Turkish Neurosurgery, 2005, Vol: 15 No: 1, 36-39

Radiation-Induced Glioblastoma Multiforme Following Surgery For Medulloblastoma in A Child With Neurofibromatosis-1: Case Report

Nörofibromatozis-1 Olan Bir Çocukta Medullobtastoma Cerrahisi Sonrası Gelişen Radyasyon Tarafından İndüklenmiş Glioblastoma Mültiforme: Olgu Sunumu

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Received : 09.02.2005
Accepted : 09.03.2005

ABSTRACT

Glioblastome multiforme (GBM) is a malignant tumor of the brain which may develop primarily or secondary to radiotherapy. The occurence of GBM following radiotherapy for medulloblastoma is a very rare condition and few cases have been reported.

A 10-year-old girl who had been treated by surgery and irradiation for a posterior fossa medulloblastoma 4 years ago was referred to our clinic with the complaint of seizure. The cranial computed tomography showed a lesion in the left frontal lobe. Histopathological examination of the lesion following surgery showed GBM.

Patients who have been operated on and irradiated for medulloblastoma must be investigated for hereditary tumor syndromes. Although association of medulloblastoma and GBM is a rare entity, this association should be kept in mind.

KEY WORDS: Glioblastoma multiforme, medulloblastoma, neurofibromatosis, radiation

ÖZ

Glioblastoma mültiforme (GBM) beynin malign tümörlerinden birisidir ve primer veya radyoterapiye sekonder olarak gelişebilir. Medulloblastoma için radyoterapi sonrası gelişen glioblastoma son derece nadir bir durumdur ve literatürde çok az bildirilmiştir.

10 yaşında, 4 yıl once posterior fossa medulloblastomu için cerrahi ve radyoterapi uygulanmış kız çocuğu kliniğimize nöbet şikayeti ile sevk edildi. Tomografi incelemesi sol frontal kitle lezyonu olduğunu ortaya çıkardı. Histopatolojik inceleme lezyonun GBM olduğunu gösterdi.

Medulloblastoma nedeniyle opere edilen ve radyoterapi gören olgular herediter tümör sendromları yönünden araştırılmalıdır. GBM ve medulloblastoma birlikteliği nadir olmakla birlikte, bu birliktelik akıldan çıkarılmamalıdır.

ANAHTAR SÖZCÜKLER: Glioblastoma mültiforme, medulloblastoma, nörofibromatozis, radyasyon

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INTRODUCTION

Irradiation can have important delayed effects on the central nervous system (CNS). Although prominent among these effects is radiation necrosis of nervous tissue, an oncogenic effect is also recognized (4). Most radiation-induced tumors are of mesenchymal origin but gliomas can occur on rare occasions (9).

A 10-year-old girl patient with a supratentorial glioblastoma multiforme (GBM) who had been operated on and irradiated for a posterior fossa medulloblastoma at 6 years of age is presented. This case emphasizes the potential risk of early development of a second primary neoplasm in children with medulloblastoma. A concise review of the pertinent literature is given.

CASE REPORT

A 10 year-old-girl was referred to our department with a history of focal motor seizure involving the right side of the face. Her family history revealed that her father had seminoma and her brother had died due to a thymoma at an early age. In 1996, at the age of 6 years, she was operated on for a posterior fossa lesion at another center (Figure 1). Histopathological examination of the posterior fossa lesion confirmed the diagnosis of medulloblastoma. The tumor was hypercellular and necrotic. The neoplastic cells were undifferentiated with hyperchromatic, round-to-oval nuclei and scant cytoplasm. After surgical removal of the medulloblastoma, the patient underwent whole craniospinal axis and tumor bed irradiation. Chemotherapy with vincristine had been administered subsequently. She had improved and remained asymptomatic for 4 years. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) scans had not showed any residual, recurrent or seeding tumor during the follow-up period. A focal motor seizure occurred in September 2000 and we investigated the patient. Neurological findings were normal. Physical examination revealed café-au-lait spots and freckles in both axillary areas. She had more than 6 café-au-lait spots and the greatest diameter was more than 5 mm. These findings supported the diagnosis of neurofibromatosis-1 (NF-1).

Cranial CT investigation revealed a left frontal mass lesion with bilateral basal ganglia calcification. Cranial MRI scans of the patient demonstrated a contrast-enhancing mass lesion on the left frontal lobe which was not present in the previous MRI scans (Figure 2).

The patient was operated on and total removal of the tumor was achieved. The postoperative period was uneventful. Histopathological evaluation of the tumor showed the characteristics of glioblastoma multiforme with marked nuclear pleomorphism and bizarre multinucleated cells. In addition, necrosis and vascular endothelial proliferation were prominent in the tumor. Neoplastic glial cells in the glioblastoma multiforme showed diffuse nuclear expression with p53 protein with immunohistochemical assessment (BP53-12, Tumor suppressor protein Ab-8, clone D0-7, NeoMarkers, Union City, CA, USA). P53 immunoexpression was more than 75% in the neoplastic cells (Figure 3). The whole spinal MRI of the patient did not show any seeding or metastasis of GBM. She underwent additional radiotherapy following the surgery. She was re-operated on for recurrence of the glioblastoma multiforme one year later and died eventually.

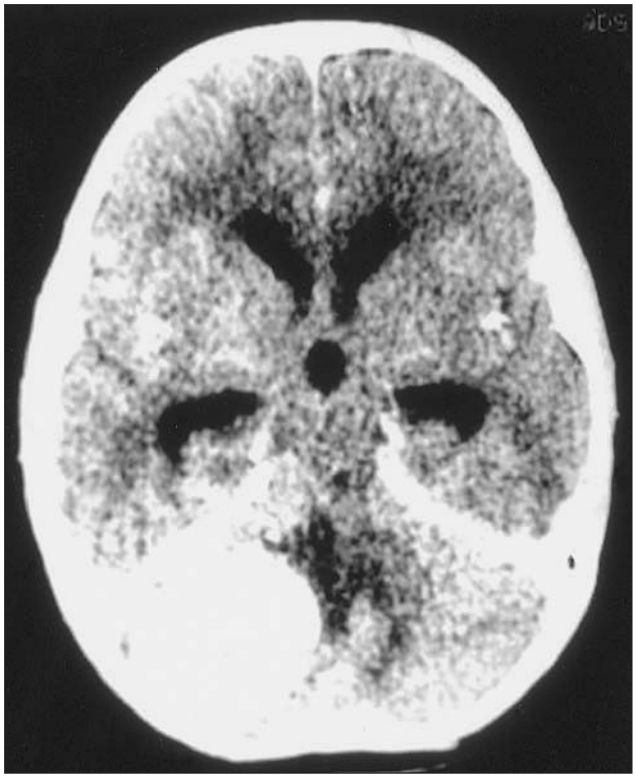

Figure 1: Axial cranial CT scan of the patient showing contrast-enhancing medulloblastoma lesion in the right cerebellar hemisphere before the first operation.

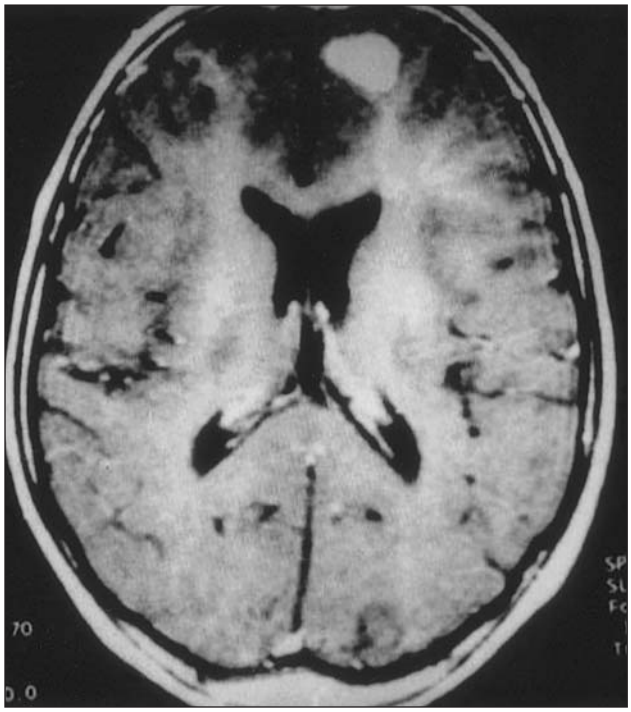

Figure 2: Preoperative axial MRI slice of the patient showing contrast-enhancing mass lesion in the left frontal lobe.

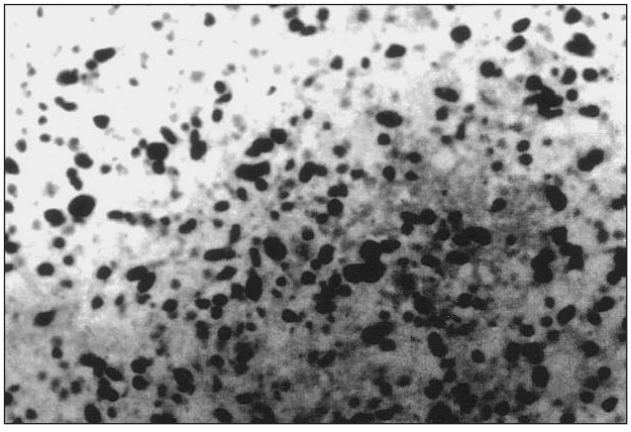

Figure 3: P53 immunoexpression of more than 75% in the neoplastic cells of glioblastoma multiforme (x200).

DISCUSSION

Medulloblastomas are one of the most common tumors in the posterior fossa and account for 4 to 10 percent of primary brain tumors (7). Although they are most commonly encountered in the first decade and located in the region of fourth ventricle, adherent to the posterior medullary velum in the midline, they may present as a laterally situated mass lesion in the cerebellar hemispheres. Early diagnosis and improved treatment modalities such as surgery followed by irradiation and chemotherapy for selected high-risk patients have contributed to a dramatic change in survival time (10). However, as survival improves, late-occurring intracranial neoplasms in medulloblastoma patients are becoming prominent. Glioblastoma multiforme in our patient was an example of a late-occurring second intracranial neoplasm in a previously treated medulloblastoma case.

Patients with medulloblastoma have a 5.4-fold higher risk of secondary cancers including astrocytomas, oligodendrogliomas, salivary gland tumors, cervical and uterine cancers, tyroid tumors, and acute lymphoblastic leukemia (3). Three possible mechanisms have been held responsible for late-occurring intracranial neoplasms in medulloblastoma patients: 1. Metastasis and differentiation of residual or recurrent medulloblastoma, 2. Radiation-induced intracranial tumors following irradiation for medulloblastoma and 3. Hereditary tumor syndromes.

Radiation has been implicated in the development of intracranial neoplasms for over 40 years. There are numerous reports in the literature of various intracranial tumors in patients following radiotherapy, but conclusive proof of a causative link has been lacking (2). Occurrence of GBM, astrocytoma, anaplastic astrocytoma, osteosarcoma, meningioma, dural fibrosarcoma, glioma of the spinal cord and trigeminal schwannoma following irradiation for medulloblastoma has been previously reported (5, 8). In order to consider a human CNS tumor to be radiation-induced, several criteria must be met; 1. The tumor must occur within the ports of radiation therapy, 2. An adequate latent period must have elapsed following radiotherapy, 3. No factors predisposing to tumor development must exist, 4. There should be a definitive diagnosis of tumor and, 5. The tumor should be of a type that would rarely occur spontaneously in a control group of non-irradiated patients. While the tumor in our patient occurred within the ports of radiotherapy, an adequate latent period had not elapsed following irradiation and the NF-1 syndrome is a factor predisposing to CNS tumor development.

P53 gene mutation due to radiotherapy may be an etiopathological factor in the development of GBM (1). In our case, the presence of a high rate immunoexpression of p53 protein in the tumor may be accepted as a supporting finding for p53 gene mutation and radiation-induced neoplasm.

Although these factors help us to distinguish spontaneously-occurring tumors from radiation-induced tumors, we are still unable to determine the exact nature of a CNS tumor (2). In our case, frontal situated GBM seems like a radiation-induced neoplasm.

The molecular basis of medulloblastoma was investigated in detail recently and some hereditary disorders such as Gorlin's syndrome, Turcot syndrome and Li-Fraumeni syndrome were found to be associated with an increased risk of medulloblastoma (8). Second primary tumors are seen a median of 73 months after the diagnosis of medulloblastoma (3).

Intracranial tumors are the associated lesions for NF-1, and astrocytomas of the optic pathway, brain stem or posterior fossa are the most common intracranial tumors in this syndrome. Other types of intracranial tumors are rare in NF-1. Medulloblastoma has been reported in patients with NF-1 syndrome (6). In our patient, we diagnosed NF-1 syndrome as a hereditary disorder and GBM was found 48 months after the diagnosis of medulloblastoma as a second primary tumor.

CONCLUSION

Secondary neoplasms following treatment for medulloblastoma are becoming relatively frequent. As most medulloblastoma patients receive craniospinal radiation, it is difficult at times to determine the relative impact of radiation versus a possible underlying genetic proclivity to malignancy. It seems beneficial to be aware of the association of hereditary tumor syndromes and medulloblastoma.

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