NEUROPATHOLOGY

Neuropathology 2020 doi:10.1111/neup.12689

Case Report

An adult case of diffuse midline glioma with *H3* K27M mutation

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Cartilaginous metaplasia is rare in primary central nervous system (CNS) neoplasms and has not been described in the histone 3 (H3) gene (*H3*) with a substitution of lysine to methionine (*H3* K27M mutant) diffuse midline glioma before. Here, we report a case of *H3* K27M mutant diffuse midline glioma with cartilaginous metaplasia in a 56-year-old woman. Magnetic resonance imaging (MRI) revealed a ring-enhanced lesion located in the medulla oblongata and extended superiorly into the fourth ventricle. The tumor was macroscopically completely resected. Histologically, the tumor was composed of a gliomatous component and a well-differentiated cartilaginous component. Microvascular proliferation and necrosis were noted. According to immunohistochemical staining, glial cells were diffusely and strongly positive for glial fibrillary acidic protein (GFAP), oligodendrocyte lineage transcription factor 2 (Olig2), H3 K27M, and S-100 protein but negative for H3K27me3. The chondrocytes also were positive for GFAP and S-100 protein. The *H3* K27M mutation was confirmed by sequencing in both the gliomatous and cartilaginous components, suggesting a common origin from the same progenitor cells. Based on these findings, the tumor was diagnosed as a diffuse midline glioma with *H3* K27M mutation with widespread cartilaginous metaplasia, corresponding to WHO grade IV. This is an extremely rare *H3* K27M mutant diffuse midline glioma with cartilaginous metaplasia, and reporting this unusual case adds to the understanding of this tumor type.

Key words: adult, cartilaginous metaplasia, diffuse midline glioma, H3 K27M mutant, medulla oblongata.

INTRODUCTION

The histone 3 (H3) gene (*H3*) K27M (*H3* K27M) mutant midline glioma is a recently described tumor entity, which was first included in the 2016 edition of the WHO Classification of Tumors of the Central Nervous System.[1] The tumor is predominantly found in children but can also be seen in adults, with the most common locations such as

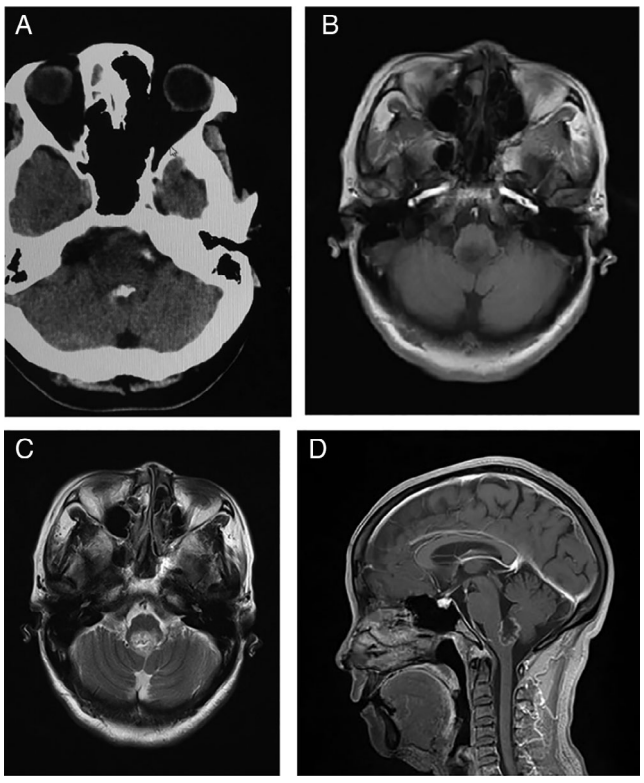

Fig 1 CT (A) and MRI (B-D) findings of the brain. CT reveals irregular calcification in the fourth ventricle (A). Axial T1-weighted (B) and T2-weighted (C) images show a round lesion with long T1 and heterogeneous T2 signals. A sagittal T1-weighted image with gadolinium contrast shows a heterogeneously enhanced ring-like lesion involving the medulla oblongata and extending into the fourth ventricle (D).

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Received 27 February 2020; revised 15 April 2020; accepted 14 May 2020.

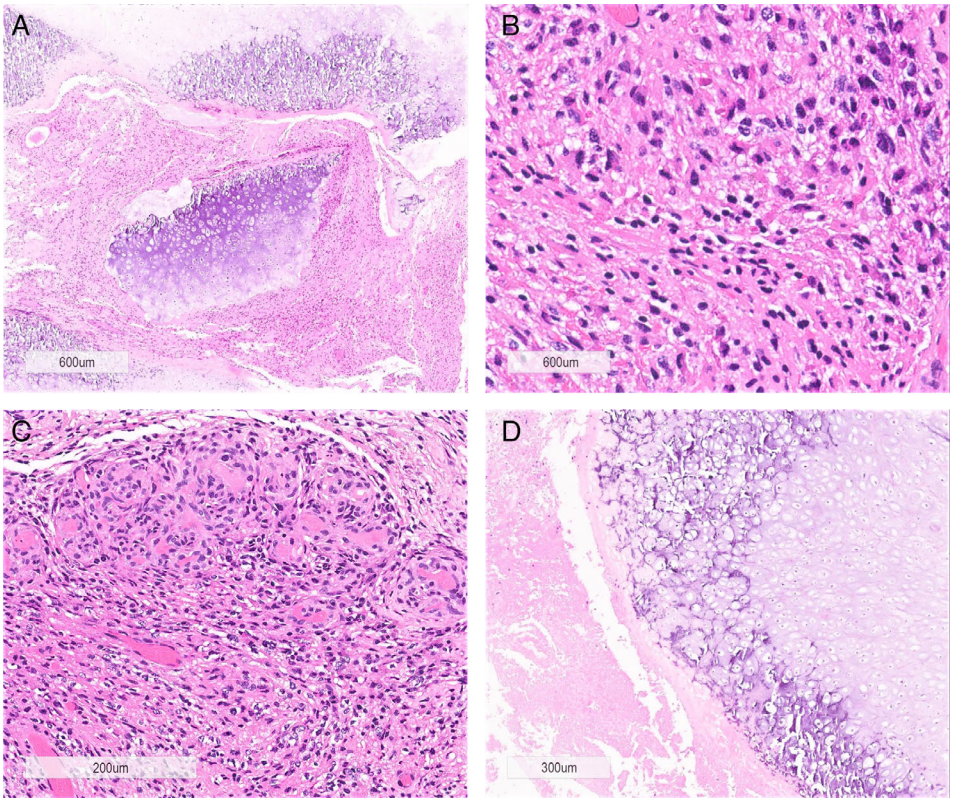

Fig 2 Histological findings in HE-stained sections of the brain tumor specimens. The tumor is composed of two different components, including glioma and cartilage (A). The tumor cells exhibit a certain degree of cellular pleomorphism with round to ovoid or slightly irregular-shaped nuclei (B). Proliferation of endothelial cells in small vessels is observed (C). Lobule formation of well-differentiated cartilaginous tissue with calcification and patchy necrosis are observed (D).

the brain stem, the thalamus, and the spinal cord, followed by the third ventricle, the hypothalamus, and the pineal region. The tumor shows an aggressive clinical behavior and has a poor prognosis.[2–6] Although the malignant tumor displays a broad spectrum of histological features,[2–4] *H3* K27M mutant diffuse midline glioma with cartilaginous metaplasia has, to our best knowledge, not been reported before. Here, we report a unique case of *H3* K27M mutant diffuse midline glioma with cartilaginous metaplasia in an adult. We also review the published literature to highlight the significance of this rare but notable tumor entity.

CLINICAL SUMMARY

A 56-year-old woman was admitted with recurrent fainting and loss of consciousness with clenched teeth for more than half a month. The symptoms relieved spontaneously but were occasionally accompanied by fatigue. The disclosed past medical history indicated no developmental abnormalities, familial inherited diseases, prior surgeries, or medications. Subsequent computed tomography (CT) revealed irregular calcification in the fourth ventricle (Fig. 1A). Magnetic resonance imaging (MRI) revealed a round mass in the medulla oblongata, measuring 2.0 × 1.6 cm in size, extending into the fourth ventricle. The tumor showed low signal intensity in T1-weighted images and heterogeneous high signal intensity in T2-weighted images. In addition, cystic degeneration could be seen in the lesion (Fig. 1B, C). The lesion showed ring enhancement in gadolinium-contrasted T1-weighted images (Fig. 1D). A diffuse midline glioma of the medulla oblongata was suggested by imaging. The patient underwent surgery for tumor resection.

PATHOLOGICAL AND GENETIC FINDINGS

Macroscopic and histological observations

In gross appearance, the specimens consisted of multiple pieces of pink–tan soft tissue and greyish white tissue of moderate hardness measuring 2.1 × 1.7 × 0.5 cm in total size. The tissue was fixed in 10% formalin and embedded in paraffin. The formalin-fixed, paraffin-emebedded 4-μm-thick sections were stained with hematoxylin and eosin (HE). Microscopic examination revealed a biphasic neoplasm with regions of gliomatous appearancce and cartilaginous metaplasia (Fig. 2A). The neoplastic glial cells showed a diffuse growth pattern and were densely arranged. The cells also demonstrated a certain degree of cellular pleomorphism. The cell nuclei were hyperchromatic and round to oval or slightly irregular in shape (Fig. 2B). Nucleoli and mitotic activity were inconspicuous. Proliferation of endothelial cells in small vessels was

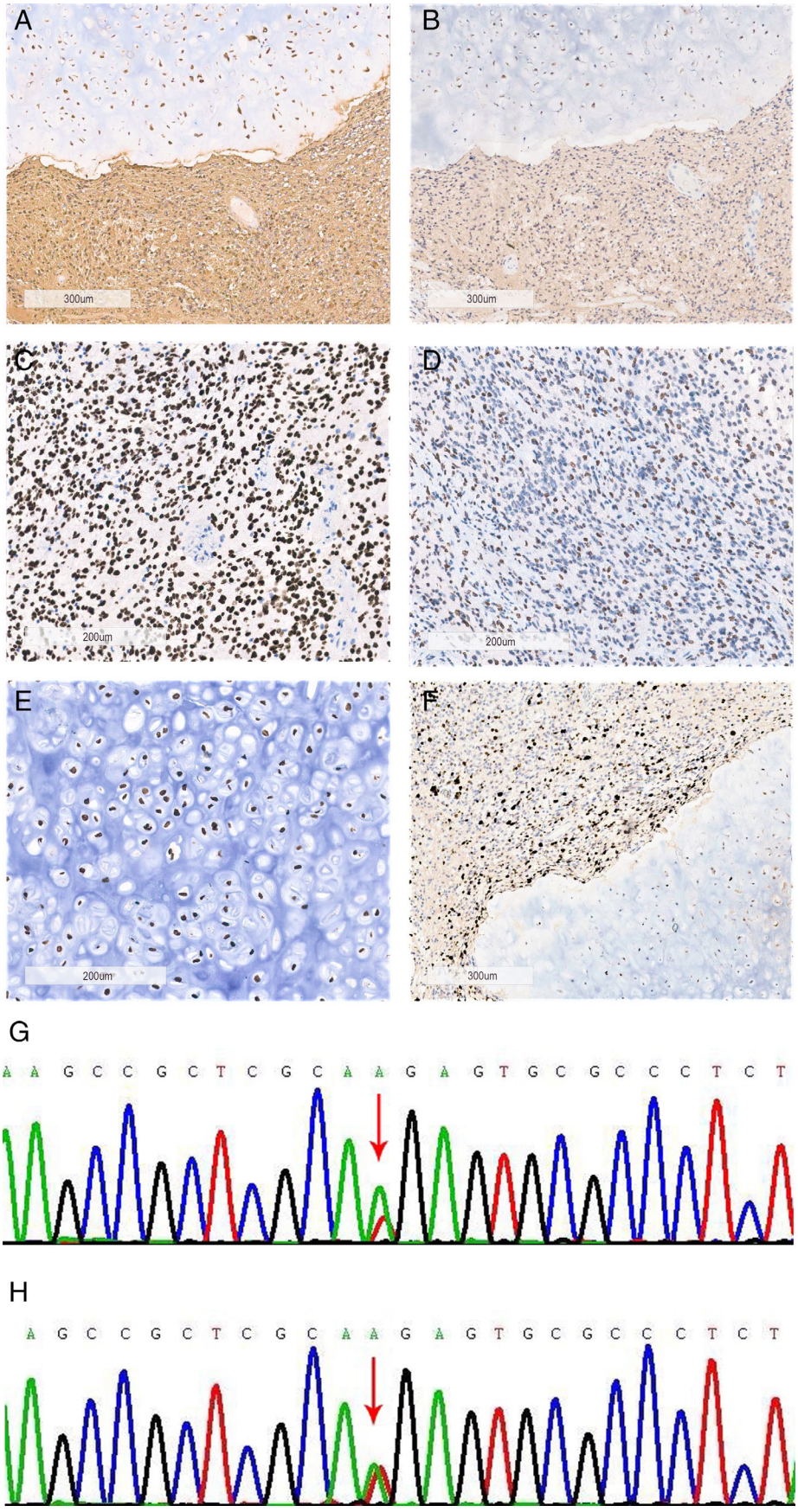

Fig 3 Results of immunohistochemistry (A-F) and sequencing (G, H) on the tumor specimens. Gliomatous and cartilaginous components of the tumor are positive for GFAP (A) and S-100 protein (B), respectively. The neoplastic cells like glia are positive for H3 K27M (C) but negative for H3K27me3 (D). The neoplastic cells like chondricytes are also positive for H3 K27M (E). The Ki-67 labeling index is as high as 20% in the gliomatous compartment and less than 1% in the cartilaginous component (F). *H3* K27M mutation (heterozygous AAG to ATG substitution at codon 27) is detected by Sanger sequencing of the gliomatous (G) and cartilaginous (H) components. Green and red (arrows) peaks indicate adenine and timine, respectively.

observed (Fig. 2C). Furthermore, glomerular hyperplasia and patchy necrosis were seen. A sharp transition was observed between the gliomatous and cartilaginous regions. The cartilaginous metaplasia was multifocal and varied in its maturity (Fig. 2D). There was no evidence of pleomorphism or mitotic activity in the cartilaginous areas, where calcification was parial.

Immunohistochemical observations

The glial cells were diffuse and strongly positive for glial fibrillary acidic protein (GFAP) (Fig. 3A), S-100 protein (Fig. 3B), H3 K27M (Fig. 3C), oligodendrocyte transcription factor 2 (Olig2), and vimentin but negative for H3K27me3 (Fig. 3D), isocitrate dehydrogenase 1 (IDH1) R132H, p53, epithelial membrane antigen (EMA), BRAF V600E, and neuronal nucleus (NeuN). The metaplastic chondrocytes were positive for S-100 protein, podoplanin (by the antibody D2-40), GFAP, and H3 K27M (Fig. 3E) but negative for Olig2, H3K27me3, IDH1 R132H, p53, EMA, BRAF V600E, and NeuN. alpha-thalassemia with mental retardation X-linked (ATRX) immunohistochemistry revealed loss of nuclear expression in both the glial cells and metaplastic chondrocytes. The Ki-67 labeling index with the specific antibody MIB-1 was as high as 20% in the gliomatous region (Fig. 3F), and less than 1% in the metaplasric cartilaginous region.

Sequencing results

The *H3* K27M mutation was confirmed by Sanger sequencing in both the gliomatous (Fig. 3G) and cartilaginous (Fig. 3H) components.

DISCUSSION

The presence of cartilage in glioma is exceedingly rare. Since Mackay's original report in 1935,[7] only a few such cases have been documented. Mathews and Mossy reported cartilaginous components in two cases of fourth ventricular ependymoma mixed with astrocytoma.[8] Furthermore, their literature review showed that glial neoplasms containing metaplastic cartilaginous components occur most often in childhood and are usually located in the midline. It has been hypothesized that cartilage may arise from metaplastic transformation of the connective tissue stroma of glial neoplasms.[8–10] Kepes *et al.* also described a different pattern of development of cartilage in four gliomas occurring in young individuals. Interestingly, these four cases were all aggressive diffuse midline gliomas, including three cases located in the pons and one involving the fourth ventricle and brainstem.[11] Unfortunately, *H3* K27M mutant diffuse midline gliomas were not defined as a distinct nosological entity at that time. It was demonstrated that neoplastic astrocytes are capable of differentiating into chondrocytes through mucopolysaccharide deposition, which may become condensed to form a chondroid matrix.[11,12]

In our case, the necrotic region was adjacent to the cartilaginous region. Cartilaginous metaplasia may be caused by necrosis. However, mere necrosis and calcification are probably not sufficient to initiate bone and cartilage formation.[8] Moreover, the partial cartilaginous components were surrounded by the gliomatous components. In other words, the transition between neoplastic glial and chondroid regions was evident. According to immunohistochemistry, both the gliomatous cells and metaplastic chondrocytes were positive for GFAP, S-100 protein, and H3 K27M in our case. Although GFAP also localizes in elastic cartilage such as the epiglottic or auricular chondrocytes, GFAP immunoreactivity is not typical of primary cartilaginous neoplasms or mature hyaline cartilage.[13,14] Expression of GFAP in chondrocytes supports their glial origin.[11] Moreover, genetic sequencing revealed the presence of *H3* K27M mutation in both the gliomatous and cartilaginous components, supporting the interpretation that both elements are derived from the same progenitor cells. This interpretation is similar to the theory explaining heterogeneous composition in gliosarcoma.[15,16] In addition, studies have shown that *H3* K27M mutation leads to changes in the epigenome, causing oncogenic insults to progenitor cells in early neurodevelopment.[17,18]

Some studies demonstrate that osseous or cartilaginous elements in gliosarcoma may indicate a high degree of malignancy.[16,19] Based on a case report and review of the literature, Wang *et al.* found that ependymoma with cartilaginous metaplasia might display more aggressive clinical behavior.[20] Because of the *H3* K27M mutation, our patient underwent radiotherapy and chemotherapy with temozolomide one month after surgery. Five months after surgery, the tumor relapsed in the same location, according to the MRI evaluation, and long-term follow up will be necessary.

In conclusion, we encountered a very rare case of adult *H3* K27M mutant diffuse midline glioma associated with extensive cartilaginous metaplastic changes. Immunohistochemistry and genetic testing supported the view that the cartilaginous elements in *H3* K27M mutant diffuse midline glioma may be a result of a metaplastic change or divergent differentiation of common progenitor cells.

ACKNOWLEDGMENTS

The authors are grateful to the patient and her family for allowing us to share this case.

DISCLOSURE

The authors declare they have no competing interests.

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