Case Report

Undifferentiated Sarcoma Induced by BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) Wafers

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Abstract
Malignant gliomas are the most aggressive type of brain tumor, with poor prognosis after recurrence. The most common site of recurrence is within two centimeters of the resection margin. BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) wafers (“BCNU wafers”) are used to deliver local high dose chemotherapy around the resection cavity, and serve as a treatment option for treating malignant gliomas in an effort to delay tumor recurrence. We present the case of a fifty three year old woman who developed rapidly progressive sarcoma in her bone flap after the placement of BCNU wafers. Initially the patient underwent resection and conventional radio-chemotherapy treatment for her disease. Once the glioma recurred, a new resection was performed and the patient underwent placement of BCNU wafers. Soon after the placement of the BCNU wafers, an aggressive sarcoma developed in the patient’s bone flap which eroded rapidly through her scalp. The patient died soon after her sarcoma diagnosis. As the patient’s bone flap was not exposed to any mutagens, such as radiation or chemotherapy, and the only chemotherapy the bone flap came into contact with was the nitrosourea from the BCNU wafers, we believe that the local chemotherapy was directly responsible for inducing the rapidly expanding sarcoma which ultimately led to the death of the patient.

INTRODUCTION
Malignant gliomas are the most common type of primary brain tumor. The prognosis after recurrence is poor and treatment options after failure of second line chemotherapy are quite limited [1, 2]. Malignant gliomas typically recur within two centimeters of the resection bed. The development of new chemotherapeutics is difficult due to the blood-brain barrier which makes the administration of chemotherapeutics a challenge for treating these malignances.

The development BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) wafers (Gliadel, Guilford Pharmaceuticals, Baltimore, MD) provided a way to give localized high dose chemotherapy to the resection cavity within two centimeters of the resection margins with minimized systemic effects [1]. The BCNU wafers are biodegradable and are implanted in the resection cavity immediately after the tumor resection, thus providing a controlled release of local chemotherapy over approximately three weeks to the tissues surrounding the resection bed.

Previous studies using BCNU wafers for the treatment of Glioblastoma Multiforme (GBM) showed improved survival rates with no marked increase in adverse effects. However, there was a marked increase in concern for complications associated with the use of BCNU wafers. These complications included malignant cerebral edema, resection cavity cyst formation, cerebrospinal fluid leak, wound healing abnormalities, and increased perioperative seizure activity. However, in the largest Gliadel cohort to date (n = 120), there was no increased incidence of any of these complications [3]. The most common complications with these events were thrombosis, pulmonary embolism, and hematotoxicity [3].

In this report we are describing the first case of secondary malignancy induced by BCNU wafer placement for the treatment of GBM.

CASE REPORT
History, Examination, and Operations
We present the case of a fifty three year old woman with glioblastoma multiforme who developed a secondary undifferentiated sarcoma of the bone flap after the placement of BCNU wafers. At the time of initial diagnosis, the patient underwent resection of a
right parietal enhancing mass at an outside hospital. The pathology was consistent with Glioblastoma Multiforme (GBM, WHO grade IV). Her original bone flap has been placed in storage. The patient underwent both radiation therapy and temozolomide chemotherapy. The tumor recurred two years later and in October 2010 the patient underwent image guided re-exploration of the left parieto-occipital craniotomy with medial craniotomy extension for microsurgical resection. We confirmed gross total resection of the recurrent GBM. Patient underwent placement of BCNU wafers chemotherapy followed by expansion duraplasty with bovine pericardium and cranioplasty with the patient’s original bone flap from storage. This was followed by complex scalp mobilization with extensive bilateral subgaleal relaxing incisions for primary closure of the wound. At four months post-surgery, patient was functioning at Karanofsky performance status of 90 with a hemianopsia. Six months after her resection she presented to clinic with a rapidly enlarging scalp mass near the inferior-posterior aspect of her incision for the past 4-6 weeks. She had no drainage from her wound, and no fevers, chills or night sweats. The scalp mass measured 4 cm in diameter and was soft and nontender. There was no skin breakdown over the mass or signs of drainage or infection at the site of the craniotomy incision.

Patient underwent a needle biopsy procedure during February 2011. The pathologic examination of the biopsy was consistent with undifferentiated sarcoma. The patient underwent en bloc resection of the involved area of her scalp in addition to removing her bone flap and her involved dura, with dural reconstruction and trapezius flap with full thickness skin graft and reconstruction. Unfortunately, both the sarcoma and the GBM recurred, and the patient passed away within two months from the last surgery.

Imaging results:
The head CT with bone windows shows that the craniotomy flap had been partially moth-eaten and eroded by a soft tissue mass (Figure 1a). A bone scan performed at the time of the diagnosis of the mass showed that the mass had increased radioisotope uptake.

The brain MRI scan obtained at the time of this diagnosis showed that the mass extended into the epidural space, and it was contiguous with the dura near the sagittal sinus (Figure 1b). A brain MRI obtained one month after the resection of the sarcoma showed recurrence of tumor in the right occipital area, at the site of the previous resection of the bone flap and soft tissue mass, directly underneath the extensive plastic reconstruction.

Pathological Findings:
Cultures obtained under sterile conditions were tested negative for bacteria on gram stain, aerobic, anaerobic, AFB and fungal cultures.

On microscopic pathologic examination the operative specimens from biopsy in June 2010 indicated GBM, showing GFAP positivity and the paucity of reticulin (Figure 2a-c).

On microscopic pathologic examination the operative specimens from biopsy in February 2010 indicated sarcoma showing cellular pleomorphic neoplasm (Figure 2d-f). At autopsy, gross pathologic examination of the brain showed massive tumors invading the brain. On microscopic examination, the left occipital tumor was consistent with undifferentiated sarcoma (Figure 2g-i). The pathologic examination showed pleomorphic cellular neoplasm that resembled what was seen in the Feb 2011 operative specimen. The reticulin stain showed the presence of a rich reticulin network (Figure 2h), while the GFAP staining of the
sarcoma sections tested negative (Figure 2i). The left parietal tumor was GFAP-positive and reticulin-negative and very consistent with GBM (Figure 2j, k).

Figure 2: [a-c] Pathology specimen from resection June 2010: [a] GBM (H&E, x50). [b] Some tumor cells show GFAP immunoreactivity (IHC, x200). [c] The tumor is devoid of reticulin (Reticulin stain, x100). [d-f] Pathology specimen from February 2011: [d] Blue round cell sarcoma (H&E, x200). [e] The tumor shows complete absence of GFAP immunoreactivity (IHC, x200). [f] The tumor shows reticulin rich staining around each individual neoplastic cell (Reticulin stain, x200). [g-i] Autopsy specimens left occipital lesion: [g] The section demonstrates blue round cell neoplasm consistent with sarcoma that resembles what was seen at Feb 2011 biopsy (H&E, x200). [h] The sarcoma has reticulin rich network surrounding each individual cell (Reticulin stain, x200). [i] The tumor shows completely negative immunostaining for GFAP (IHC, x200). [j-k] Autopsy specimen form left parietal lesion: [j] The section shows neoplastic cells with rounded hyperchromatic nuclei (H&E, x400). [k] Some tumor cells show immunoreactivity for GFAP (IHC, x400).
DISCUSSION

Malignant gliomas are highly aggressive primary brain tumors [1] with very few treatment options following recurrence [2,3]. BCNU wafers are commonly used in the treatment of GBM to deliver high dose chemotherapy within two cm of the tumor resection margins [2]. Known complications of this form of treatment are poor wound healing, seizures, intracranial infections and brain edema [2]. Cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with BCNU wafers, including one case leading to brain herniation and death [4]. To date, no secondary malignancies have been reported with placement of BCNU wafers. We present the case of a fifty three year old woman, who developed undifferentiated sarcoma following the placement of BCNU wafers. This is possibly the first case of BCNU wafers induced secondary malignancy reported in the literature.

In our opinion, it is highly possible that BCNU wafer implantation was responsible for the development of the undifferentiated sarcoma by acting as a mutagen which induced a mutation in the bone flap tissue. There were approximately four months between the time the Gliadel wafers were placed and the time the sarcoma was first diagnosed. The bone flap was completely naïve to radiation or chemotherapy prior to the BCNU exposure. The bone flap had been placed in storage, in standard bone flap storage media at the Orange County Tissue Bank. While the patient’s brain and surrounding tissues had been exposed to temozolomide chemotherapy and radiation before the placement of BCNU wafers, the tissue from the bone flap had not been previously exposed to any mutagens. Although Bhaskar et al. claim that the bone flaps do not have viable osteoclasts after storage for more than 6 months at -30 degrees Celsius [5]. They also agree that different storage media can affect the preservation of osteoclasts during storage [5]. The storage media used by the Orange County Tissue Bank was different from the storage media used in the Bhaskar et al. study. Therefore, we believe that viable osteoclasts were present in the bone flap tissue.

At the time of the diagnosis of the mass osteomyelitis, probability of recurrence of the GBM, radiation-induced scalp mesenchymal malignancy or BCNU wafer chemotherapy-induced scalp mesenchymal malignancy was entertained. The pathology examination confirmed the diagnosis of sarcoma. The intraxial high-grade brain tumor was GFAP-positive and reticulin-negative which was consistent with GBM. The sarcoma was GFAP-negative and reticulin-positive. The presence of rich reticulin network is indicative of sarcoma. The two tumors were therefore completely distinct from each other. Furthermore this tumor is not a gliosarcoma. A gliosarcoma consists of a glioma admixed with sarcoma cells. However, these tumors are completely separate neoplasms.

BCNU induced secondary malignancies are not uncommon. Secondary malignancies were reported during animal studies - Zeller et al reported cases of development of secondary malignancies in rats after cure of acute leukemia with BCNU treatment [6]. Horning et al reported that six out of seventy four patients who received BCNU for the treatment of refractory Hodgkin’s disease developed secondary malignancies [7], two patients had solid tumors, and four patients developed myelodysplasia/leukemia. Secondary and acute leukemias have been described in the past at a rate of 5% to 10 % [8, 9] with administration of BCNU chemotherapy. In these cases the secondary malignancies developed as a result of systemic BCNU chemotherapy and not from locally administered treatment with BCNU wafers.

Secondary malignancies induced by radiation are not a rare occurrence either. A significant number of acute lymphocytic leukemia survivors who have received cranial radiation subsequently develop secondary malignancies such as meningiomas [10] or sarcomas [11, 12]. Our patient received radiation as part of her treatment. However, the bone flap had been in storage and thus it did not receive any radiation. Therefore the sarcoma which arose from the bone flap cannot be attributed to the radiation treatment.

In conclusion we believe that this case constitutes the first report of secondary malignancy induced by BCNU wafers. It is very likely that the BCNU wafers acted as a mutagen in this patient and induced the bone flap tissue, which was naïve to both radiation and chemotherapy, to form an aggressive sarcoma.

DISCLOSURES

Authors declare that they have no any conflict and disclosure.

REFERENCES


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