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Late Brain Stem Radionecrosis Seventeen Years After Fractionated Radiotherapy

Fraksiyone Radyoterapiden 17 Sene Sonra Geç Beyin Sapı Radyonekrozu

Fatih BAYRAKLI[1]
Alp DİNÇER[2]
Aydın SAV[3]
Erkan VARDARELİ[4]
Selçuk PEKER[5]

1 Acibadem Maslak Hospital, Department of Neurosurgery, Istanbul, Turkey
2 Acibadem Kozyatagi Hospital, Department of Radiology, Istanbul, Turkey
3 Acibadem Kozyatagi Hospital, Department of Pathology, Istanbul, Turkey
4 Acibadem Kozyatagi Hospital, Department of Nuclear Medicine, Istanbul, Turkey
5 Acibadem University, School of Medicine, Department of Neurosurgery, Istanbul, Turkey

ABSTRACT

The appearance of a new lesion several years after radiation treatment for a primary brain tumor may represent different kind of pathologies. We present a 24-year-old patient who suffered from right-sided hemiparesis and ataxic gait with a history of an operation due to left frontoparieal grade II fibrillary astrocytoma and fractioned radiotherapy. His cranial MRI study showed heterogeneous signal intensity of brain stem radionecrosis in the pons spreading through the mesencephalon and left brachium pontis. The leading diagnosis was high-grade glial tumor. The patient underwent stereotaxic biopsy and histopathological examination revealed radionecrosis. Radiation necrosis has a radiological appearance similar to various important pathologies. Tissue sampling for histopathological examination is mandatory for definite diagnosis and correct treatment of the disease.

KEYWORDS: Radiation necrosis, Glial tumor, Radiological differential diagnosis

ÖZ

Primer beyin tümörünün radyasyon tedavisinden yıllar sonra görülen yeni lezyon farklı çeşit patolojilerden biri olabilir. Hikayesinde sol frontoparietal evre II fibriler astrositom nedeni ile opere olan ve radyoterapi alan 24 yaşındaki hasta, sol hemiparezi ve dengesiz yürüyüş şikayeti ile kliniğimize başvurdu. Kranial MRI tetkikinde beyin sapında ponstan mezensefalona ve sol brakium pontise doğru uzanan heterojen sinyal yoğunluklu lezyon saptandı. Öncelikli teşhis yüksek evreli glial tümördü. Hastaya stereotaktik biopsi yapıldı ve histopatolojik tetkik sonucu radyasyon nekrozu olarak bildirildi. Radyasyon nekrozu farklı önemli patolojilerle benzer radyolojik görünüme sahiptir. Hastalığın kesin teşhisi ve doğru tedavisi için histopatolojik tetkik için doku örneklemesi yapılmalıdır.

ANAHTAR SÖZCÜKLER: Radyasyon nekrozu, Glial tümör, Radyolojik ayırıcı tanı

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Correspondence address:
Fatih BAYRAKLI
E-mail: fbayrakli@hotmail.com

INTRODUCTION

Late radiation necrosis is a progressive and irreversible serious complication of radiation therapy to the brain and often occurs within 2 years after radiation therapy. It can be observed with radiotherapy doses less than 50 Gy but generally increases with increasing radiation dose, fraction size, and the administration of chemotherapy (2,10,16).

The lack of specificity of conventional computerized tomography and magnetic resonance imaging (MRI) in distinguishing radiation necrosis from lesions that have similar radiological appearances poses a significant problem for clinicians in the follow-up of irradiated brain tumors.

In this report, we describe a patient with brain stem radiation necrosis 17 years after radiation treatment for frontoparietal low grade astrocytoma.

CASE REPORT

The patient was a 24-year-old man who had been suffering from speech disorder and balance difficulty for 2 months. His neurological examination showed right-sided hemiparesis and ataxic gait. His medical history revealed an operation due to left frontoparietal grade II fibrillary astrocytoma and fractioned radiotherapy (total dose was 5320 cGy) as adjuvant therapy 17 years ago when he was 7 years old. Cranial MRI study showed heterogeneous signal intensity in pons spreading through the mesencephalon and left brachium pontis in T2-weighted and heterogeneous contrast enhancement in T1-weighted images (Figure 1B). Radiological diagnosis was compatible with high-grade glioma. The patient underwent stereotaxic biopsy and histopathological examination revealed diffuse vasogenic edema and fibroblastic proliferation, vascular sclerosis, and focal coagulation necroses (Figure 2A,B,C). The histopathological diagnosis was radiation necrosis. A perfusion study showed that the lesion was totally hypoperfusive. MR spectroscopic study revealed loss of choline and NAA peaks and marked elevation of macromolecule peak. Positron emission tomography revealed a hypometabolic lesion (Figure 1A). High-dose steroid treatment (dexamethasone) had been given to patient for 6 weeks and the patient's hemiparesis and ataxic gait had improved. After 2 years of follow-up, the lesion showed almost total regression on cranial MRI (Figure 1C) and clinically there was no neurological sequel.

DISCUSSION

The incidence of radionecrosis has been reported to range from 3% up to 24% for patients treated on aggressive experimental protocols (6, 10). Ruben et al. (10) reviewed 426 glioma patients who received radiation therapy. Radiation necrosis was diagnosed in 21 (4.6%) of these patients. Their follow-up period was at least 3 years. Total radiation dose for these patients was ranged from 45 Gy to 78 Gy. Kumar et al. (6) reported the incidence of pure radiation necrosis as 14% in a series of 148 patients with treated malignant glioma and another 11% of patients with a mixture of predominantly radiation necrosis intermingled with limited residual and/or recurrent tumor. Total radiation

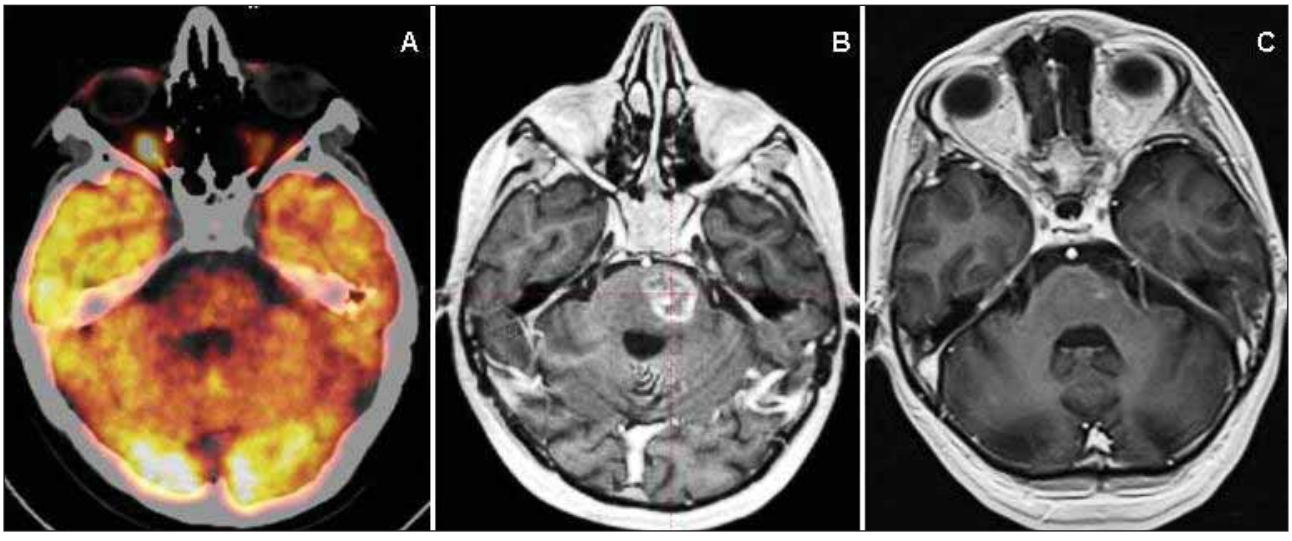

***Figure 1: A.** Hypometabolic lesion in PET, **B.** Heterozygously constrast enhancing brain stem lesion (pretreatment), **C.** After treatment and two years of follow-up period, lesion showed almost total regression.*

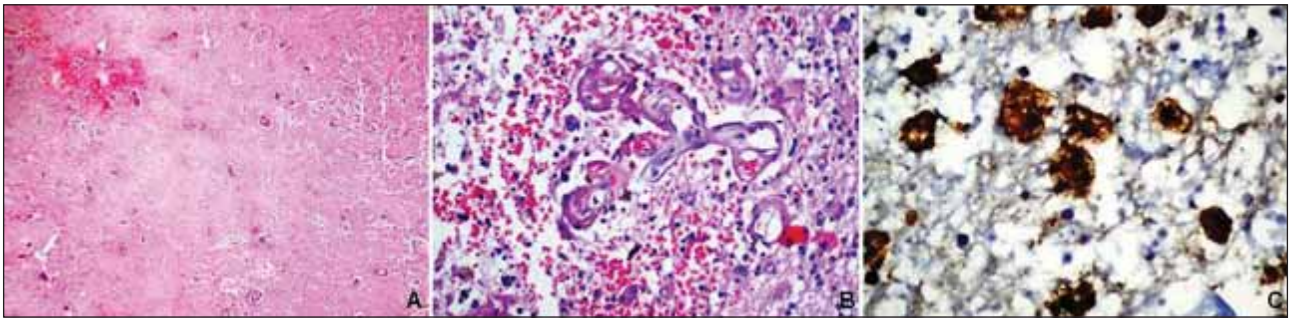

Figure 2: **A.** *Disseminated coagulation necrosis in lesion (HE, x100),* ***B.*** *Hyalinized capillary sized vessels in necrosis (HE, x200),* ***C.*** *Dotted vimentin (+) histiocytes in necrosis (Streptavidine-biotin,Vimentine, x400).*

dose of 57-60 Gy was given to these patients. These patients received carboplatin-based chemotherapy besides the radiotherapy. A 5% incidence of radiation necrosis was reported by Marks et al. (8) in 139 patients who received 4,500 rad or more for the treatment of primary brain tumors. Mikhael reported an incidence of 3.3% in patients irradiated for glioma and found that the radionecrosis coincided with the volumes of brain receiving 4,500 rad or more on dose reconstruction maps (10). The North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group intergroup trial of high- vs. low-dose radiotherapy for low-grade glioma reported on Grades 3–5 radionecrosis and found a crude incidence of 6% and 1% in the 64.8-Gy and 50.4-Gy arms, respectively (12).

Known risk factors for the development of radiation necrosis include total radiation dose and fraction size (7,8,10,13,14). Clinical experience also suggests that chemotherapy increases the risk of subsequent necrosis (14). Ruben et al. (10) proved the relationship between chemotherapy and radiation necrosis development with their study showing that the administration of chemotherapy produced a greater than four-fold increased risk for cerebral necrosis. They also stated that the total dose of radiation is the most important risk factor for development of cerebral necrosis. Shaw et al. [12] reported that patients who received 60.8 Gy had a significantly higher actuarial incidence of necrosis than those who received 50.4 Gy. Marks et al. (8) reported one patient who developed radionecrosis at a dose of 50.4 Gy. Sheline et al. (14) reported that 20 out of 80 total radionecrosis patients received doses 50 Gy or less.

Lee et al. (7) showed the influence of fraction size by using the product of total dose and fraction size in Gy. Fraction size was found to be the most significant predictive factor for necrosis in that study. Ruben et al. (10) confirmed the significance of fraction size and also demonstrated that average fraction size is a significant independent risk factor.

Radiation necrosis usually manifests after latency period of many months, but has been reported as early as 3 months, and as late as 47 years after radiotherapy [1,10]. In our case, the latency period was 17 years.

The mechanisms that may have a role in radionecrosis development are collected in four groups: a) vascular injury, b) glial and white matter damage, c) effects on the fibrinolytic enzyme system, d) immune mechanisms (6). Acute radiation causes transient vasodilatation and change in vascular permeability. Chronic radiation injury causes vascular endothelial damage. Vascular abnormalities occur before parenchymal changes (4). The pathologic findings consist of endothelial damage, vascular ectasia, and telangiectasia that all result in increased vascular permeability. Progressive vascular changes include vessel wall thickening caused by hyalinization resulting in thrombosis, infarction, and necrosis (6). Oligodendrocytes are extremely sensitive to radiation and their destruction is associated with radiological evidence of the demyelization that ensues. There is sufficient loss of cellular components, primarily in the white matter, to account for the observed reduction in brain volume that accompanies central nervous system radiation toxicity (6). Sawaya examined necrotic brain tissue samples obtained in patients with radiation-induced necrosis and found an absence of tissue plasminogen activator and an excess of urokinase plasminogen activator. These enzymes are members of a complex fibrinolytic pathway that has potent variable effects on blood vessels and brain tissue. Tissue plasminogen activator affects fibrinogen during blood clotting, whereas urokinase plasminogen activator is active in extracellular proteolysis. An increase in urokinase plasminogen activator with a concomitant decrease in tissue plasminogen activator may contribute to cytotoxic edema and tissue necrosis (6).

Various histological features have been reported for different areas of the irradiated brain (5). Radiation causes fibrinoid necrosis in vessels, resulting in vascular occlusion followed by tissue necrosis. Furthermore, irradiation may affect paracellular permeability and hypoxia mediates vascular endothelial growth factor expression, which appears to play an important role in CNS injury (9,17). Furthermore, endothelial cell damage causes microvascular permeability changes and loss of blood brain barrier integrity and circulatory disturbance resulting in tissue necrosis (3,17). As for the appearance of an inflammatory response, reactive astrocytes and lymphocytes may be observed around the necrotic area (15,17).

A variety of intracranial pathologies can present as ring-enhancing lesions on MR images including metastasis, abscess, glioma, infarct, contusion, demyelinating disease, radiation necrosis and lymphoma. The most common MRI characteristics of radiation necrosis consist of an enhancing mass with a central area of necrosis (16). Schwartz et al. (11) reviewed 221 ring-enhancing lesions seen on MR images and reported that 40% were gliomas, 30% were metastases, 8% were abscesses, and 6% were demyelinating disease. Radiation necrosis was seen in only 2% of lesions. They discussed different radiological views between these lesions and stated that there was significant overlap existing between the appearances of ring-enhancing lesions on MR images. They concluded that although the characteristics of lesions may aid in narrowing the differential diagnosis, the clinical history and serial examinations are often necessary to arrive at the correct etiology. In our opinion, the correct etiology must be proven with the direct sampling and histopathological examination of lesion because different kinds of pathologies may have a similar radiological appearance. The leading diagnosis was high-grade glial tumor in our case and we performed further neuroradiological evaluation after the histopathological examination.

In conclusion, radiation necrosis has a similar radiological appearance to different important pathologies. Tissue sampling for histopathological examination is mandatory for definite diagnosis and right treatment of the disease.

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