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CASE REPORT

Intraventricular H3K27-Altered Diffuse Midline Glioma in Lateral Ventricle: A Case Report

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CASE PRESENTATION

A 41-year-old man with glucose-6-phosphate dehydrogenase deficiency who was a light smoker of 5 pack years and social drinker first presented in 2022 in Hong Kong with left hemiparesis, unsteady gait and headache, with Glasgow Coma Scale score of 13. Non-contrast axial computed tomography of the brain revealed a tumour at the foramen of Monro with hydrocephalus (Figure 1a). Mannitol was administered and urgent external ventricular shunting was performed to relieve the hydrocephalus. A well-defined solitary intraventricular tumour (Figure 1b-h) measuring 2 × 2.3 × 2.7 cm^3 was seen on subsequent magnetic resonance imaging (MRI), epicentred at the right lateral ventricle/foramen of Monro. It was T1 iso- to hypointense, and T2 hyperintense with restricted diffusion and internal small foci of enhancement. There was no abnormal blooming artefact. The mass displaced the septum pellucidum to the left while the third ventricle was displaced to the left and inferiorly. Owing to its intraventricular location, it was first suspected to be a subependymoma, ependymoma, or central neurocytoma. Frozen section of a limited endoscopic biopsy was consistent with a glial tumour. Given the clinical history, an ependymoma or subependymoma remained possible but no definitive diagnosis was reached.

More formalin-fixed paraffin-embedded tissue was subsequently examined. The glial tumour (Figure 2a) showed moderate cellularity, moderate nuclear pleomorphism, enlarged hyperchromatic nuclei, and fibrillary eosinophilic cytoplasm. Mitotic count was up to 4 mitotic figures per 10 high-power fields. There was microvascular proliferation but no necrosis was seen. There was no rosette or pseudorosette. Immunohistochemical studies revealed that the tumour cells were positive for GFAP (glial fibrillary acidic protein), Olig2 (oligodendrocyte transcription factor

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Ethics Approval: This study was approved by the Hong Kong East Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: HKECREC-2022-057). The patient was treated in accordance with the Declaration of Helsinki and patient consent was waived by the Committee due to no disclosure of patient's identity.

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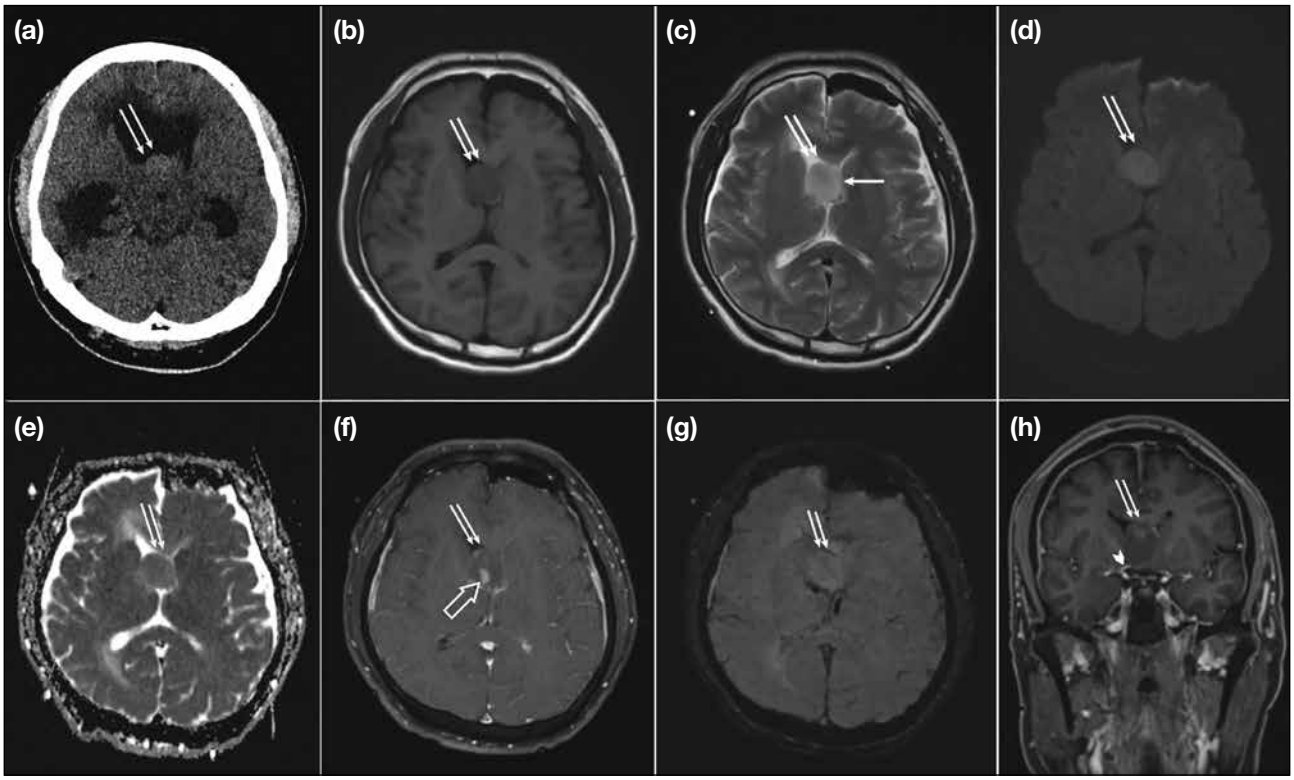

Figure 1. Non-contrast axial computed tomography (CT) and gadolinium-enhanced magnetic resonance imaging (MRI) in a 41-year-old man with diffuse midline glioma, H3K27-altered. (a) Non-contrast axial CT of the brain showing a round isodense mass (double arrow) at the foramen of Monro with hydrocephalus. (b-f) Axial MRI of the brain showing a well-defined solitary intraventricular tumour measuring 2 × 2.3 × 2.7 cm^3 (transverse × anteroposterior × craniocaudal) epicentred at the right lateral ventricle/foramen of Monro (double arrows). It is (b) T1 iso- to hypointense, (c) T2 hyperintense with restricted diffusion with (d) high diffusion-weighted imaging and (e) low apparent diffusion coefficient values. (f) Internal small foci of enhancement (hollow arrow) were seen in the post-contrast T1-weighted images. (g) There was no abnormal susceptibility artefact to suggest calcification or prior haemorrhage. The mass displaced the septum pellucidum (arrow in [c]) to the left while the third ventricle was displaced left and inferiorly. There was no definite suprasellar extension. (h) Coronal T1-weighted post-contrast MRI of the brain showing the mass (double arrow) abutting the right A1 segment of the anterior cerebral artery inferiorly (arrowhead), which remained patent.

2) and H3K27M (Figure 2b), with retained ATRX (alpha-thalassemia/mental retardation, X-linked). Staining for p53 showed a wild-type pattern, while staining for H3K27me3 was lost in tumour cell nuclei. Stainings for epithelial membrane antigen and IDH1 (isocitrate dehydrogenase 1) R132H were negative. The Ki-67 proliferative index was up to 30%. Histone H3 Sanger sequencing detected a mutation of c.83A>T (p.Lys28Met) [K27M] in the *H3F3A* gene. The overall findings were consistent with diffuse midline glioma (DMG), H3K27-altered (grade 4 of the World Health Organization [WHO] Classification of Tumours of the Central Nervous System).

Following discussion with local colleagues, a final diagnosis was made of H3K27-altered DMG. Subsequent workup including MRI of the whole spine (not shown) revealed no spinal cord involvement.

There were limited randomised data and no consensus on treatment for H3K27-altered DMG for the patient. Based on available evidence, resection and chemoradiotherapy with temozolomide was scheduled followed by adjuvant temozolomide if grade 4 disease was confirmed. As expected and considering the presence of infiltration of the basal part, post-resection MRI showed partial resection (Figure 3). Final histology of the resected specimen was similar to the previous biopsy, confirming the diagnosis of a grade-4 H3K27-altered DMG (Figure 2a). Further molecular studies showed no *IDH1* or *IDH2* gene mutation on sequencing and no *MGMT* (O^6-methylguanine-DNA methyltransferase) gene promoter methylation evident on polymerase chain reaction.

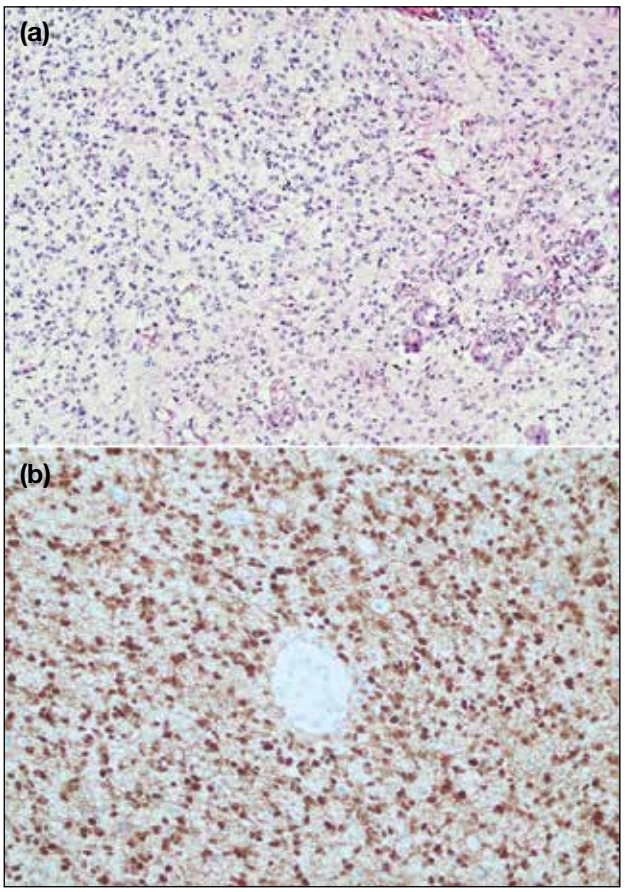

Figure 2. Histopathological and immunohistochemical studies in the same patient with H3K27-altered diffuse midline glioma as in Figure 1. (a) The biopsy and resection specimens of the glial tumour showed moderate to high cellularity with areas of microvascular proliferation. No necrosis was seen. There was no rosette or pseudorosette (hematoxylin and eosin staining, × 100). (b) On immunohistochemical studies, the tumour cells were positive for H3K27M (× 200).

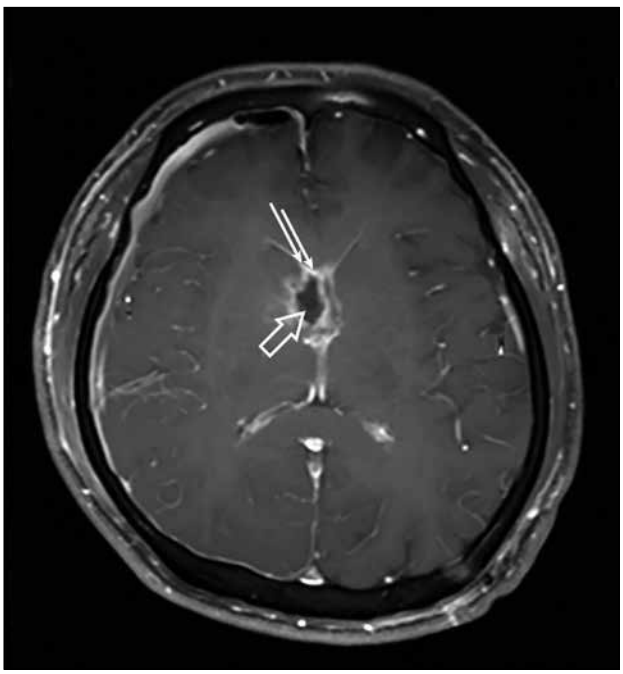

Figure 3. Post-contrast T1-weighted axial magnetic resonance image of the brain 1 week post resection showing possible residual tumour as evidenced by a well-defined solitary intraventricular area measuring 1 × 1.6 × 1.9 cm^3 (transverse × anteroposterior × craniocaudal) epicentred at the right lateral ventricle/foramen of Monro (double arrow). It is T1 iso- to hypointense, T2 hyperintense (not shown) and possibly with tiny internal foci of enhancement (hollow arrow).

Chemoradiotherapy was completed and the patient was scheduled for review with possible subsequent adjuvant chemotherapy.

DISCUSSION

Intraventricular tumours are rare and represent only 0.8% to 1.6% of all intracranial tumours.[1] Most intraventricular tumours are benign and are more common in children than in adults, comprising about 16% of childhood and adolescent intracranial tumours.[1] Common intraventricular tumours include: (1) neoplasm of the choroid plexus, e.g., choroid plexus papillomas, choroid plexus carcinomas, meningioma, and metastases; (2) neoplasm of the ventricular wall and septum pellucidum, e.g., ependymoma, subependymoma, subependymal giant cell astrocytoma, and central neurocytoma; (3) secondary intraventricular tumours, e.g., glioblastoma multiforme; and (4) non-neoplastic lesions, e.g., colloid cysts, arachnoid cysts, ependymal cysts, and choroid plexus cysts.[1] The most common clinical presentations of intraventricular tumours are secondary to hydrocephalus and subsequent increase in intracranial pressure, including headache and vomiting with papilledema in adults.[1]

Patient age, tumour location and imaging features will narrow the list of differential diagnoses. Ependymomas and choroid plexus tumours are more often found in children, and meningiomas and central neurocytoma are more usually seen in adults. Tumours such as central neurocytomas and subependymal giant cell astrocytomas are predominantly found in the anterior aspect of the lateral ventricles, whilst ependymomas and subependymomas are more commonly found in the fourth ventricle.[1]

H3K27M-mutant DMG was included in the 2016 WHO Classification of Tumours of the Central Nervous

System, according to its histological and molecular characteristics. It is usually located in the midline structures. In the 2021 updated guideline, it was renamed 'H3K27-altered'.[2] It is a diffusely infiltrative WHO grade 4 tumour with very poor prognosis and a 5-year survival of < 1%. Patients with H3-mutant DMGs have a significantly shorter overall survival than those with the H3 wild-type.[3] The most common locations at presentation are the brainstem, thalamus, and spinal cord. A study has reported better prognosis for patients with this type of DMG in unusual anatomical locations (e.g., lateral ventricles) compared with those at the typical location (i.e., brainstem).[3] It is a unique entity affecting children and very rarely adults.[4] The average age at presentation of H3K27M-altered DMG is 7 to 11 years.[5] Its presentation in the lateral ventricle is extremely rare with only two reported adult cases.[3,5] It is therefore uncommon to have H3K27-altered DMG in the intraventricular region and occurrence is also rare in adults.

The radiological appearances of H3K27-altered DMG are highly heterogeneous and lack specificity.[4] On MRI, the tumours are typically T1 iso- or hypointense and T2 hyperintense, and signal intensities are homogeneous on fluid-attenuated inversion recovery images. Restricted diffusion can be seen with invasive growth of the tumour. Intratumoral haemorrhage and necrosis are common and ring enhancement of the tumour can be seen although enhancement is usually not significant.[2] A connection between imaging findings and the H3K27-altered histone changes is not known due to the lack of relevant research making the diagnosis by imaging alone difficult.[2]

Due to the intraventricular location of this high-grade tumour, surgical resection is difficult.[2] The management plan for our case was maximal safe surgical resection plus adjuvant radiotherapy. Complete excision was not possible as the disease was quite infiltrative at the basal part.

In summary, we report an extremely rare case of primary lateral ventricle H3K27-altered DMG in a middle-aged man. Its intraventricular location made diagnosis based on imaging findings difficult, with our initial differential diagnoses of subependymoma, ependymoma and central neurocytoma incorrect. Further endoscopic biopsy helped confirm the final diagnosis and the patient underwent resection followed by chemoradiotherapy, and likely subsequent adjuvant chemotherapy. Early biopsy and molecular characterisation are the key to accurate diagnosis and prompt treatment. A high index of suspicion is needed to avoid missing the diagnosis. New clinical, imaging and histopathological information remain to be established but will aid in the diagnosis of this rare disease.

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