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Case Report

The Development of Glioblastoma Multiforme in Early Period After Intracranial Radiotherapy

Sait OZTURK[a1], Necati UCLER[2], Ismail DEMIREL[3], Metin KAPLAN[1]

[1]*Firat University School of Medicine, Department of Neurosurgery, Elazig, TURKEY*
[2]*Adıyaman University School of Medicine, Department of Neurosurgery, Adıyaman, TURKEY*
[3]*Firat University School of Medicine, Department of Anesthesiology and Reanimation, Elazig, TURKEY*

ABSTRACT

Side effects seen after many years of radiotherapy are defined as long-term side effects. Radiation necrosis is one of the most common long-term complications which is followed by secondary cancers. We have presented a case of glioblastoma multiforme detected in only 11 months after radiotherapy, and discussed the rarely reported case in detail.

Key Words: Glioblastoma Multiforme, Pontine Lesion, Radiotherapy, Side Effects

ÖZET

İntrakranial Radyoterapi Sonrası Erken Dönemde Glioblastom Multiforme Gelişimi

Radyoterapiden yıllar sonra görülen yan etkiler geç dönem yan etkiler olarak tanımlanır ve radyasyon nekrozu en sık görülen geç dönem komplikasyon olup bunu ikincil kanserler takip eder. Çalışmamızda radyoterapiden sadece 11 ay sonra saptanan ve literatürde nadir olarak rapor edilmiş sekonder glioblastom multiforme tanılı olguyu detaylı olarak tartıştık.

Anahtar Kelimeler:Glioblastom Multiforme, Pons Lezyonu, Radyoterapi, Yan Etkiler

The main aim of radiotherapy is the destruction of tumoral tissue and protection of healthy tissues at the maximum level. The side effects seen in months or years following radiotherapy are defined as long-term side effects. Neurological complications associated with radiotherapy include radiation necrosis, recurrence, cognitive decline, myelopathy, neuropathy, optic neuritis, hearing loss, and secondary neoplasms (1). Among these complications, neoplasms secondary to radiotherapy are seen very rarely and often associated with a high rate of morbidity and mortality (1, 2). Although the most common secondary tumors following radiotherapy in central nervous system (CNS) are meningiomas, gliomas have also been rarely reported in the literature (3, 4).

In this case report, we have discussed the association between age, dose of radiotherapy and the detection time of a secondary CNS tumor detected following intracranial radiotherapy in a pediatric patient.

CASE REPORT

12-year-old male patient was admitted to our clinic with complaints of dizziness, difficulty in maintaining balance, gait disturbance, hoarseness and difficulty in swallowing. His physical examination revealed an ataxic gait and left sided central facial paralysis with House-Brackmann grade IV and uvula and tongue deviation to the left. The patient's previous medical records showed a diagnosis of diffuse intrinsic pons glioma 11 months ago and subsequent radiotherapy with a total of 54 Gray (Gy), delivered in 1,8 Gy fractions**,** 5 days per week over 6 weeks (Elekta Synergy Linear Accelerator, 2004, Stockholm / Sweden).

Past medical records also revealed a history of chemotherapy with oral temozolomide (75 mg/m^2) during radiotherapy and an additional 6-cycle temozolomide regimen 4 weeks following radio the rapy.

[a]Corresponding/ Yazışma Adresi/: Dr. Sait ÖZTÜRK. *Firat University School of Medicine, Department of Neurosurgery*, Elazıg, Turkey
Phone: + 90 4242 333555 e-mail: drsaitozturk@yahoo.com
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Brain magnetic resonance imaging (MRI) on the admission showed a 49x30 mm sized novel lesion in the left cerebellar hemisphere which was absent on MRI obtained prior to radio the rapy. The lesion was hypointense at T1-weighted images and showed contrast enhancement at contrast enhanced T1-weighted images. At T2-weighted images the lesion was heterogeneous-hyperintense and it showed peripheric hyperintensity and central hypointensity at FLAIR images (Figure 1).

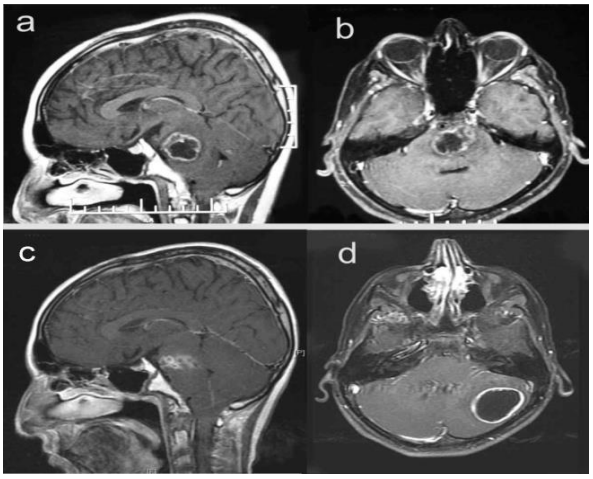

Figure 1. Images before radiotherapy (a, b): *Mid-sagittal* ***(a)*** *and axial* ***(b)*** *contrastenhanced T1-weighted MRIs show a lesion with well-circumscribed heterogeneously contrast enhancement which was 30 mm in diameter.* ***Images obtained 11 monthsafter radiotherapy (c, d):*** *Mid-sagittal* ***(c)*** *contrastenhanced T1-weighted MRI shows the initial lesion which reduced significantly in size. Axial contrastenhanced T1-weighted MRI* ***(d)*** *shows a novel peripherally enhanced heterogeneous lesion with 30 mm in diameter on the left cerebellar hemisphere.*

The patient underwent surgery for left-sided cerebellar mass. Complete resection of the lesion was achieved via left suboccipital paramedian approach. Histopathogical examination confirmed a diagnosis of glioblastoma multiforme (GBM) (Figure 2).

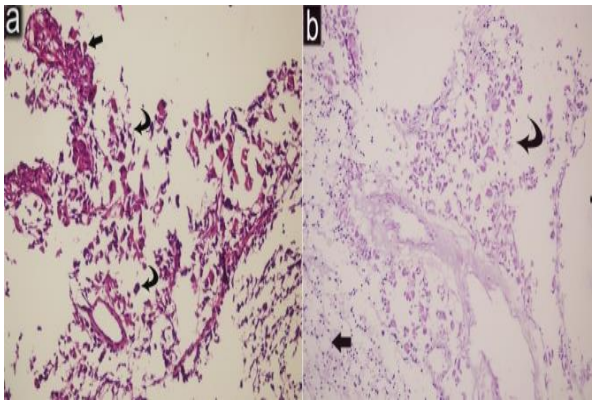

Figure 2. *Histopathological sections of secondary tumor:* ***(a)*** *the proliferation on vascular endothellium (glomeruoid) (straight arrow) is seen between atypical cells (curve arrows) (H&E X200).* ***(b)*** *thenecrotic tumoral tissue (straight arrow) adjacent to brain tissue with increased cellularity (curve arrow) (H&E X200).*

DISCUSSION

The development of a histopathologically different tumor other than the primary neoplasm is known as secondary neoplasm. Secondary neoplasms might occur at the time of the treatment as well as many years after primary treatment (5). CNS toxicity is a rare but serious complication of radiotherapy and its mechanism is still not clarified. Currently, despite well known early and late complications, radiotherapy is an essential treatment with good prognosis and high survival rates for many oncological patients. Radiotherapy and chemotherapy associated late-term side effects become an important issue in life expectancy of oncological patients. Three decades ago, the incidence of secondary neoplasms was 6% of all malignities but today this ratio reaches up to 16% (5). However, close follow-up of surviving patients is also thought to contribute this increased ratio. It is suggested that the development of a secondary neoplasm has a multifactorial etiology involving gene-environment and gene to gene interactions (5).

It is well known that radiotherapy and anti-cancer treatments are major causal factors for secondary tumors following primary pediatric and adult malignites. Depending on organ sensitivity, ionising radiation may cause many cancer types. Exposure to radiation at younger age is the greatest risk factor for secondary neoplasms. The risk of secondary neoplasm following radiotherapy increases with proportion to the length of period after exposure and the amount of radiation delivered (5). Bhati et al reported that secondary brain tumors are more frequently seen in patients who are treated and diagnosed at early ages for primary tumors and develope after a latent-period of 9-10 years following cranial radiotherapy (6). Additionally, a report including 14361 pediatric cancer cases showed that 116 cases developed a CNS tumor secondary to radiotherapy. It was emphasized in this study that gliomas developed in 9 years, whereas meningiomas developed in 17 years after primary diagnosis (6). The report also showed that chemotherapy has no effect on secondary CNS tumor development after radiotherapy. The incidence of secondary malignities were linearly increased depending to radiotherapy dose delivered for primary tumor (7). It was reported that cumulative glioma incidence was 2.7% in 15 years follow-up of patients who underwent radiotherapy for pituitary adenoma (8). Ron et al reported that among over 10.000 patients exposed to radiotherapy for tinea pedis, glioma incidence was 2.6 times higher than the patients who were not exposed to radiotherapy (9). In our pediatric case, radiotherapy was given to the patient at same time with chemotherapy and the tumor secondary to radiotherapy developed in only 11 months after radiotherapy. We think that the development of a secondary brain tumor in this pediatric patient may be

related to high radiation sensitivity of neuronal tissue at early age.

Currently, the maximum radiation dose to cerebral paranchyma is calculated as 1.8-1.9 gray/day (Gy) and a total dose of 45-60 Gy. Despite these radiation dose limits, the side-effect ratio was reported as 3-5%, which is still remarkably high. Moreover, some publications reported side-effect in up to %24 of the patients (10). Tumor secondary to radiotherapy was detected at a very early period in our case, despite a total radiotherapy dose within safe limits. We also think that early development of secondary tumor may be linked to additional exposure to chemotherapy at pediatric age.

The incidence of secondary neoplasms increase due to high survival rates obtained with intense anti-cancer treatments for primary tumors. Long term follow-up of patients is very important especially by pediatric patients with a history of radiotherapy, since secondary tumors are the second cause of death in surviving patients with primary tumors. We suggest that aggressive radiotherapy protocols may be avoided in patients with good prognostic tumor characteristics for the prevention of secondary tumors, and the incidence, mortality and morbidity of secondary tumors may decrease dramatically as a result of this theraphy algorithm.

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