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CASE REPORT

Tonsillary carcinoma after temozolomide treatment for glioblastoma multiforme: treatment-related or dual-pathology?

E. Binello · I. M. Germano

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Abstract Glioblastoma multiforme is a primary malignant brain tumor with a prognosis of typically less than 2 years. Standard treatment paradigms include surgery, radiation therapy and temozolomide. Little data exists for temozolomide recommendations after the first 6 months. We present a case of a patient with glioblastoma multiforme treated with surgery, radiation and chronic temozolomide for 6 years. He continues to survive glioblastoma-recurrence-free, but developed tonsillary carcinoma. This case raises the question of whether this secondary solid-organ malignancy is treatment-related or dual pathology.

Keywords Glioblastoma multiforme · Temozolomide · Tonsillary carcinoma

Introduction

Glioblastoma multiforme (GBM), the most malignant and aggressive type of primary brain tumors, is the most common among malignant brain tumor and frequently affects patients between 45 and 70 years of age [1]. Neurologic symptoms depend on the area of the brain affected, ranging from nonfocal with headaches and/or seizures to focal deficits such as hemiparesis, aphasia and sensory loss. The prognosis for patients with glioblastoma multiforme is poor, with average survival of 12 months in spite of aggressive treatment [2].

E. Binello · I. M. Germano (✉)
Department of Neurosurgery, Mount Sinai Medical Center,
1 Gustave L. Levy Place, Box 1136, New York, NY 10029, USA
e-mail: isabelle.germano@mountsinai.org

E. Binello
e-mail: emanuela.binello@mssm.edu

Current treatment paradigms consist of aggressive surgical tumor debulking, followed by radiotherapy, usually a median dose of 60 Gy given over the course of 6 weeks, with concomitant temozolomide (TMZ), an oral alkylating agent. A randomized trial comparing radiotherapy versus radiotherapy plus TMZ (including both concomitant and adjuvant) demonstrated a small but statistically significant survival benefit in the patients receiving TMZ [2]. This treatment paradigm has become standard of care and endorsed by practice guidelines [3, 4]. TMZ toxicity mostly involves the hematopoietic system, including leucopenia, neutropenia and/or thrombocytopenia; up to 7% of patients manifest these in the TMZ concomitant phase and 14% in the TMZ adjuvant phase [2]. There have also been several reports of myelodysplastic syndrome/acute myelogenous leukemia [5, 6] and aplastic anemia [7, 8] associated with TMZ treatment. However, there have been no reports of solid organ malignancies in the context of TMZ treatment.

Tonsillary carcinoma is relatively uncommon, with an incidence in the US of approximately 2.7 per 100,000, compared to brain at 7.3 and lung at 85.3 [9]. The most common histologic type is squamous cell carcinoma, followed by lymphoma [10]. While tobacco and alcohol are the traditionally established risk factors, human papilloma virus also plays a role in tonsillar malignancy [11]. Immunosuppression may contribute to the development of tonsillary carcinoma [12]. However, to date, there is no evidence linking chemotherapeutic agents to the development of tonsillary cancer.

Case description

The patient is a 61-year-old Asian male who initially presented in October of 2001 with symptoms including

depression. Subsequently, he developed difficulty understanding the spoken English language, while maintaining good control of Mandarin (his primary language). A brain MRI in May 2002, revealed a large left temporoparietal irregularly contoured and enhancing mass measuring approximately 5.9 × 5.2 × 5.7 cm in maximal dimensions (Fig. 1a). The patient was brought to the OR that month and underwent gross total resection of the mass, using speech mapping and frameless computer-assisted navigation. Pathologic examination confirmed the diagnosis of GBM. Follow-up MRI on post-operative day #1 demonstrated minimal faint enhancement consistent with gross total resection of the enhancing mass (Fig. 1b). The patient's speech deficit improved within 1 month of surgery. The patient then received radiotherapy according to standard protocol with concomitant and adjuvant TMZ for six cycles. The patient then strongly wished to continue treatment with TMZ and was maintained on TMZ cycles at 6-week intervals. The patient had follow-up MRI scans twice a year. His most recent MRI, in May 2008, was negative for recurrent tumor (Fig. 2a). The patient was doing well neurologically, remaining at his baseline, with a Karnofsky score of 100, and fluent speech in both languages.

In May of 2007, the patient developed discomfort and a sense of fullness in the left side of his throat. Physical examination showed a large left sided tonsillar mass. CT of the neck confirmed the presence of a left-sided tonsillar mass with mild enhancement (Fig. 2b). Positron emission tomography demonstrated significantly increased FDG uptake in the left tonsil as expected, as well as mildly increased uptake in the right tonsil and several lymph nodes bilaterally. The patient underwent a biopsy of the tonsillar mass in June 2007. Histopathology was consistent with squamous cell carcinoma, negative for HPV

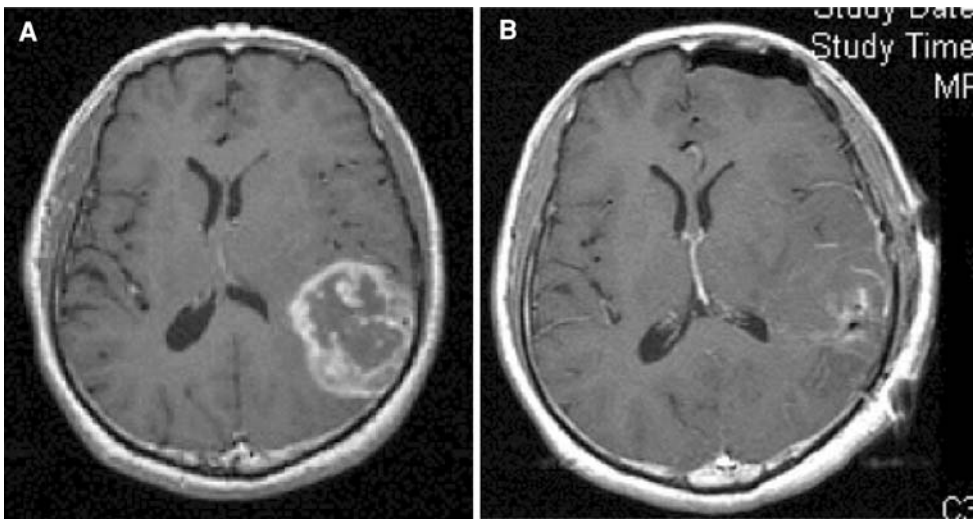

Fig. 1 Initial presentation and resection. **a** Pre-operative brain MRI with contrast showing a left temporoparietal irregularly contoured enhancing mass with pathology consistent with GBM. **b** Brain MRI with contrast 24 h after surgery shows minimal faint enhancement in the surgical bed, consistent with gross total resection

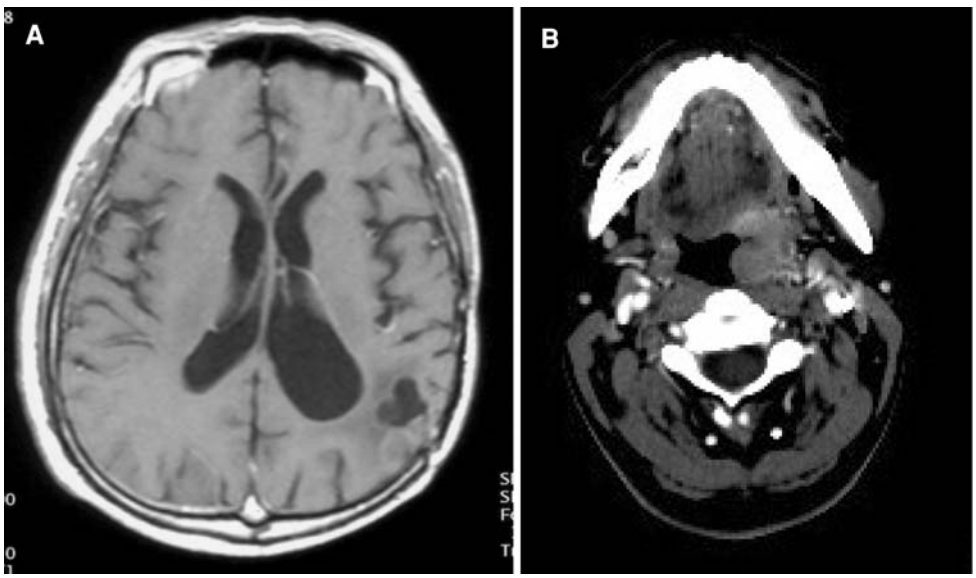

Fig. 2 Long-term follow-up after surgical resection, radiotherapy, and TMZ (both concomitant and adjuvant) for over 6 years. **a** Brain MRI with contrast showing lack of recurrence 6 years post-resection. **b** Neck CT showing a left tonsillar mass with pathology consistent with squamous cell carcinoma

(wide-spectrum, as well as strains 6, 11, 16, 18 tested specifically). The patient was treated with both radiation and chemotherapy (taxol and carboplatin). He continues to do well and has started eating again.

Discussion

This case highlights a patient with a history of GBM and an unusual course, significant for an extended survival time on long-term treatment with TMZ and subsequent diagnosis of tonsillary carcinoma, a new solid organ malignancy. This raises the question of potential oncogenic effect of this drug in the presence of prolonged intake and survival exceeding the median expected for GBM patients.

The study establishing significant survival benefit of TMZ spanned the course of 2 years and was based on six cycles of adjuvant treatment [2] leading to practice guidelines that recommend 6 months of treatment after radiation and surgery [3]. In this case, the patient wanted to continue TMZ for 6 years. There are no readily available data in the literature regarding the use of TMZ beyond the standard 6 months. Part of the difficulty may lie in the dismal survival rates, with 5 and 10-year survival rates in the 55 to 64 year age group of 1.4 and 0.5%, respectively [1].

To date, the only reported treatment-related malignancies associated with TMZ have been associated with the hematopoietic system, specifically myelodysplastic syndrome, developing into acute myeloid leukemia [5, 6] and aplastic anemia [7, 8]. To the best of our knowledge, there are no reports of treatment-related solid organ malignancies after TMZ treatment. Does the case reported here represent the first incidence of TMZ-related solid organ malignancy or is it an incidence of dual pathology?

TMZ is an alkylating agent whose cytotoxicity is mainly based on the methylation of guanine bases at the O6 and N7 positions, resulting in nucleic acid transitions. Other mechanisms of action include autophagy, both directly [13] and with the use of a sensitizer [14]. In vivo studies using murine bone marrow cells demonstrated that mutational load increased by a factor of 22 with TMZ treatment, mostly point mutations [15]. These data highlight TMZ's mutagenic potential and raise the possibility of this occurrence in humans, particularly with long-term exposure to TMZ. This would be more likely to translate to leukemic malignancies. However, it could be applicable to solid organ malignancies, lending support to this case as TMZ-related malignancy. The fact that the tonsillar carcinoma in this case was negative for HPV (recently implicated in its development) lends further support to this case as treatment-related etiology.

Conversely, this case could represent an incidence of dual pathology. There has been one case report in the literature of concurrent GBM and tonsillar carcinoma [16]. In this case, the patient first presented with tonsillar carcinoma. During routine imaging to determine the extent of the mass, a ring-enhancing lesion was revealed in the left temporal lobe. The patient underwent a left craniotomy for gross total resection and pathology was consistent with GBM. The patient subsequently underwent resection of the tonsillar neoplasm and pathology confirmed squamous cell carcinoma that was positive for HPV. Although the authors speculated on possible genetic links, there was no obvious association between malignancies, leading to the conclusion of two separate processes. The case presented in our report was HPV negative, but there are still unknowns to the etiology of tonsillar carcinoma such that dual pathology cannot be ruled out.

In conclusion, as the number of patients with prolonged survival after diagnosis and treatment of malignant gliomas with TMZ increases, the issues surrounding long-term use of TMZ will become increasingly relevant and warrant careful clinical and laboratory investigation.

Conclusions

We present the unusual case of a patient with GBM who remained recurrence-free for 6 years after treatment with surgical resection, radiotherapy and chronic TMZ, and subsequently developed tonsillary squamous cell carcinoma. This represents a possible treatment-related solid-organ malignancy; however, the occurrence of dual pathology cannot be ruled out. The risks and benefits of long-term TMZ are unknown, and as patient survival is prolonged, will become increasingly relevant.

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