The influence of postoperative infection in survival of patients with high-grade gliomas

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ABSTRACT

High-grade gliomas are the most common type of brain tumors. Of these, glioblastoma account for 60-70% and despite treatment carries a dismal prognosis. Postoperative surgical site infection has been associated with prolonged survival. Herewith, we present a case of glioblastoma and a case of anaplastic oligoastrocytoma that developed postoperative infection of the surgical site and had prolonged survival. A thorough literature review is also presented.

Key words: Glioblastoma, high-grade glioma, infection, survival

INTRODUCTION

High-grade gliomas are the most common type of primary brain tumors and carry a dismal prognosis.[1] Glioblastoma is by far the most common type occurring in adults. This devastating disease is usually incurable and despite aggressive treatment the median survival time remains in the range of 15 months.[1] Median survival for anaplastic tumors is usually 2-3 years with anaplastic oligodendroglioma having a better survival.[2] There have been reports that patients with postoperative infection of the craniotomy site experienced long term survival.[3,4] Herewith, we report on two cases of high-grade gliomas with confirmed postoperative infection and prolong survival.

CASE REPORT

Case 1

A 48-year-old woman underwent a brain magnetic resonance imaging (MRI) because of persisted headache and dizziness. A left frontal lesion (4.2 cm × 3.7 cm × 5 cm) with prominent peri-focal edema and mass effect was revealed. The lesion enhanced after gadolinium administration, The Karnofsky performance scale (KPS) score was 100. The patient underwent a left frontal craniotomy with radical resection of the lesion. Histological examination revealed the presence of a glioblastoma. The postoperative KPS at the time of discharge was 100. The patient received concomitant temozolomide (TMZ) with radiotherapy (60 Gy) followed by adjuvant TMZ. Eleven months later the patient had a generalized seizure. Follow-up MRI revealed a lesion suspicious of tumor recurrence. Brain single-photon emission computed tomography (SPECT) with ^{99m}Tc-tetrofosmin demonstrated increased tracer uptake suggesting tumor recurrence. The patient was re-operated, and carmustine wafers were placed around the resection cavity. The postoperative period was uneventful, and the patient was discharged home on the 7th postoperative day. One week later the patient was hospitalized because of discharge from the surgical wound. Wound cultures were obtained. Identification and antimicrobial susceptibility of the microorganisms were performed by the automatized VITEK 2 System (BioMerieux, France). The results showed the presence of *Staphylococcus haemolyticus* (coagulase-negative *Staphylococcus*, CoNS) resistant to penicillin, oxacillin, levofloxacin, moxifloxacin and gentamycin. The patient received proper antibiotic treatment, and the infection was resolved. The patient remained free of disease for 27 months when recurrence was noted on follow-up MRI. Anti-VEGF treatment was administered; however, she died 3 months later. Her overall survival was 42 months.

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Case 2

A 22-year-old man underwent a brain MRI because of seizures. The MRI revealed a 5 cm × 3.2 cm × 4.3 cm left frontal lesion. The lesion had a heterogeneous cystic and solid appearance that enhanced after gadolinium administration. The patient underwent surgical resection, and gross total excision was performed. Histological examination revealed the presence of an astrocytoma Grade II. Postoperative radiation treatment was administered. On follow-up MRI 7 years later a lesion suspicious for tumor recurrence was noted. The patient was re-operated, and the histology revealed the presence of an anaplastic oligoastrocytoma. The patient received TMZ-based chemotherapy. Nevertheless, 28 months later the patient had uncontrolled seizures. Brain MRI demonstrated a lesion suspicious of tumor recurrence. Brain SPECT with ^{99m}Tc-tetrofosmin was positive for recurrent disease. The patient was re-operated. A new recurrence was noted 23 months later, and the patient re-operated, carmustine wafers were placed around the resection cavity. Postoperatively, the patient had fever and discharge from the wound. Brain CT showed findings consistent with infection and there was contrast enhancement. The patient was re-operated, and craniectomy was performed. Cerebrospinal fluid cultures showed the presence of *Staphylococcus epidermidis* (CoNS) resistant to penicillin, oxacillin, erythromycin and clindamycin. After proper antibiotic treatment, the patient improved. The patient did not show any sign of the tumor reappearance for 37 months until recurrence was noted. Two months later he died. The overall survival was 14 years.

DISCUSSION

High-grade gliomas are the most common brain tumors in adults and are highly malignant.[2] Treatment includes surgery, postoperative radiotherapy, and concomitant and adjuvant chemotherapy.[2] Nevertheless, even receiving the same treatment, the clinical outcome of patients varies significantly.[1] Age, 1p19q deletion status and isocitrate dehydrogenase (IDH) mutational status are of prognostic significance.[5,6]

A survival benefit for patients that developed postoperative infection in the tumor removal site has been reported.[3,4] Postoperative infection is generally considered when wound and/or bone flap infection, cerebral abscess, or meningitis, occur within 2 months from surgery.[2] Its incidence has been reported to range between 0.75% and 2.3% for intracranial operations.[7] De Bonis *et al*. studied 197 patients operated for glioblastoma and found 10 cases of postoperative bacterial infection. Patients that developed infection had a median survival of 30 months whereas patients without postoperative infection had a median survival of 15 months. The difference was statistical significant. In 5 cases there was a surgical abscess, in 3 cases abscess and wound infection and in 2 cases surgical wound and bone flap infection required surgical revision. In 6/10 cases *Staphylococcus aureus* was isolated.[2] In the present study, the patient with glioblastoma had an overall survival of 42 months. In a previous study in our institute, the median survival of patients with glioblastoma was 15.5 months.[8] Bowles *et al*. also reported 4 cases of malignant brain tumors with prolonged survival after postoperative infection. In those cases, *Enterobacter aerogenes* was isolated. The authors suggested that in addition to the bacteria direct oncolytic effect, an immune adjuvant responses to tumor suppression might play a role.[4] Nevertheless, Bohman *et al*. did not find a survival advantage in 18 patients with postoperative infection after glioblastoma resection out of 382 patients included in their study.[9]

Regarding experimental data, a recent study showed that intracerebrally implanted heat-inactivated staphylococcal epitopes mixed with 9L gliosarcoma cells in Wistar rats, resulted in significant prolong survival than controls. In one case there was complete regression of an already grown mass.[10] William Coley, a pioneer in immunotherapy, was the first injecting a mixture of live streptococcus bacilli and subsequently heat-killed *Streptococcus* into tumors and managed to induce remission of inoperable sarcomas.[11] This vaccine was also successful in cases of melanoma and lymphomas.[12] According to Coley, the induction of fever was a key element.[12] The inflammation cascade induced by bacteria and the presence of factors such as interferon-alpha, tumor necrosis factor-alpha, interleukin-2, have been considered as the cause of this effect.[12] Tanaka *et al*. injected intratumorally an immunopotentiator, Picibanil, in 13 patients with brain tumors.[13] Picianil was a low virulent mutant strain of Lancefield's Type 111, Group A *Streptococcus pyogenes*. The results showed significant tumor regression in 6/12 patients for whom CT was performed.[13] More recently, Jeys *et al*. investigated the effect of postoperative infection in patients treated for osteosarcoma, using endoprosthetic replacement and neo-adjuvant chemotherapy. The results showed that patients who developed an infection had a significantly longer survival. Furthermore, infection was an independent prognostic factor on cox regression analysis.[14] Ruckdeschel *et al*. reported improved survival rates for patients who developed the empyema after lung cancer compared with noninfected patients.[15]

In the present study, both patients were treated at recurrence with carmustine wafers that were placed around the resection cavity. Carmustine wafers have been shown to yield better survival rates of 1-2 months in primary high-grade gliomas.[16] Thus, the prolonged survival of both patients cannot be attributed to the implanted wafers.

In conclusion, the role of infection provides a rationale for further research in cancer treatment. Certainly, there is a need for larger studies that may provide more accurate answers. This may also lead to a subgroup analysis that would better define if patients survival is influenced by bacterial strain, location of the infection or time to infection.

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