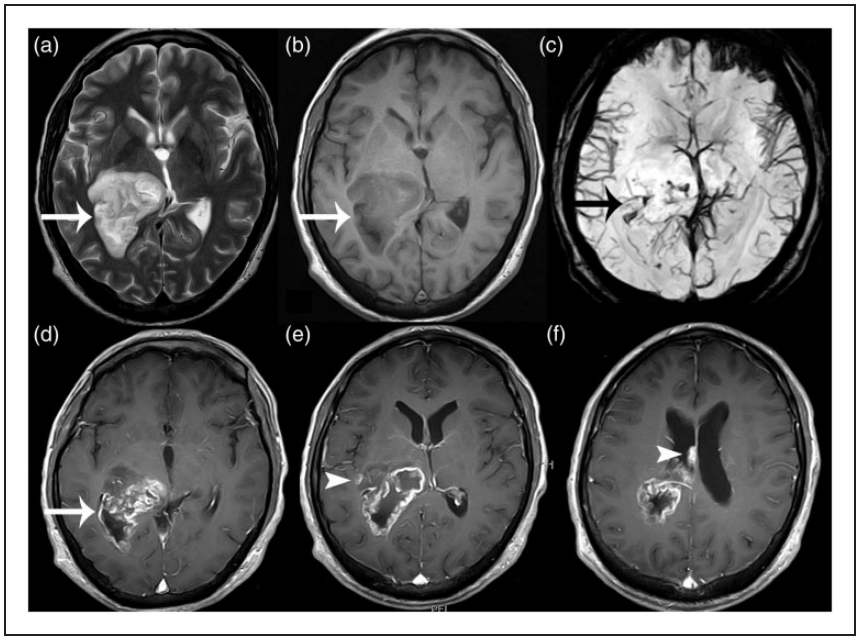

Figure 1. Pathologically confirmed intraventricular glioblastoma, not otherwise specified (NOS), in a 32-year-old male. (a) Axial T2-weighted sequence showing a heterogeneously hyper-intense lesion in the trigone of the right lateral ventricle (arrow). (b) The legion was iso- to hypo-intense on plain axial T1-weighted images (arrow). (c) Areas of susceptibility are seen on susceptibility-weighted imaging (SWI; black arrow). (d)–(f) Axial post-contrast T1-weighted images showing irregular peripheral enhancement (arrow) with a parenchymal nodule in the right temporal lobe (arrowhead in (e)) and a satellite nodule in the body of the right lateral ventricle (arrowhead in (f)).

ventricular GBM is more common in the frontal horn or body, and is frequently attached to the septum pellucidum. However, rare trigonal lesions have also been described.[8] Previously reported risk factors for CSF dissemination in such cases include direct invasion of the ependyma, with deposits in the sub-ependymal and/or sub-pial regions, fissuring of the ependyma secondary to hydrocephalus, fragmentation of the tumour in contact with CSF and surgical intervention.[11] In such cases of GBM with leptomeningeal spread, complete neuraxis imaging is warranted.

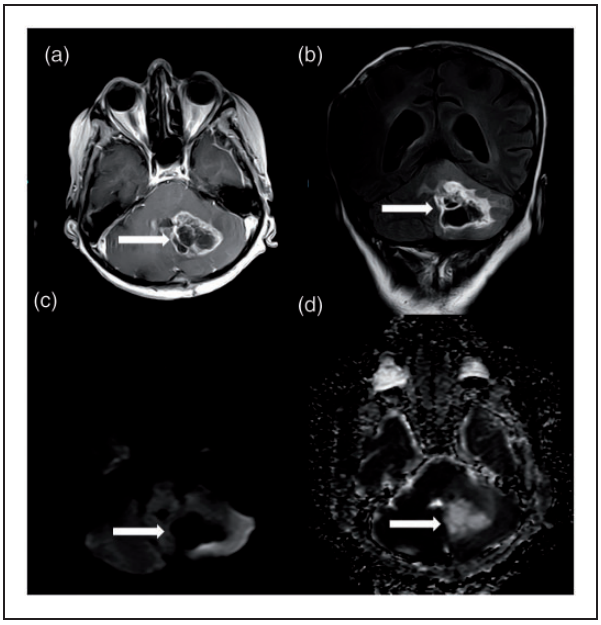

Figure 3. Cerebellar glioblastoma, NOS, in a 44-year-old female. (a) Axial post-contrast T1 images showing a heterogeneously enhancing necrotic lesion in the left cerebellum in close proximity to the fourth ventricle. (b) Coronal FLAIR showing peri-lesional oedema. (c) No diffusion restriction is seen within the lesion on diffusion-weighted imaging (DWI). (d) Apparent diffusion coefficient (ADC) maps show high values.

Cerebellar and cerebellopontine angle glioblastoma

Occurrence of primary infra-tentorial glioblastoma in adults is rare, and few cases have been published to date. Their localisation in the cerebellum is highly unusual, and such tumours presenting as a cerebellopontine angle (CPA) mass is even rarer. The incidence is estimated to be 1.5% in the cerebellum and 4.1% in the brainstem, with most cases encountered in the paediatric age group.[12,13] Adult patients with cerebellar GBMs are typically younger and have smaller average tumour sizes. They are less common in Caucasians in contrast to supra-tentorial GBM.[5] They are also more often located close to the ventricular system (Figure 3).[14] Metastasis, anaplastic astrocytoma, hemangioblastoma and ependymoma are close differentials in this region.

Most of the previous reported cases of CPA GBM are primary intra-axial masses arising from the cerebellar hemisphere or the brainstem, with exophytic extension into the CPA.[14,15] Additionally, the distinction of an extra-axial versus intra-axial mass at the CPA may become obscured in some cases because of adjacent encephalomalacia. There may also be exophytic extension into the internal auditory canal (IAC; Figure 4).

Only one other case of primary extra-axial GBM in the CPA has been reported with intra-canalicular extension into the IAC.[16] Primary cerebellar or brainstem GBM may involve the CPA through either lateral extension from the fourth ventricle through the foramen of Luschka or direct exophytic growth from the site of origin.[17]

The diagnosis of primary cerebellar and CPA glioblastoma may be made when imaging features are suggestive of a heterogeneous signal intensity lesion with the presence of haemorrhage; irregular, heterogeneous and ring-like enhancement with areas of necrosis and peri-tumoural oedema disproportionate to the size of the lesion; and no evidence of metastasis from an

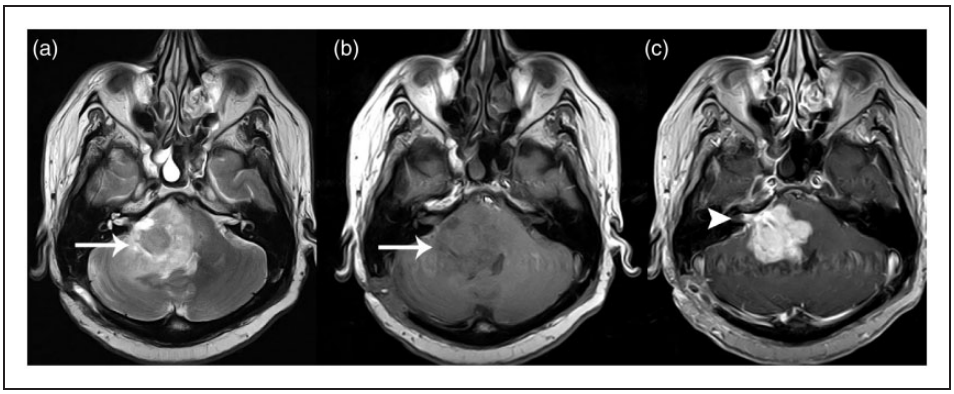

Figure 4. A 42-year-old male with cerebellopontine angle (CPA) glioblastoma, NOS. (a) Axial T2-weighted sequence showing a heterogeneously hyper-intense lesion in the right CPA, involving the right pons and middle superior cerebellar peduncle with disproportionate surrounding oedema. (b) Axial plain T1-weighted image showing that the lesion is isointense. (c) Post-contrast axial T1-weighted image showing avid enhancement in the lesion with intra-canalicular extension into the right internal auditory meatus (arrowhead).

intra-cerebral glioblastoma or any other extra-cranial malignancy. Differential diagnoses at the CPA include metastasis, WNT subgroup of medulloblastoma and lymphoma and even less malignant lesions such as vestibular schwannoma and meningioma.[14] Magnetic resonance (MR) diffusion/perfusion imaging and spectroscopy may provide a clue in differentiating high-grade gliomas from other diseases. However, histological examination is sometimes the only way to arrive at a definitive diagnosis. Prior immunohistochemical studies have detected a higher incidence of IDH1 mutations, p53 mutation immunopositivity and epidermal growth factor receptor immuno-negativity in cerebellar glioblastoma in contrast to supra-tentorial GBMs.[5,18]

Multicentric glioblastoma

Multicentric GBMs have been reported in <2% of patients with malignant gliomas, and their appearances may be difficult to differentiate from brain metastases.[19] Certain imaging features such as variable lesion morphology, mild peri-tumoural oedema and irregular tumour margins and peripheral enhancement can point towards the diagnosis of multifocal or multicentric GBM. There have also been case reports of multicentric GBMs with internal haemorrhage[20] (Figures 5 and 6).

Multifocal glioma are defined as tumour masses separated by white-matter tracts within the same cerebral hemisphere. Multicentric glioma, on the other hand, consist of tumours in opposite hemispheres or separated by the tentorium.[21,22] To date, there is still no single theory regarding the pathophysiology of multifocal and multicentric GBMs. Several hypotheses and theories have been proposed with regards to the spatial relationship of the lesion to the sub-ventricular zone (SVZ). Neural stem cells within the SVZ may give rise to multifocal and multicentric GBM because of expression of matrix metalloproteinases, which are proteolytic enzymes involved in tumour spread and growth. Additionally, the SVZ is thought to be a highly permissive location for tumour proliferation and cellular migration.[23,24]

Individual tumours in cases of multicentric GBM usually have the same histological and pathological characteristics.[19] Prior immunohistochemical studies on multicentric gliomas have demonstrated negative

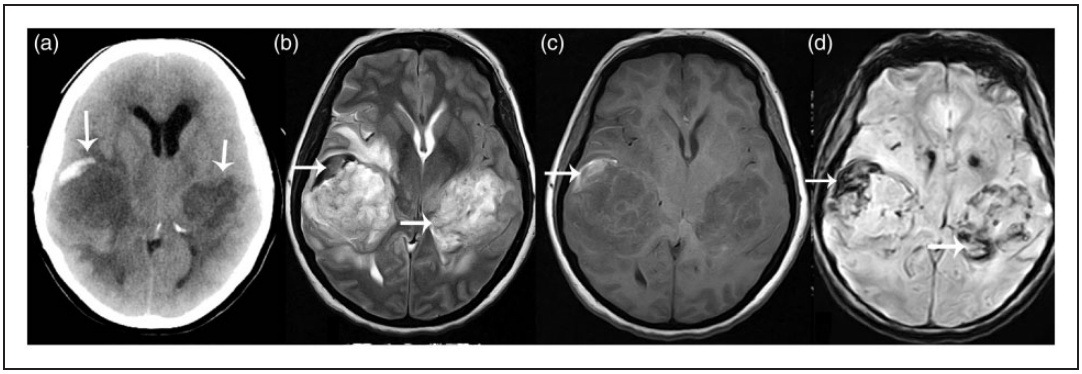

Figure 5. Multicentric glioblastoma, NOS, in a 43-year-old female. (a) Axial computed tomography (CT) showing bilateral cerebral low-density lesions with areas of haemorrhage (arrows). (b) Axial T2- and (c) T1-weighted images of magnetic resonance (MR) imaging showing bilateral heterogeneous masses in the temporo-parietal regions with surrounding oedema, and internal haemorrhage on SWI (arrows in (d)).

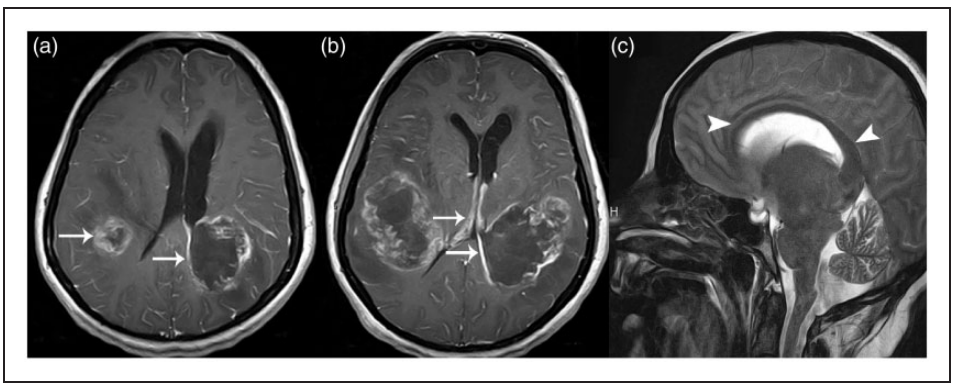

Figure 6. (a) and (b) Axial T1-weighted post-contrast sequences showing irregular peripheral enhancement of the lesions with internal areas of necrosis (arrows). Close relationship of the masses to the sub-ventricular zone is noted (arrows in (b)). Sagittal T2-weighted image showing that there was sparing of the corpus callosum (arrowheads in (c)).

IDH1 mutation and 1p19q co-deletion. This suggests that the pathogenesis of multicentric gliomas is different from the mutant IDH1-R132H pathogenesis of lower-grade glioma and secondary glioblastomas.[25]

Multifocal and multicentric GBMs have a poorer prognosis than solitary GBM, with a median patient survival time of six to eight months after different treatment regimens. However, patients with multifocal tumours without sub-ependymal and subarachnoid dissemination have had a similar prognosis as patients with solitary GBM.[22]

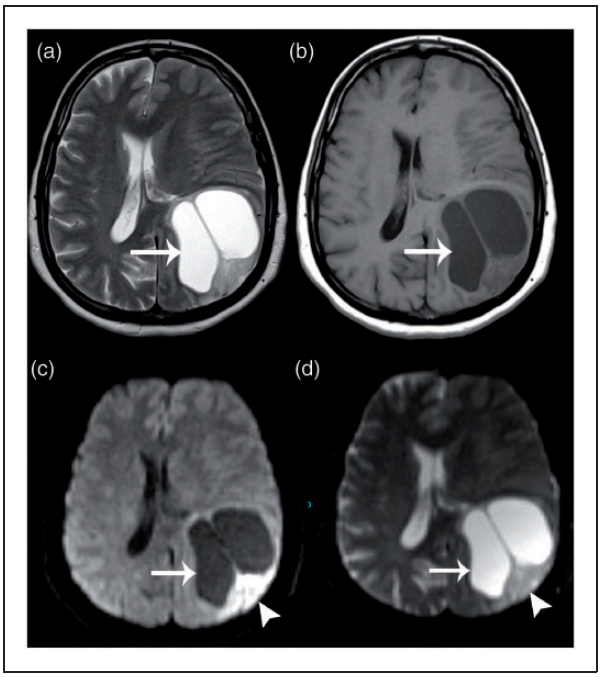

Figure 7. Cystic glioblastoma multiforme (GBM) in a 62-year-old female with negative IDH1 (R132H and R132C) or IDH2 (R172K and R172M) point mutations. (a) Axial T2-weighted image showing a septated cystic lesion in the left parietal lobe with associated mass effect (arrow) and small solid component posteriorly. (b) On axial T1-weighted imaging, the lesion is hypo-intense (arrow). (c) and (d) Axial DWI from B-1000 and corresponding ADC maps showing no diffusion restriction within the cystic component. However, positive diffusion is seen in the solid component (arrowheads).

Cystic glioblastoma

Cystic GBM is a term for a type of glioblastoma that contains a large cystic component. Cysts are frequently found in low-grade astrocytoma, especially pilocytic astrocytoma, but the occurrence in high-grade gliomas such as GBM is rare. The exact incidence is unknown.[26] Cystic GBM may occur because of malignant transformation in prior undiagnosed primary cystic low-grade gliomas, and therefore usually occur in younger patients.[27] The other schools of thought regarding the basis of cyst formation are necrotic degeneration of the tumour tissue, central haemorrhage and subsequent liquefaction, entrapment of adjacent CSF space and blood–brain barrier disruption.[28]

Imaging features of cystic GBM may be a well-defined intra-axial cystic lesion with or without a soft-tissue component. The cystic areas show hyperintensity relative to CSF due to higher protein contents on FLAIR sequences. Diffusion-weighted imaging is useful because there is no restriction for the cystic component. The solid component may show restriction according to the grade, and apparent diffusion coefficient maps show high values in the cystic component (Figure 7). There is usually peripheral ring enhancement, sharp boundaries and less peri-focal oedema than non-cystic GBMs or GBMs with internal necrosis (Figure 8). MR spectroscopy frequently shows a high choline/creatinine ratio, and MR perfusion shows no appreciable perfusion changes within the cystic component.[28,29]

The main diagnostic dilemma in such cases is to differentiate between other intracranial cystic lesions such as cerebral abscess, or from other malignant cystic lesions such as metastasis which have different management. Patients diagnosed with cerebral glioblastoma containing a cystic component have a better prognosis and survive longer than those without cystic components, as found in a study by Maldaun et al.[30]

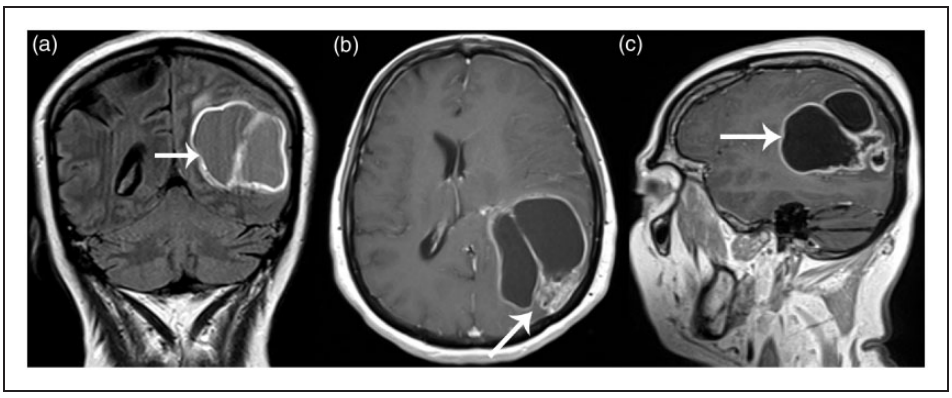

Figure 8. (a) Coronal FLAIR showing peripheral enhancement in the cystic component (arrow). Only minimal peri-focal oedema is seen around the lesion. (b) and (c) Axial and sagittal post-contrast T1-sequences showing ring enhancement around the lesion with irregular enhancement in the solid component posteriorly (arrow in (b)).

Some prior studies have also found a lower frequency of IDH1 mutation in the cystic GBM cohort. This does not favour the hypothesis that they arise from malignant transformation of previously undiagnosed low-grade gliomas.[31]

Parafalcine glioblastoma

Typically, GBMs usually occur in the frontal (40%), parietal (25%) and temporal (25%) locations.[32] Midline location with falx localisation and meningeal attachment is fairly atypical and unusual in GBMs. Heterogeneity of the tumour tissue, patches of necrotic areas, presence of infiltration into the brain parenchyma, vascular endothelial proliferation and disproportionate vasogenic oedema can point towards a high-grade glial lesion such as GBM (Figure 9). However, similar imaging features are seen in gliosarcomas, which tend to have a dural-based/meningeal attachment, and are therefore the closest differential. These lesions also parallel high-grade gliomas on diffusion-weighted and perfusion imaging.[33]

Although rare, similar neuroradiological findings can be seen in atypical or malignant meningiomas. There have been multiple case reports of parafalcine masses being mistaken for typical or atypical meningiomas which have turned out to be GBM.[34,35] Even though masses along the falx bring to mind meningiomas or other dural-based pathologies such as gliosarcoma in the first instance, it should be considered that GBMs may also occur in this localisation. Further clinical, histopathological and neuroradiological studies are, however, needed to make a definitive diagnosis.

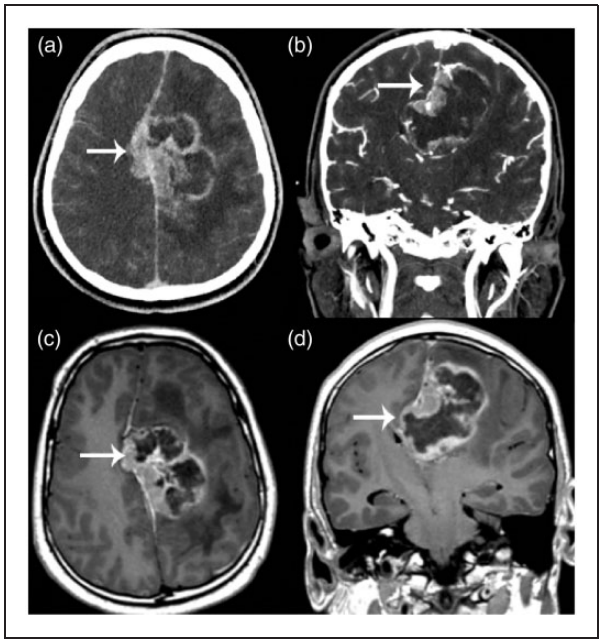

Figure 9. Parafalcine glioblastoma grade IV in a 30-year-old male. Axial and coronal images from a CT scan with contrast (a) and (b) and post-contrast T1 MR imaging (c) and (d) showing a large infiltrative lesion in the left parasagittal frontal lobe with associated mass effect, internal areas of necrosis and surrounding vasogenic oedema (arrows). The lesion is dural based, attached to the falx and displacing it towards the right side (arrows in (a) and (c)). There is also involvement of the corpus callosum (arrow in (d)).

Brainstem glioblastoma

Brainstem gliomas are primarily found in the paediatric population, and are most commonly low grade (WHO I or II). Adult brainstem gliomas are a rare entity, accounting for 1–2% of primary brain tumours, with a slight male predominance.[36] Malignant brainstem gliomas constitute a rare minority of these cases. These are found most commonly in the pons, followed by the medulla oblongata. The lesions often cause a diagnostic dilemma due to the difficulty of surgical resection and sometimes even absence of pathological diagnosis. Treatment decisions in these cases have mostly depended on radiological diagnosis and surveillance.

Brainstem GBMs invariably show focal or ring enhancement with variable areas of necrosis on MR imaging that are characteristic of a high-grade lesion (Figure 10).[36] Multifocality and supra-tentorial extension have been reported, and lesions frequently extend into other brainstem regions. Diffusion and perfusion MR imaging, thallium single photon emission computed tomography and positron emission tomography (PET) are emerging as potentially promising imaging techniques for characterising aggressive brainstem lesions.[37] Additionally, MR spectroscopy can be a useful aid for diagnosis, as elevation of the choline/N-acetylaspartate ratio is often detectable in adult brainstem gliomas.[38]

Four typical classifications of brainstem gliomas have been described based on imaging: diffuse intrinsic low-grade gliomas, enhancing malignant gliomas, focal tectal gliomas and exophytic gliomas.[39] Diffuse intrinsic midline gliomas are low-grade non-enhancing masses in contrast to GBM. However, in the updated WHO classification, H3K27-mutant diffuse midline gliomas comprise a distinct entity within IDH-wild-type gliomas and are classified as WHO grade IV irrespective of histologic grade. They predominantly affect paediatric patients, but they may on rare occasions present in adults, where they have imaging features similar to glioblastoma. Because of their diffuse growth and infiltrative pattern, they can also result in gliomatosis cerebri and leptomeningeal gliomatosis on imaging.[40]

Spinal glioblastoma

Spinal GBM is a highly malignant lesion that constitutes approximately 7.5% of all intramedullary

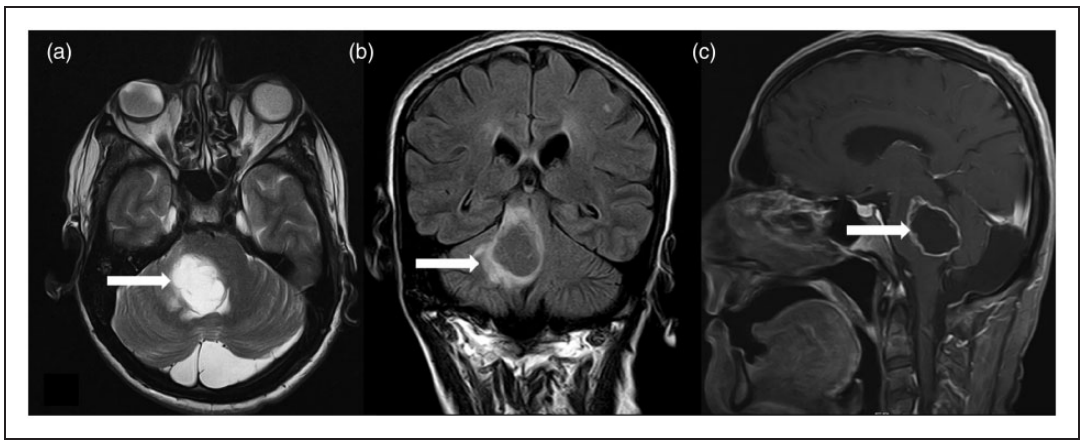

Figure 10. Pathologically proven brainstem glioblastoma, NOS, in a 46-year-old male. (a) Axial T2-weighted image showing a hyper-intense lesion involving the right side of the brachium pontis and posteriorly compressing the fourth ventricle (arrow). (b) Peri-lesional oedema seen on coronal FLAIR. (c) Heterogeneous ring enhancement is seen in the lesion on sagittal T1 post-contrast sequence.

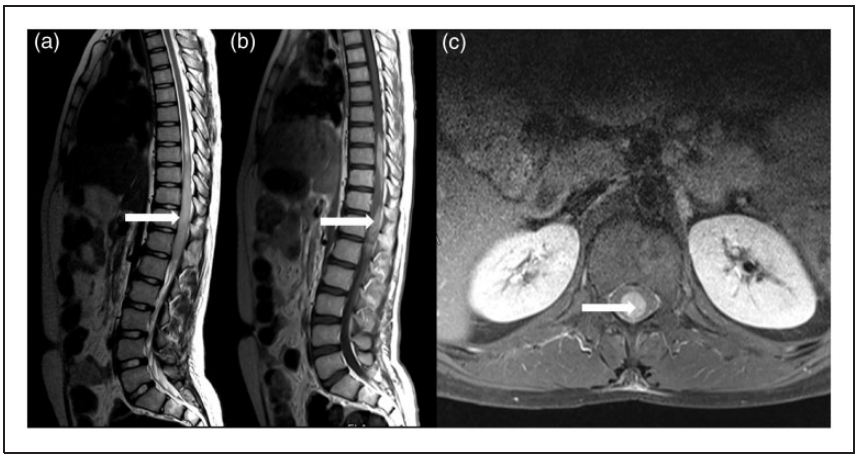

Figure 11. A 15-year-old boy with spinal glioblastoma with oligodendroglioma component, World Health Organization grade IV. (a) Sagittal T2 sequence showing an expansile hyper-intense long segment intramedullary lesion extending from T8 to L1 vertebral levels and also involving the conus medullaris. (b) and (c) The lesion shows diffuse enhancement on post-contrast sequences.

gliomas and makes up roughly 1.5% of all spinal cord tumours.[41] They are generally found at the cervical and thoracic regions. However, conus medullaris lesions have also uncommonly occurred.[42] These tumours affect relatively younger individuals (mean age of 26 years) with a slight male predominance (57.1%), and usually carry a grave prognosis.[43]

Usually, primary spinal GBMs appear as infiltrative and expansile intramedullary lesions with high T2 signal, and variable heterogeneous enhancement on post-contrast T1-weighted sequences (Figure 11). Distinction of primary spinal GBM from other pathologies such as transverse myelitis or other intramedullary tumours such as fibrillary astrocytoma or ependymoma is often difficult, as the findings are non-specific and frequently overlap. Additionally, there is no known specific molecular marker for

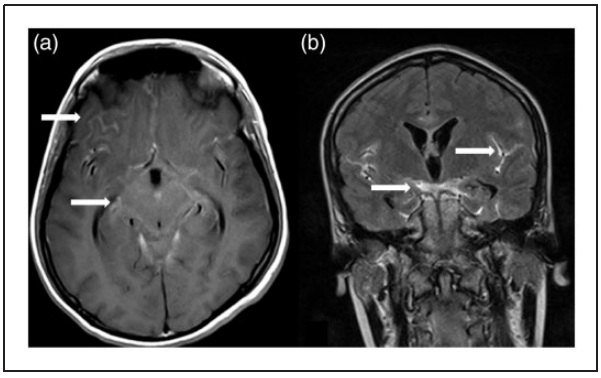

Figure 12. (a) and (b) Follow-up MR imaging axial and coronal post-contrast sequences in the patient from Figure 11 after one year of treatment showing diffuse leptomeningeal enhancement with meningeal-based deposits, indicative of disseminated intracerebral gliomatosis (arrows).

spinal GBM.[44] There have been reported cases in children with intracranial dissemination from primary spinal GBM, particularly with conus medullaris and thoracic lesions (Figure 12).[45] Diffusion tensor imaging and perfusion can aid in the diagnosis with decreased fractional anisotropy and increased relative cerebral blood volume in the lesions. F-18-fluoro-deoxy-glucose PET has also been performed for further characterisation of inflammatory versus neoplastic lesions. However, tissue biopsy is almost always necessary.[46]

Conclusion

While the classical appearance of GBM is generally recognisable, it is imperative to bear in mind that many variations of the usual presentation can occur, and atypical findings on imaging may be observed. Even innocuous foci of signal abnormality, heterogeneity of lesions, cystic tumours, meningeal pathology, intraventricular and infra-tentorial masses, multicentric/multifocal lesions and spinal cord lesions may represent GBM. Although a definitive diagnosis of GBM in these atypical cases warrants histological analysis, certain aspects of neuroimaging can provide a clue for diagnosis and subsequent initiation of prompt treatment.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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