Radiation-induced glioblastoma occurring 35 years after radiation therapy for medulloblastoma: case report

Abstract A 41-year-old man was admitted in June 2007 with a 1-month history of headache and cerebellar ataxia. At the age of 5 years, in May 1971, he had presented with headache, vomiting, and gait disturbance. Cerebral angiographical study demonstrated vascular shift caused by a mass lesion in the cerebellar vermis. He had immediately undergone partial removal. Histological diagnosis was medulloblastoma (MB). Postoperatively he received a total of 40 Gy radiation to the whole brain and 30.5 Gy to the spine without chemotherapy. He was again seen 35 years later with a radiation-induced glioblastoma (GB) that arose in the region of the original MB. The tumor was surgically removed, and he received radiotherapy and chemotherapy with ACNU, procarbazine, and vincristine. Postoperative irradiation reduced the size of the second tumor.

Key words Radiation-induced glioma · Medulloblastoma · OLIG2

Introduction

Malignant gliomas have been reported to arise in the radiation field of patients with previously radiation-treated brain tumors.1,3 Although the incidence of radiation-induced brain tumors is low at approximately 1%,4 it is an important complication. Brain tumors that develop after radiotherapy (RT) tend to be high-grade gliomas with astrocytic differentiation or glioblastoma (GB). The induction of second brain tumors by radiation-treated medulloblastoma (MB) has been documented; these tumors are more frequently seen in the cerebellum of children. In adults, they represent less than 1% of all brain tumors.5,6 Most recurrent MB are local in adults7 and children7; 75% recur within the first 2 years after initial treatment and 29% are seen after 5 years.

Here we report a 41-year-old man with a cerebellar glioblastoma that developed at the cerebellar hemisphere treated 35 years earlier by radiotherapy. The site of the MB was the cerebellar vermis; however, radiotherapy was performed for the whole posterior fossa. The second tumor manifested different histological features; it was diagnosed as a GB and fulfilled the criteria of radiation-induced neoplasm. Radiation-induced MGMT hypermethylation and p53 mutations may play a role in the development of a subgroup of radiation-induced gliomas (RIG),3 suggesting that these molecular alterations are directly involved in the genesis of postirradiation GB.2,4,8 We cannot unequivocally state that the GB in our patient is attributable to genetic changes because the 35-year interval between the first and second tumors appears to be excessively long. Our search of the literature found no other RIG arising after such a prolonged period after initial radiation treatment for MB.

Case report

Clinical course

In May 1971, at the age of 5, this patient was first admitted to our hospital with headache, vomiting, gait disturbance, and neck stiffness. Neither he nor his family had any known genetic diseases predisposing to cancer. Cerebral angiography revealed a hypervascular mass lesion in the posterior fossa. The tumor, grossly totally resected in June 1971, was histologically diagnosed as an MB. Postoperatively, he received a total of 40 Gy radiation to the whole brain including the posterior fossa and 30.5 Gy to the spine without chemotherapy. During the next 15 years, he was regularly followed by computed tomography (CT) and magnetic resonance imaging (MRI) studies; there was no evidence of recurrence up to 1987, and thus follow-up was stopped. He was readmitted in June 2007 at the age of 41 years with a 1-month history of headache and cerebellar ataxia. CT
revealed a large, poorly delineated enhanced mass with areas of calcification at the original tumor site. MRI demonstrated an irregular well-enhanced mass lesion in the posterior fossa extending to the left cerebellopontine angle and suggesting brainstem invasion (Fig. 1a,b). The tumor was partially removed and diagnosed as a GB. His preoperative symptoms disappeared with the administration of ACNU, procarbazine, and vincristine and radiotherapy (50 Gy); although the size of the residual tumor decreased, he died of intratumor hemorrhage in January 2008 at the age of 42 years.

Pathological findings

Surgical specimens from the first (1971) and second operation (2007) were fixed, embedded in paraffin, and 4-μm sections were prepared. The sections were deparaffinized in xylene and rehydrated in a graded ethanol-to-water series. Endogenous peroxidase activity was blocked with hydrogen peroxide. Histological study of the 1971 sample revealed a highly cellular neoplasm composed of cells with scanty cytoplasm and uniformly round nuclei; the morphological features were of classic MB (Fig. 2). Immunohistochemical staining was performed using the avidin–biotinylated enzyme complex (ABC) method (VECTASTAIN ABC kit; Vector Laboratories, Burlingame, CA, USA). Immunohistochemically, the neoplastic cells diffusely expressed the neuronal marker synaptophysin (data not shown). The tumor removed in 2007 manifested necrotic undifferentiated cells (Fig. 3a), prominent vascular proliferation (Fig. 3b), and pseudo-palisading (Fig. 3c). The mitotic rate was high; MIB-1 (DAKO) proliferation index was 61.7% (Fig. 3d). Immunohistochemically, the cells were slightly positive for glial fibrillary acidic protein (GFAP) (DAKO, Tokyo, Japan) (Fig. 4a), strongly positive for TUJ1 (Covance; The Development Services Company) (Fig. 4b), and negative for synaptophysin (DAKO). Their nuclei were strongly positive for OLIG2 (#18953 IBL; Gunma) (Fig. 4c,d). Based on these findings of necrosis, vascular proliferation, and pseudo-palisading, and the finding that MB cells are reportedly OLIG2 negative, we made a diagnosis of GB.

Discussion

RIG have been reported in patients who had previously been treated with radiotherapy (RT); the estimated cumulative risk for malignant brain tumors is 0.5%–2.7% at 15 years post-RT. Radiation-induced malignant glioma (RIMG) occurred within 10 years after RT in 81% of patients with acute lymphoblastic leukemia/lymphoma, in 59% of those with brain or other tumors, and in 18% with benign conditions. The RIMG was glioblastoma in 69 (75%) and anaplastic astrocytoma in 23 (25%) of 92 patients and was not correlated with sex, age at RT, the initial condition treated with RT, the RT dose or volume, surgery, or...