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Olgu Sunumu / Case Report

Secondary Lymphoma in a Patient with a History of Unilateral Retinoblastoma

Retinoblastom Öyküsü Olan Bir Hastada İkincil Lenfoma

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ABSTRACT

Second malignancies develop with increased incidence in patients with herediter retinoblastoma. The most common second malignancies in retinoblastoma survivors are soft tissue sarcoma and osteosarcoma. Lymphoma developing as a second malignancy has rarely been reported. Here we report a case of lymphoma diagnosed in a 13 year-old-boy, 12 years after the diagnosis of unilateral retinoblastoma having heterozygous p.R552 (c.1654C> T) mutation, treated with enucleation and radiotherapy. The risk of second tumour is higher in the hereditary retinoblastoma, especially in cases undergoing external beam radiation therapy.

Key words: lymphoma, retinoblastoma, second neoplasm, children

ÖZET

İkincil malign hastalıklar herediter retinoblastomlu hastalarda artmış bir sıklıkta gelişebilmektedir. Retinoblastom yaşayanlarında en sık rastlanan malign hastalıklar yumuşak doku sarkomları ve osteosarkomdur. İkincil tümör olarak lenfoma gelişmesi ise nadiren bildirilmiştir. Bu yazıda ünilateral retinoblastom nedeniyle enükleayon ve radyoterapi ile tedavi edilen, 12 yıl sonra lenfoma tanısı alan ve heterozigot p.R552 (c.1654C> T) mutasyonu saptanan 13 yaşında bir hasta rapor edilmiştir. İkincil tümör gelişme riski özellikle radyoterapi verilmiş herediter retinoblastomlu hastalarda daha fazladır.

Anahtar kelimeler: lenfoma, retinoblastom, ikincil tümör, çocuklar

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy of infancy and childhood, that arises in the retina. It is unilateral in 60% of cases and most of those forms are not hereditary[1]. Forty percent of retinoblastomas are bilateral. All bilateral and multifocal unilateral forms are hereditary[2]. Retinoblastoma is the first disease for which a genetic etiology of cancer has been described and the first tumor supressor gene identified[3]. Loss or mutations of both alleles of the retinoblastoma gene RB1, localized to chromosome 13q1.4, are required to develop the disease[4]. Survivors of hereditary retinoblastoma have an elevated risk of developing second malignancies. External beam radiation, when administered before the first year of life, and chemotherapy may also increase the risk of development of second neoplasms. The rates for osteosarcoma and soft tissue sarcomas are particularly high. Lymphoma very rarely develops after retinoblastoma[5]. Here we present a case of

unilateral hereditary retinoblastoma who developed lymphoma, 13 years after diagnosis retinoblastoma. To our knowledge this is the first case of second lymphoma associated with heterozygous p.R552 (c.1654C> T) mutation in RB1 gene.

CASE

In 1998, 13 month-old male infant was admitted to our clinic with swelling and redness in the left eye. Leucocoria was detected in the left eye. Computed tomography (CT) demonstrated a calcified lesion which was showing contrast uptake in the left bulbus oculi, at the posterolateral localization in the vitreous. Tumor which was spreading to more than half of the retina, was accepted Group 5 according to Reese Ellsworth Classification. Bone marrow aspiration and lumbar puncture was performed, there was no evidence for involvement. Molecular genetic analysis from bone marrow aspirate showed p.R552 (c.1654C> T) (heterozygous) mutation. Enucleation was performed and retinoblastoma was reported pathologically (Figure 1). There was no tumor in the surgical margin of the optic nerve. Patient underwent external-beam radiotherapy, but no chemotherapy was administered. He was followed for every 4-6 weeks in the first year of treatment, and then every 2-3 months up to 5 years. Patients who remained disease-free life, did not come to follow-up after 5 years.

The patient was 14 years old in 2011, re-admitted to our clinic with complaining of swelling of the left side of the neck. Physical examination revealed left cervical conglomerate lymphadenopathy and revealed splenomegaly. CT scan showed conglomerate lymphadenopathy with a diameter of 4,5 cm in the neck (Figure 2). Thoracal and abdominal computed tomography were normal. Lumbar puncture and bone scintigrapy were normal. Bone marrow aspiration was unremarkable. Cervical lymph node excision was performed for diagnostic purposes. There were lymphocyte infiltration and Sternberg cells with visible nucleoli in the specimen and positivity of cluster of differentiation 30 and 20 in immunohistochemical analysis. B-cell lymphoma, unclassified, diffuse large B-cell lymphoma and classical Hodgkin's lymphoma containing inter specifications (WHO 2008) was reported (Figure 2). Non-Hodgkin lymphoma (NHL) was considered clinically. NHL-BFM 90 protocol chemotherapy was started (6). After completion of chemotherapy, no lesions were seen in CT of the neck, bone marrow aspiration and cerebrospinal fluid (CSF) examination was normal. The patient is currently being followed at our outpatient clinic without disease for 30 months.

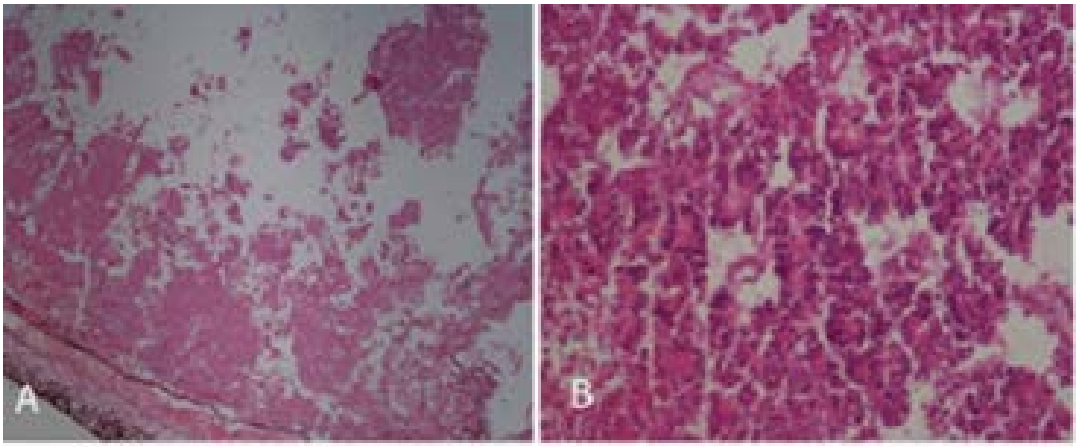

Figure 1. Neoplastic structure containing large areas of necrosis, retinoblastoma (H and E, x40) (A). Flexner-Wintersteiner (FW) rosette, retinoblastoma, small round cell tumor with hyperchromatic nuclei (H and E, x400) (B).

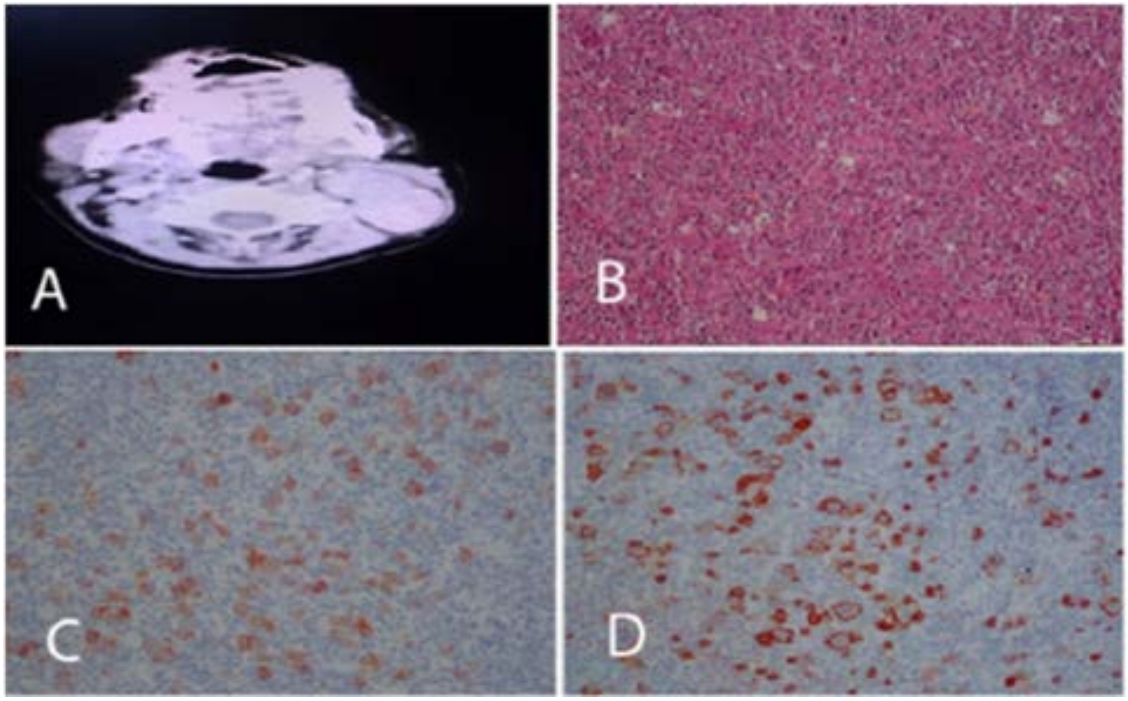

Figure 2. CT of the neck shwing conglomerated lymphadenopathies (A). Histopathologic appearance of the lymph node (H and E, x200) (B). Cluster of differentiaton 30 (+) positivity (C). Cluster of differentiaton 20 (+) positivity (D).

DISCUSSION

Genetic susceptibility, the type of first malignant neoplasm (FMN), previous therapy, the time since the initial diagnosis, age at diagnosis are known to be associated with the risk of developing second malignant neoplasms (SMN) among patients treated for childhood cancer[7]. In recent years, studies in hereditary retinoblastoma have shown that as follow-up time increases, the incidence of SMN increased over the years. The reported cumulative incidence of subsequent cancers in hereditary retinoblastoma has ranged from 8,4% at 18 years from diagnosis to 36% after 50 years[8]. MacCarthy et al[9] carried out a cohort study that included 1927 cases of retinoblastoma. The cumulative risk of developing such a tumour 50 years after retinoblastoma diagnosis was 48,3% in the heritable and 4,9% in the nonheritable cases. 102 of the heritable and 13 of those classified as nonheritable developed a non ocular tumour. Only one patient with the nonhereditary form developed Hodgkin lymphoma (HL). In our case, lymphoma has developed 13 years after the diagnosis of retinoblastoma.

In patients diagnosed with retinoblastoma, the most frequent SMN are osteosarcomas, soft tissue sarcomas (especially leiomyosarcoma) and cutaneous melanomas. Brain tumors, lung cancers, breast cancer and cancers of the nasal cavity are shown in the lower rate. Lymphoma very rarely develops after retinoblastoma[10]. Marees et al[5] carried out a study that incuded 668 cases of retinoblastoma survivors in Netherlands, diagnosed from 1945 to 2005. This study demonstrated that survivors of hereditary retinoblastoma are at risk for epithelial cancers that develop 30-40 years after diagnosis, including bladder,lung and breast cancers. Two patients with the hereditary retinoblastoma developed NHL. In other study including 963 hereditary, 638 nonherditary retinoblastoma patients, only three patients with the hereditary and one patient of the nonherditary form developed HL[8].

Hongeng et al[11] reported that second Burkitt lymphoma occured in a retinoblastoma patient with 13q deletion syndrome. In our case p.R552 (c.1654C> T) (heterozygous) mutation was detected in the RB1 gene, causing stop codone which leads to severe damage to proteins[12]. We did not encounter any case of second lymphoma associated with p.R552 (c.1654C>T) mutation in English medical literature. Without a positive family history, our patient was considered as having nonhereditary retinoblastoma initially. A small percentage of unilateral retinoblastoma survivors without a family history of retinoblastoma may have had a germline mutation[13]. Genetic analysis revealed that the patient had the hereditary form of the disease. Studies have shown that the risk of second tumour is higher in the hereditary form, especially in cases undergoing external beam radiation therapy. This risk is higher in patients receiving radiation therapy under the age of one. When hereditary patients treated with chemotherapy and radiation compared to patients treated with radiation alone, Marees et al[5] observed slightly elevated risks associated with combined chemotherapy and radiation for all sites. Our patient received radiotherapy treatment when he was 13 month-old and did not receive chemotherapy.

Many chidren diagnosed with retinoblastoma survive into adulthood and are prone to develop subsequent cancers, particulary hereditary patients, who have germline mutations. Long term follow up and early counselling regarding the risk of second primary tumors is very important in retinoblastoma survivors. It should be kept in mind that second malignancy may develop in individuals with unilateral retinoblastoma. In the hereditary form, there is the risk of recurrence of the mutation in future pregnancies and prenatal diagnosis should be offered.

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