Malignant Transformation of Craniopharyngioma: A rare case after 32 years of follow-up

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ABSTRACT

Craniopharyngiomas are rare, benign epithelial tumors of the sellar region, with malignant transformation being exceedingly uncommon. We report a case of squamous cell carcinoma arising 32 years after the initial diagnosis of adamantinomatous craniopharyngioma. The patient underwent four surgical resections and two courses of radiotherapy. Following seven years of stable imaging, a rapidly enlarging lesion emerged, invading adjacent skull base structures. Histopathological examination confirmed malignant transformation, characterized by squamous cell carcinoma with beta-catenin positivity. This case highlights the diagnostic and therapeutic challenges posed by such transformation and underscores the importance of long-term follow-up in craniopharyngioma patients. Although radiation therapy has been speculated as a risk factor, its causal relationship remains unproven. Malignant craniopharyngiomas carry a poor prognosis, with limited benefit from conventional therapies. Increased awareness and documentation of such rare cases are essential to improve understanding of underlying mechanisms and guide future management strategies.

KEY WORDS

Craniopharyngioma, Malignant transformation, Squamous cell carcinoma, Radiotherapy.

INTRODUCTION

Craniopharyngiomas are benign, slow-growing epithelial tumors originating from remnants of Rathke's pouch.[1] They are most commonly located in the suprasellar region and present with symptoms such as visual disturbances, headaches, and endocrine dysfunction due to mass effect on surrounding structures.[2]

Craniopharyngiomas are classified into two histological subtypes: the more common, often cystic adamantinomatous type, typically seen in children, and the rarer papillary type, predominantly observed in adults.[3] Despite their benign histopathological nature, craniopharyngiomas frequently demonstrate locally aggressive behavior, invading adjacent tissues and adhering to critical neurovascular structures. They also have a well-recognized propensity to recur after surgical excision, especially following incomplete resection.[3] While local invasion is common, distant metastasis remains exceedingly rare.[4]

Malignant transformation of craniopharyngioma is an exceptionally rare clinical phenomenon, first described by Salyer et al. in 1973.[4] A recent review by Elerjani et al. identified only 31 reported cases of malignant craniopharyngioma between 1980 and 2020.[5] A more recent literature review conducted in 2025 identified a total of 44 cases of malignant craniopharyngioma, with a median age of 28 years and a median overall survival of six months.[6]

The pathogenesis of this transformation remains unclear, although prior radiation therapy has been implicated as a potential contributing factor in some cases. However, 17 of the 44 cases reported in the literature had no history of radiation therapy.[6]

Given its rarity and diagnostic challenges, each case provides valuable insights into the natural history and potential risks associated with craniopharyngioma management. Here, we present a rare case of malignant transformation into squamous cell carcinoma occurring 32 years after the initial surgery in a patient with a history of multiple recurrences and prior radiotherapy.

CASE REPORT

A 39-year-old male patient with a history of four craniopharyngioma surgeries beginning 32 years earlier was referred to our hospital's Neurosurgery Department after magnetic resonance imaging (MRI) revealed signs of tumor recurrence. Following the initial surgery, the patient underwent conventional radiotherapy with a total dose of 54 Gy, and approximately seven years ago, he received stereotactic radiosurgery (SRS) delivering 22.5 Gy. He presented with right retroorbital pain, nausea, and severe headache. Neurological examination revealed right-sided ptosis.

After four surgical interventions, the patient remained stable for nearly seven years, with annual MRI scans showing a residual lesion. However, follow-up imaging revealed a newly developed recurrent mass adjacent to the residual tumor. This new lesion appeared iso- to hypointense on both T2-weighted (T2W) and T1-weighted (T1W) sequences, demonstrated homogeneous contrast enhancement on post-contrast T1W images, and exhibited restricted diffusion on the apparent diffusion coefficient (ADC) map (Fig. 1).

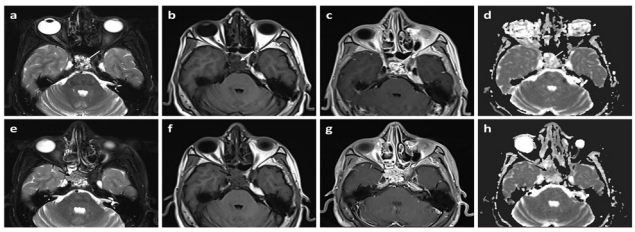

Figure 1. Follow-up MRI in a 39-year-old male with craniopharyngioma showing residual and recurrent lesions.

Axial images (a-d) from one year prior depict a residual suprasellar lesion: (a) T2W, (b) T1W, (c) post-contrast T1W, and (d) ADC map show a heterogeneous, calcified mass with heterogeneous enhancement (c) and facilitated diffusion (d) (white arrow). One year later, axial (e) T2W, (f) T1W, (g) post-contrast T1W, and (h) ADC map reveal a new iso-hypointense lesion adjacent to the original, with homogeneous enhancement (g) and diffusion restriction (h), indicating recurrence (black arrow).

Two months after the detection of recurrence, imaging demonstrated a rapidly enlarging mass invading the right cavernous sinus and Meckel's cave, extending into the right orbital apex and sphenoid sinus, causing bony destruction of the skull base, and exhibiting intense fluorodeoxyglucose (FDG) uptake on positron emission tomography–computed tomography (PET-CT) (Fig. 2).

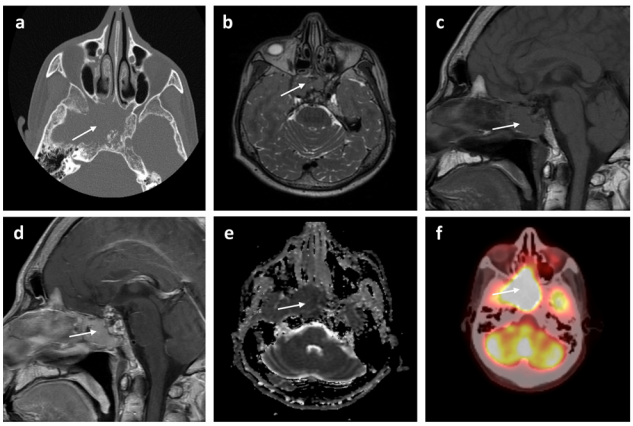

Figure 2. Imaging two months after recurrence detection in a craniopharyngioma patient, showing rapid tumor progression.

Axial CT (a) shows a lytic skull base lesion. Axial T2W (b) and sagittal T1W (c) reveal an isointense mass extending into the right orbital apex and sphenoid sinus. Post-contrast sagittal T1W (d) shows homogeneous enhancement. The ADC map (e) demonstrates marked diffusion restriction, and PET-CT (f) shows intense FDG uptake. Findings indicate a rapidly growing mass suggestive of malignant transformation (white arrow).

The patient underwent tumor resection via a transcallosal approach. Intraoperatively, a soft, grayish mass filling the sphenoid sinus was noted. Histopathological analysis revealed squamous cell carcinoma arising in the background of craniopharyngioma, confirmed by positive nuclear beta-catenin immunostaining. The patient's symptoms improved in the early postoperative period; however, due to the extent of the disease, he was deemed inoperable and was referred for radiotherapy.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

Craniopharyngioma is a benign, WHO grade I intracranial tumor that most commonly arises in the sellar and infundibulotuberal regions.[7] Malignant transformation is extremely rare and has been reported predominantly as squamous cell carcinoma arising from pre-existing adamantinomatous craniopharyngiomas.[6] This transformation is thought to be associated with molecular alterations such as CTNNB1 mutations and nuclear beta-catenin accumulation.[8] Histologically, adamantinomatous craniopharyngioma shows ameloblastoma-like morphology with palisading nuclei, wet keratin, stellate reticulum, and

dystrophic calcification, while papillary craniopharyngioma is characterized by well-differentiated non-keratinizing squamous epithelium and BRAFV600E mutation.[7]

According to the literature, the pathological spectrum of malignant craniopharyngioma is diverse, encompassing histological variants such as squamous cell carcinoma, myoepithelial carcinoma, ameloblastoma, ameloblastic carcinoma, and lesions resembling odontogenic ghost cell carcinoma.[9] To date, there are no universally accepted histopathological criteria for the diagnosis of malignant craniopharyngioma. Nonetheless, analysis of previously documented cases suggests that malignant transformation is commonly associated with a combination of specific histological features. These include increased cellularity with a reduced cytoplasmic-to-nuclear ratio, marked nuclear pleomorphism with hyperchromatic nuclei, elevated mitotic activity or increased proliferative indices such as proliferating cell nuclear antigen (PCNA), and areas of coagulative necrosis. Additional features may comprise solid architectural patterns, disruption of the basement membrane, invasive growth into surrounding tissues, and evidence of microvascular proliferation. Importantly, most reported cases demonstrate at least three of these defining histopathological characteristics.[9]

In the present case, malignant transformation of a craniopharyngioma occurred approximately 32 years after the patient's initial surgery, following four surgical interventions for recurrent disease. Notably, a previously stable residual lesion monitored annually for seven years demonstrated new radiological evidence of recurrence, which progressed rapidly over a two-month period. This case underscores the importance of prolonged surveillance in patients with craniopharyngioma, considering the potential for late malignant transformation even decades after initial treatment. According to the literature, malignant transformation typically occurs at a mean age of 31.1 ± 15.2 years, with an average interval of 12.2 ± 8.4 years from the diagnosis of benign craniopharyngioma to the development of malignancy.[5]

Malignant craniopharyngioma carries a poor prognosis, with a mean postoperative survival of 5.3 ± 4.3 months reported in the literature, and no clear survival benefit has been demonstrated for radiotherapy or chemotherapy.[5]

There are various hypothesized mechanisms underlying the malignant transformation of craniopharyngiomas; however, the exact pathogenesis remains unclear, largely due to the rarity of reported cases. Notably, a history of radiotherapy was documented in 61% of malignant transformation cases reported in the literature. Earlier, Sofela et al. using Spearman rank correlation analysis, found no significant association between radiotherapy use (correlation coefficient: −0.25; $p < .05$) or radiation dose (correlation coefficient: −0.26; $p < .05$) and malignant transformation.[10] Similarly, in a subsequent review, Elerjani et al. also reported no significant impact of radiotherapy on the risk of malignant transformation ($p = 0.379$).[5] Although no causal link between radiotherapy and malignant transformation has been established, its long-term risks warrant caution, especially in benign histology and pediatric cases. Radiotherapy should therefore be reserved for residual or recurrent tumors unsuitable for further surgery.

This case highlights the importance of long-term surveillance in craniopharyngioma patients, emphasizing the potential for malignant transformation and the need to investigate underlying mechanisms in cases of rapid progression following recurrence.

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