Glioblastoma developing at the site of a cerebellar medulloblastoma treated 6 years earlier

Case report

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The authors report the highly unusual development of a glioblastoma multiforme at the site of excision of a medulloblastoma 6 years earlier. The patient was operated on for a cerebellar medulloblastoma at the age of 13 years. Postoperative treatment included irradiation and chemotherapy. Six years later, a glioblastoma multiforme was found at the original site of the medulloblastoma. Intensive multimodality treatment is considered the likely cause for the later tumor development.

KEY WORDS • glioblastoma multiforme • medulloblastoma • radiotherapy • chemotherapy • brain neoplasm

Cerebellar medulloblastoma and glioblastoma, although grouped together by the World Health Organization (WHO) classification, are distinct tumor types affecting patients at different ages and locations. They also differ in prognosis. Little attention has been given to their relationship. We report here the case of a 21-year-old man in whom a glioblastoma developed at the cerebellar site where 6 years earlier a medulloblastoma had been removed; the patient had then undergone irradiation and chemotherapy.

Case Report

This patient was first admitted in 1979, at the age of 13 years, because of occipital headache, vomiting, and marked head tilting to the left during the previous 3 months. Neurological examination revealed cerebellar ataxia, bulbar speech disturbance, hypodiadochokinesia of the right upper extremity, bilateral horizontal nystagmus, and papilledema. Ventriculography and computerized tomography (CT) showed obstructive internal hydrocephalus and a large lesion in the right cerebellar hemisphere compressing the fourth ventricle and partially extending into the left hemisphere. Operative resection was performed with the aid of microsurgical techniques. The tumor extended from the medullocervical junction to the tentorial hiatus without infiltration of the tentorium. There was a distinct border between the tumor and the cerebellar parenchyma due to capsular connective tissue. The tumor was richly vascularized, soft, and reddish-gray. On the right dorsolateral surface of the medulla oblongata, the tumor capsule adhered to the brain stem. Except for this small area, total removal of a tumor measuring 6 × 5 × 5 cm was achieved.

On histological examination, the tumor was highly cellular and uniform in appearance. The tumor cells had rounded or elongated nuclei and ill-defined cytoplasm (Fig. 1A); mitoses were moderately numerous. A few Homer Wright rosettes with a delicate central neurofibrillary network (Fig. 1B) were seen in areas with immunoreactivity for neuron-specific enolase. A prominent network of reticulin fibers was present in many areas of the tumor, but there were also large areas without reticulin. There was no evidence of glial differentiation as indicated by phosphotungstic acid hematoxylin stain for glial fibers or by immunocytochemical tests for glial fibrillary acidic protein (GFAP). A diagnosis of partly demoplastic medulloblastoma with signs of neuroblastic differentiation was made.

Postoperatively, the cranium was irradiated with a dose of 60 Gy from a 6-MeV x-ray source, accompanied and followed by nine courses of chemotherapy with vincristine and CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) in accordance with the recommenda-
FIG. 1. Photomicrographs of the medulloblastoma. A: This highly cellular tumor is composed of darkly staining cells with hyperchromatic nuclei and ill-defined cytoplasm. H & E, × 250. B: This Homer Wright rosette, formed of small dark nuclei surrounding a delicate central neurofibrillary network, indicates neuroblastic differentiation. Bodian silver, × 750.

FIG. 2. Computerized tomography scans. A: Control scan obtained in June, 1985, showing a large cavity at the original tumor site (Fig. 2A). For 6 years there was no evidence of tumor recurrence. The patient did well until the end of October, 1985, when at the age of 20 years he developed progressive right-sided hemiataxia, headache, vomiting, and speech disturbance. A CT scan showed moderate enlargement of the ventricular system and a large well-delineated enhancing mass at the original tumor site (Fig. 2B). A large, mostly soft, reddish-gray, partially necrotic tumor was radically resected by microsurgical techniques.

The histological features of this mass were strikingly different from those of the original tumor. The tumor cells were highly pleomorphic and had irregular hyperchromatic and sometimes multiple nuclei, broad cytoplasm, and distinct fibrillary processes (Fig. 3) which were immunoreactive for GFAP. The tumor cells tended to cluster around necroses, resulting in a pseudopalisading appearance (Fig. 3A); mitoses were numerous (Fig. 3B). Vascular changes included a telangiectatic pattern as well as marked endothelial proliferations, sometimes resembling glomeruli with broad reticulin fiber arrangements. A diagnosis of glioblastoma multiforme was made.

After the second operation, the patient received ra-
Glioblastoma following medulloblastoma

Fig. 3. Photomicrographs of the glioblastoma. A: Pleomorphic gliomatous tissue showing an area of pseudopalisading with central necrosis. H & E, x 160. B: Highly anaplastic irregular glial cells with hyperchromatic and sometimes multiple nuclei, frequent mitoses (arrows), and a glial fibrillary network. Few proliferating tumor vessels are seen. H & E, x 400.

diotherapy to the posterior fossa (total dose 55 Gy), supplemented by chemotherapy with a variety of cytotoxic drugs. He was able to work until November, 1986, when he developed cerebellar ataxia, crippling paresthesia of the right upper extremity, and slight motor impairment of the right hand. Magnetic resonance imaging demonstrated a high-intensity signal lesion in the right cerebellar region. Microsurgical exposure of the previous resection area revealed a large cyst containing xanthochromic fluid but no evidence of tumor recurrence. Histological investigation of the material removed at surgery showed no tumor tissue; the changes were interpreted as a postradiation lesion consisting of necrosis, gliosis, vascular fibrosis, and few pleomorphic giant nuclei of non-neoplastic appearance within the cyst wall. At follow-up examination in January, 1987, the patient was doing well.

The patient deteriorated rapidly in the spring of 1987, and died in June, 1987. Autopsy confirmed a huge area of postirradiation necrosis in the right cerebellar region, and glioblastoma multiforme spreading to the brain stem, hypothalamus, temporal lobe, and basal ganglia on the right. The histology was identical with that of the mass resected at the second operation. Additionally, the lungs contained a small superficial nodule of squamous-cell carcinoma.

Discussion

Since the description of the medulloblastoma as a clinicopathological entity, its differentiating potential along neuronal and glial cell lines has repeatedly been emphasized. Attention has also been drawn to the relationship between differentiating medulloblastoma and dedifferentiating cerebellar astrocytoma. Although the occurrence of primary malignant gliomas in the cerebellum has been reported in rare cases, and the development of gliomas has been described after radiation therapy for different conditions, occurrence of a malignant glioma at the site of a preexisting medulloblastoma is exceptional. Development of a cerebellar glioblastoma at the site of a medulloblastoma treated by multimodality therapy might be interpreted in four ways, as set out below.

The tumor might be a recurrence of the original neoplasm, but this is unlikely in view of the strikingly different histopathologies. However, remnant medulloblastomatous tissue might have differentiated and finally dedifferentiated along glial lines ("glioblastomatous" differentiation). The reportedly almost complete removal of, and the lack of glial differentiation in, the original tumor argue against this assumption. Furthermore, the first tumor appeared to differentiate along neuronal lines; such signs were lacking in the second tumor which had evidence of astroglial derivation. It must be admitted, however, that there is the possibility of phenotypic alteration of a recurrent tumor, as found previously in anaplastic gliomas after intensive irradiation and chemotherapy.

A de novo tumor might have been induced. Glial cells of the cerebellar parenchyma surrounding the medulloblastoma might have been transformed, possibly as a consequence of intensive postoperative therapy. It is accepted by most authors that neoplasms can be induced by irradiation and possibly also by cytotoxic agents, apparently due to the mutagenic capacity of the therapy. However, malignant gliomas which were attributed to previous irradiation for different conditions have been rarely documented. In our case,
the applied cytotoxic chemotherapy appears as the likely cause for the later tumor development, since at autopsy a carcinoma was also detected in the nonirradiated tissues of the lungs.

Tumorigenic matrix cells which originally gave rise to a medulloblastoma might have been reinduced to give rise to another neoplasm which may also originate from a primitive stem cell, such as the glioblastoma multiforme. It is conceivable that the applied chemotherapy and/or irradiation may have influenced this process, resulting in a completely different tumor type. The occurrence of the glioblastoma might be coincidental. This seems very unlikely, considering the age of the patient, the rarity of a cerebellar site of the glioblastoma, and the exact correspondence of the site of both tumors.

In conclusion, the applied intensive multimodality treatment seems pivotal for development of the secondary tumor, either by influencing tumor remnants or primitive stem cells, or by inducing a malignant tumor de novo, resulting in a new tumor phenotype. As the number of long-term survivors of brain tumors increases due to intensive combined treatment, more examples of such a previously poorly appreciated tumor development might occur.

References

9. Herpers MJ, Budka H: Primitive neuroectodermal tumors including the medulloblastoma: gial differentiation signaled by immunoreactivity for GFAP is restricted to the pure desmoplastic medulloblastoma ("arachnoidal sarcoma of the cerebellum"). Clin Neuropathol 4:12-18, 1985

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