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Case report

H3K27M-mutant diffuse midline glioma presenting as synchronous lesions involving pineal and suprasellar region: A case report and literature review

Jia Xu Lim [a,b,*], Adriel Leong [b], Ai Peng Tan [c], Char Loo Tan [d], Vincent Diong Wen Nga [b]

[a] Department of Neurosurgery, National Neuroscience Institute, Singapore
[b] Division of Neurosurgery, Department of Surgery, National University Hospital, Singapore
[c] Department of Diagnostic Imaging, National University Hospital, Singapore
[d] Department of Pathology, National University Hospital, Singapore

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ABSTRACT

Introduction: The differential diagnoses for multifocal lesions with pineal and suprasellar involvement in a young adult include germ cell tumour and intracranial metastasis. Other differentials include atypical teratoid/rhabdoid tumour and pineoblastoma. We present the first known case of multicentric H3K27M mutant diffuse midline glioma, which is typically defined by its diffuse nature, midline location, and H3K27M mutation.

Case report: A young Chinese female presented subacutely with giddiness, right abducens nerve palsy and unsteady gait. Magnetic resonance imaging (MRI) of the brain with contrast revealed a moderately sized pineal region tumour, extending into the third ventricle, associated with hydrocephalus. There were two other synchronous lesions noted in the suprasellar and left occipital region. Serum and cerebrospinal fluid tumour markers, along with a computed tomography scan of her thorax and abdomen and were unremarkable. She underwent an endoscopic third ventriculostomy and biopsy of pineal and suprasellar lesions. Histology demonstrated a poor prognosis variant multifocal glioblastoma multiforme that was IDH wildtype, H3K27M positive, and MGMT unmethylated. MRI of the whole spine did not reveal any drop metastasis. The patient subsequently underwent adjuvant chemotherapy and radiotherapy after she was deemed to be unsuitable for surgical resection.

Conclusion: Although rare, multicentric H3K27M mutant diffuse midline glioma should be included in the list of differential diagnoses for multifocal enhancing lesions with involvement of the pineal and suprasellar regions, especially if the lesions demonstrate imaging features atypical for more common diagnosis such as germ cell tumours.

1. Introduction

Diffuse midline gliomas (DMG) with H3K27M mutation, is a subtype of diffuse glioma [1] that was included in the 2016 revised 4th edition of World Health Organization (WHO) Classification of Tumours of the Central Nervous System (CNS) [2]. The diagnostic criteria for this entity are defined by 1) a diffuse growth pattern; 2) a midline location (commonly brainstem, thalamus, and spinal cord); 3) glioma, and 4) H3K27M mutation [3–7]. These lesions are classified as WHO grade IV tumours regardless of their histological grade in view of the poor prognosis, with 2-year survival being less than 10% [8].

Multicentric glioblastoma is defined as multiple glioblastomas diagnosed at the same time that is spatially independent of each other (not linked by a clear path of spread suggested by hyperintensity in T2-FLAIR weighted sequences) [9–13]. This is a rare variant of glioblastoma, accounting for 2–6% of cases (with multifocal glioblastomas being 12–35%) [14–19]. It has an abysmal prognosis even compared to unifocal glioblastoma [10,20–22]. Pineal gliomas are rare and comprise of only 0.1% of all CNS gliomas [23]. There were only eight reported cases of H3 K27M-mutant DMG that originated from the pineal gland [1,24,25]. Suprasellar gliomas are also rare and there have not been any reports of H3 K27M-mutant DMG presenting in the suprasellar region.

* Corresponding author at: National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore.
E-mail address: jiaxu.lim@mohh.com.sg (J.X. Lim).

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We report an interesting case of a patient with a multicentric H3 K27M-mutant DMG located in the pineal, suprasellar and paramedian occipital region, the first of its kind in the literature.

2. Case description

Our patient is a right-handed 22-year-old Chinese female with no significant past medical history. She initially presented to another hospital with a subacute presentation of giddiness, horizontal diplopia in the right extreme gaze, and unsteady gait. On examination, besides a right sided abducens nerve palsy, she had an otherwise unremarkable physical examination. There were no suggestions of raised ICP, Parinaud's syndrome, or cerebellar signs.

Contrasted magnetic resonance imaging (MRI) of the brain was performed in view of her unrelenting symptoms and it demonstrated a moderately large pineal region tumour, 2.2 × 2.1 × 2.0 c m, extending into the third ventricle, associated with ventriculomegaly and transependymal shift of cerebrospinal fluid (CSF), there was also concurrent enhancing lesions located in the suprasellar and left occipital region, 2.0 × 1.4 × 0.9 cm. (Fig. 1). The lesion was mildly hyperintense on T2 weighted images, hypointense on T1W images and had patchy enhancement with contrast administration. The lesion also had internal restricted diffusion. There was no radiological evidence of leptomeningeal or subependymal spread. She underwent insertion of right frontal external ventricular drain and was transferred to our institution. Serum alpha-1 fetoprotein and beta-hCG were not elevated. Cerebrospinal fluid studies, obtained during insertion of the external ventricular drain, including beta-hCG, CEA, AFP and ALP were unremarkable. A computed tomography of the thorax and abdomen performed subsequently did not reveal any significant abnormality .

At this juncture, the differential diagnoses of the synchronous lesions were either germ cell tumours (typically germinoma) or multiple cerebral metastasis.

Our patient underwent an endoscopic third ventriculostomy and biopsy of pineal and suprasellar lesions subsequently. Intraoperatively, lesions corresponding to the scans were observed in the floor and the posterior wall of the third ventricle (Fig. 2). The lesion in the floor, arose from the suprasellar region. It was reddish, soft, and of moderate vascularity. The lesion located at the posterior wall of the third ventricle was also visualised and had a similar appearance and texture as the former lesion. Both lesions were successfully biopsied. Intraoperative pathological consult was obtained and found a small blue cell tumour with frequent mitotic figures (Fig. 3a, b). As the lesion in the floor was obstructing the tuber cinereum, decision was made for the insertion of a ventriculoperitoneal shunt in the same sitting, instead of performing a third ventriculostomy, for CSF diversion.

Both biopsies from the pineal and suprasellar lesions showed similar histopathological findings of a densely cellular tumour composed of sheets of small blue cells with brisk mitotic activity (Fig. 3A). Necrosis, microvascular proliferation, rosette formation and rhabdoid morphology were all not observed. Tumour cells were diffusely positive for GFAP and Olig2 (Fig. 3B), suggestive of glioma. In view of the midline location, H3K27M immunostain (Fig. 3C) was performed, which showed a diffuse strong nuclear reactivity in the tumour cells, clinching the diagnosis of H3K27M-DMG. ATRX was retained, p53 was overexpressed in approximately 15% of tumour cells and IDH sequencing did not show any mutation. A panel of immunostains including OCT4, LIN28A, CAM5.2, CD45, desmin and INI was also performed to rule out differentials such as germ cell tumour, metastatic carcinoma, lymphoma, and atypical teratoid/rhabdoid tumour. They were all negative. MGMT was unmethylated. Intraoperative cerebrospinal fluid sent for cytological examination did not reveal any malignant cells. MRI of the whole spine did not reveal any drop metastasis (Fig. 4).

Postoperatively, the patient had an uneventful recovery with resolution of her right abducens palsy. Humphrey's visual field shows deficits in the right superonasal field and left temporal field. She was discussed at the Neuro-oncology multidisciplinary rounds and deemed to be unsuitable for surgical resection and was treated with concurrent adjuvant chemotherapy and radiotherapy (Stupp protocol). Interestingly, despite her poor prognostic markers, she has significantly improved clinically and radiologically (Fig. 5). At the time of the report, she is 7 months after surgery and has returned to work.

3. Discussion

The two main radiological differential diagnoses for multifocal enhancing lesions with involvement of the pineal and suprasellar regions in a young adult include germ cell tumour and intracranial metastasis from an extracranial primary malignancy. Other possibilities include atypical teratoid/rhabdoid tumour (a rare entity that occurs in the adult female [26]) and pineoblastoma. Multifocal H3K27M-mutant DMG with involvement of the cerebral hemisphere, pineal and suprasellar regions has never been reported before, to the best of our knowledge.

Histopathological findings in H3K27M-mutant gliomas range from glioblastoma to diffuse astrocytoma, oligodendroglioma and anaplastic astrocytoma, likely the reason for the diverse imaging features in this group of molecularly defined tumours. Aboian et al found no distinguishing imaging features on conventional MRI between H3K27M-mutant and H3K27M wild-type tumours [27]. Chen et al. demonstrated that minimal ADC ($\times 10^{-3}$ mm^2/s) with a threshold of 0.728 is a potential imaging biomarker for

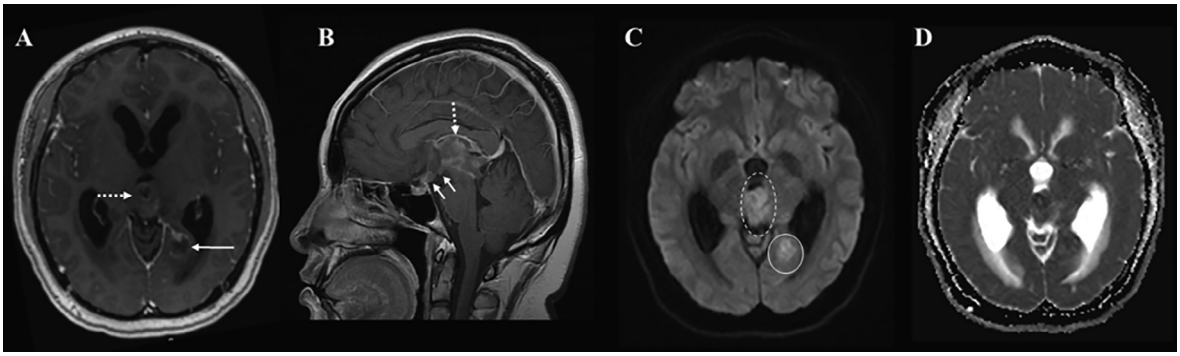

Fig. 1. Pre operative MRI IMAGES.

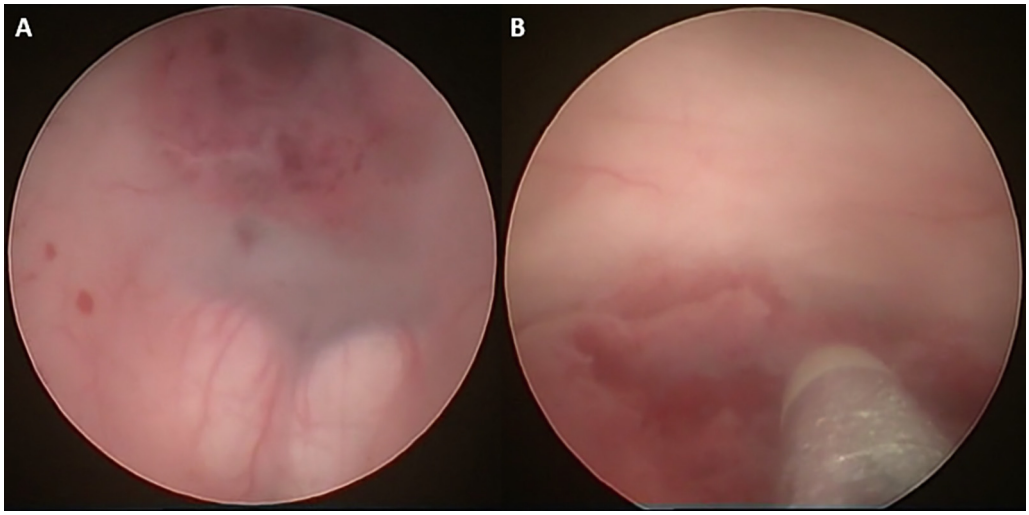

Fig. 2. Intraoperative Images.

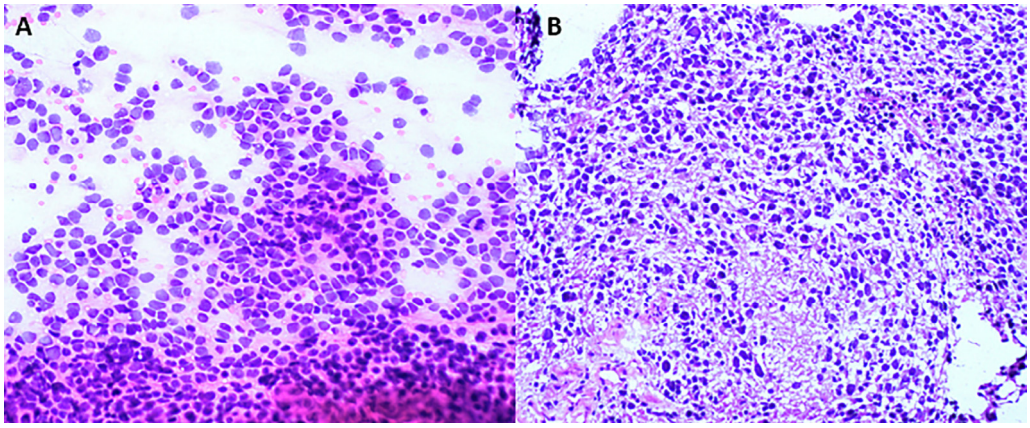

Fig. 3. Intraoperative Histopathological Slides.

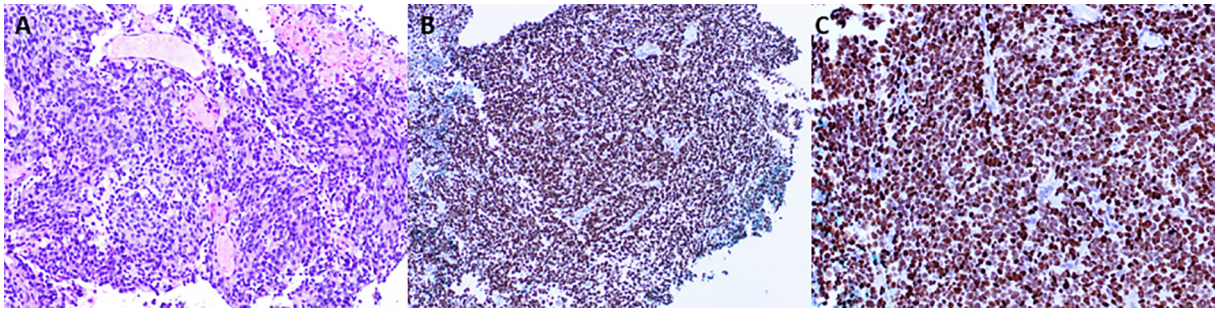

Fig. 4. Histological Analysis.

the prediction of H3K27M mutational status in diffuse midline gliomas [28]. A large series of adult H3K27M-mutant DMG reported that most of these tumours showed partial to no enhancement, were predominantly solid and had diffusion restriction on diffusion-weighted imaging [29], as shown in our reported case. Germinomas although also predominantly solid lesions with restricted diffusion, tend to show homogeneous intense enhancement [30]. The main enhancement patterns observed in adult H3K27M-mutant DMG; 1) ring-like enhancement; 2) patchy enhancement; 3) homogeneous enhancement; and 4) cyst with nodular enhancement [29]. The lack of consistent tumour enhancement suggests that the degree of enhancement is not representative of tumour grade, but rather that the histopathological heterogeneity of these tumours. Haemorrhage and necrosis are rare in both H3K27M-mutant DMG and germinoma [29,30]. Indeed, much is still unknown about H3K27M-mutant DMG.

Compared to the known recent literature on H3 K27M mutant DMGs (Table 1), our patient is the ninth known case of H3 K27M mutant DMG involving the pineal gland and the first one arising from the suprasellar region and of a multicentric variation. At the time of diagnosis and during early follow up, there was no radiological or cytological (via CSF) suggestion of metastasis. This is in

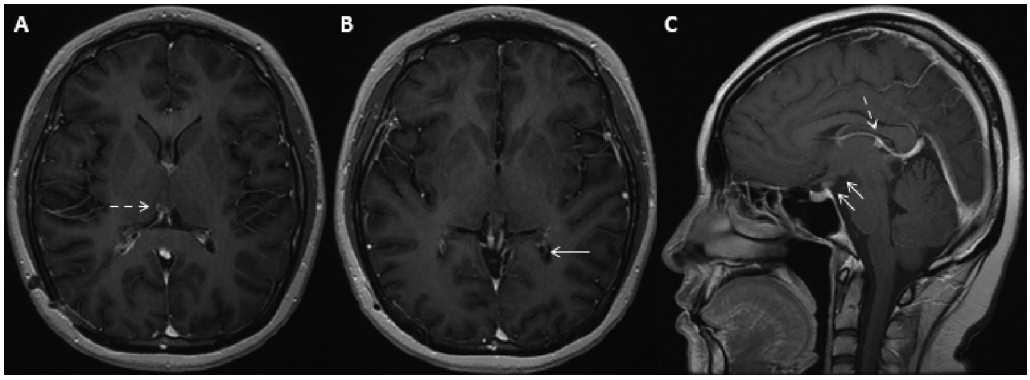

Fig. 5. Post treatment MRI IMAGES.

Table 1
Summary of major case series with H3K27M mutant diffuse midline glioma.

	Enomoto [33]	Haihui [25]	Karisa [34]	Tianming [8]	David [31]
Country	Fukuoka University, Japan	Tiantan Hospital, China	John Hopkins, United States	Huashan Hospital, China	Hospices Civils de Lyon, France
Journal, Year	Neurologia Medico-Chirurgica, 2000	Neuro-Oncology, 2019	Journal of Neuro-Oncology, 2019	Journal of Neurosurgery, 2019	Neuro-Oncology, 2017
Number	23 (11 H3K27M mutants)	57	18	66	21
Female (%)	43.5	40.4	56	39.4	62.5
Age (median, years)	47	–	–	–	32
Age (mean ± SD, years)	–	21.8 ± 15.8	45.1 ± 12.8	–	–
Age (20–29 years, %)	30.4	–	–	36.4	–
Location (%)	Thalamus (52.5) Thalamus – Midbrain (8.7) Pons (21.7) Medulla (4.3) Cervical spinal cord (4.3)	Thalamus (57.9) Brainstem (26.3) Pineal gland (8.8) Spinal cord (5.3) Hypothalamus (1.8)	Cerebellum (33.3) Pons (22.2) Thalamus (16.7) Midbrain (11.1) Spinal cord (11.1) Corpus callosum (5.6)	Thalamus (57.6) Brainstem (15.2) Disseminated (12.1) Corpus callosum (4.5) Spinal cord (6.1) Hemispheric (3.0) Hypothalamus (1.5)	Thalamus, hypothalamus, pineal (33) Spinal cord (29) Brainstem (24) Cerebellum (14)
Genetic (%)	IDH1 mutation (0) ATRX loss (2)	IDH mutation (0) 1p/19q codeletion (0) MGMT methylation (0)	IDH1 mutation (0) ATRX loss (8.3) MGMT methylation (20)	–	IDH mutation (0) MGMT methylation (5)
Overall Survival, Median (months)	17.0	16.0	17.6	–	19.7

SD: standard deviation; IDH: isocitrate dehydrogenase; ATRX: alpha thalassemia/mental retardation gene; MGMT: O-methylguanine-DNA methyltransferase.

accordance with what is described with regards to tumour dissemination being uncommon at around 12.0% [8]. Molecular subtyping studies also showed typical findings that were similar to other case series, including no IDH mutation and no MGMT methylation [25,31,32].

4. Conclusion

H3K27M diffuse midline glioma is defined by its diffuse nature, midline location, and H3K27M mutation. We present the first known case of multicentric H3K27M mutant DMG and add to the currently limited literature on it. Although rare, this entity should be included in the list of differential diagnoses for multifocal enhancing lesions with involvement of the pineal and suprasellar regions, especially if the lesions demonstrate imaging features atypical for more common diagnosis such as germ cell tumours.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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