Variation in response to CCNU of glioblastoma multiforme in brain and cervical lymph node

Case report

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The case is reported of a patient in whom a cervical lymph node metastasis decreased in size while the primary intracranial glioblastoma continued to grow during chemotherapy with CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea). This is the first such case reported in humans. Possible explanations for this phenomenon are discussed.

KEY WORDS • glioblastoma • extracranial metastasis • chemotherapy • nitrosourea • CCNU

The failure of a malignant glioma to respond to chemotherapeutic agents is in part related to the sensitivity of the tumor cells to the drug, but it is also dependent on the ability of the drug to reach the dividing tumor cells. The nitrosoureas are lipid-soluble and, when given systemically, easily penetrate the brain and the brain tumor. One might expect that the response of the brain tumor would be related mainly to the sensitivity of the tumor cells to the nitrosourea. We have had the opportunity to study a patient who developed palpable cervical metastases from a glioblastoma. After administration of CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), the peripheral tumor appeared to shrink but at the same time the intracranial tumor continued to grow. The metastatic tumor eventually disappeared after chemotherapy and radiation, but the primary neoplasm killed the patient.

Case Report

This 27-year-old female nurse presented to the Vancouver General Hospital in January, 1977, with a history of focal left-sided motor seizures.

Operations and Course. On examination, she was neurologically normal, but a computerized tomography (CT) brain scan showed an abnormality in the right frontal lobe. On January 18, 1977, a low-grade astrocytoma was subtotally removed. Postoperatively, the patient experienced occasional seizures despite anticonvulsant therapy; otherwise she had no neurological abnormalities.

She was readmitted on May 18, 1980, complaining of headaches; on examination, she had bilateral papilledema, but no focal neurological deficits. A repeat CT scan showed a large irregular enhancing lesion in the right frontal lobe with extension across the midline. On May 22, 1980, partial removal of the tumor was accomplished, and the pathology now revealed considerable anaplasia. Postoperatively, the patient received cobalt-60 radiotherapy to the region of the tumor. The total dose was 5000 rads in 25 fractions over 5 weeks. Thereafter, she remained clinically well, and the tumor was seen to decrease in size on repeated CT brain scans.

In October, 1980, the patient developed a painless mass in the submental region. This was removed and was proved to be a metastatic glioblastoma. Chest radiographs, bone scan, and liver function tests were normal. She was given a course of adriamycin and cyclophosphamide, and then received radiation therapy to the submental region, for a total dose of 3000 rads in 10 fractions over 2 weeks.

In July, 1981, another swelling appeared in the right anterior triangle of the neck. This rapidly enlarged over 1 month and analysis of needle aspiration revealed an anaplastic tumor. She was given a single dose of CCNU on August 27, 1981, and 1 week later the neck mass had decreased from 7 × 8 cm to 5 × 5 cm. The neck
Response of glioblastoma multiforme to CCNU

FIG. 1. Lymph node biopsy specimen. Left: Photomicrograph of the metastatic tumor showing sheets of small, undifferentiated cells, among which lie occasional multinucleated giant tumor cells. H & E, × 383. Right: Electron micrograph of the same specimen. The tumor cells have irregular nuclei, often with prominent nucleoli, and angular or rounded cytoplasm. There are mitochondria, but few other organelles, and no junctions. × 4200.

was then irradiated to a dose of 3500 rads in 15 fractions over 3 weeks, and by early October, 1981, the cervical mass was no longer palpable. Chemotherapy with CCNU, procarbazine, and vincristine was continued, and there never was any further clinical evidence of metastatic disease.

The brain tumor remained stable on CT scanning until July, 1981, when the cervical metastasis was identified. On a repeat CT scan in October, 1981, the tumor in the right frontal lobe was noted to be enlarging, despite the definite response of the cervical metastasis to CCNU at the same time. The brain tumor continued to enlarge, and in January, 1982, the patient showed signs of increased intracranial pressure; shortly thereafter she developed a left hemiparesis. On February 18, 1982, a partial resection of the tumor was performed, and she was given experimental immunotherapy with intratumoral mononuclear cell infusions. The histopathology of the tumor was that of a glioblastoma multiforme. She died on March 30, 1982.

Postmortem Examination. At autopsy, the right frontal lobe was found to be replaced by a large, mostly hemorrhagic and necrotic tumor. It extended across the corpus callosum a small distance into the left frontal lobe. Foci of gelatinous viable glioma and an occasional small cyst were noticeable. The dura was tightly adherent to the frontal lobe. The tumor extended 10 cm back to the striatum. A large recent hemorrhage occupied the posterior part of the neoplasm and appeared to be the direct cause of death. Subfalcine and hippocampal herniations had occurred, and there were Duret hemorrhages in the brain stem. No masses were palpable in the submental region, where the lymph node had been biopsied, and dissection of the neck at the site of the needle aspiration and elsewhere did not reveal any residual tumor. The bone marrow contained small gray areas. No other gross tumor was found anywhere else in the body.

Pathological Examinations. The tumor excised in 1977 was gray and firm. Microscopically it consisted of well differentiated astrocytes with scanty cytoplasm and thin processes. A specimen obtained at the second resection in May, 1980, revealed considerable anaplasia in some parts, evidenced by increased cellularity, atypicality of cells (including occasional multinucleated giant cells), and vascular proliferation. The last tumor removed in 1982 still showed large areas of low-grade astrocytoma but also foci of a highly malignant glioblastoma, composed partly of large atypical gemistocytic astrocytes, and partly of small undifferentiated cells with many mitoses. Dense fibrous scar, infiltrated by a few lymphocytes, adhered to the surface of the brain, and the vessels were hyalinized.

The biopsy of the submental lymph node, obtained in October, 1980, revealed a tumor in the peripheral sinuses and also replacing a good deal of the node. The cells were irregular in outline and loosely arranged in small sheets; occasional multinucleated giant cells were present. The appearance was consistent with a glioblastoma multiforme (Fig. 1 left). Glial fibrillary acidic
protein (GFAP) stains were negative. Electron microscopy showed rounded cells, closely apposed to each other (Fig. 1 right). Cytoplasmic processes were only rarely seen in loose areas and there were no glial filaments. The dearth of organelles and lack of desmosomal attachments and cytoplasmic interdigitations indicated that the tumor was glial and not epithelial. Examination of the specimen from the cervical mass obtained at aspiration in July, 1981, yielded clumps and a diffuse scatter of anaplastic cells similar to those seen in the lymph node section.

Microscopically, the glioma in the right frontal lobe consisted partly of large bizarre gemistocytic astrocytes with numerous giant forms, and partly of small undifferentiated cells (Fig. 2). These two patterns merged with each other. On GFAP preparations only the large cells were weakly stained, while nontumorous reactive astrocytes were strongly impregnated. Phosphotungstic acid hematoxylin (PTAH) stains demonstrated glial fibrils in the cytoplasmic processes, but not in the perikaryon of the large cells. In sections from the root of the patient’s neck, occasional small lymph nodes were encountered but no tumor. However, random sections from the vertebrae, ribs, and sternum contained multiple fibrosed metastases of glioblastoma multiforme. Here also, as in the lymph nodes, only the very anaplastic, small-cell glioblastoma had metastasized.

Discussion

Extracranial metastases from glioblastoma multiforme are rare, but have been well documented. In many instances the cervical lymph nodes have been involved, and, occasionally, the cervical lymph node metastasis has been the first indication of the glioblastoma.

The occurrence of a palpable metastasis in the neck in our patient allowed us to readily document the response of the tumor to treatment and to compare the effects of chemotherapy on the cervical tumor versus the intracranial tumor. It was striking that while the cervical tumor was actually decreasing in size, indicating sensitivity to CCNU, the intracranial tumor was enlarging. This phenomenon, whereby an intracerebral tumor continues to grow while the same tumor in an extracerebral location diminishes in size in response to systemic chemotherapy, has been documented in both animal models and humans. Cyclophosphamide was shown to be effective against intraperitoneal and intramuscular mouse Ehrlich carcinoma and sarcoma 180, while the same intracerebral tumors were little affected.

In humans, intracerebral metastases progressed while tumor in systemic sites was responding to adriamycin. Our patient is the first in whom a documented systemic metastasis from a glioblastoma has been shown to regress with the use of a nitrosourea while the intracerebral tumor continued to grow. Possible explanations include inadequate drug delivery to the intracranial tumor, different sensitivities of the intra- and extracerebral tumors, or a combination of these factors. It was interesting that, whereas the tumor in the brain was made up of large and small cells, the metastatic tumor contained only the small-cell population. It may be that this small-cell population was more sensitive to the CCNU than was the brain tumor as a whole. This phenomenon, where metastatic tumors are composed of cells more sensitive to chemotherapeutic agents than the majority of cells in the primary tumor, has been observed in other tumor types and is compatible with the somatic mutation theory, which proposes that the primary tumor mass, by virtue of being the oldest tumor mass, would be expected to be the most drug-resistant.

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Biochem Pharmacol 24:21–26, 1975


Manuscript received November 12, 1984.

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