



Differentiated Thyroid Papillary Carcinoma with Cerebellar Metastasis: A Case Report

Serebellar Metastazı Olan Diferansiye Tiroid Papiller Karsinom Olgusu

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Abstract

Differentiated thyroid cancer (DTC) has usually good prognosis and long-term survival. DTC distant metastasis rate is 5-15%. The major sites of distant metastases are the lung and bone. Metastases to the cerebrum, breast, liver, kidney, muscle, and skin are rare or relatively rare. A study of the molecular mechanisms of papillary thyroid carcinoma (PTC) has demonstrated that the BRAFV600E gene mutation was a significant event in the process of this disease. These mutations in PTC are associated with extrathyroidal spread, lymph node metastasis, tumor recurrence and mortality. We present a 55-year-old male patient with PTC with lung, bone, liver, adrenal and cerebellar metastases, in whom BRAF mutation was positive. Metastasis to cerebrum is rare in DTC. Distant metastasis may show different symptoms, according to the region. Positive BRAFV600E gene mutation may indicate agresiveness of PTC.

Keywords: Differentiated thyroid cancer, metastasis, BRAF mutation, cerebrum

Öz

Diferansiye tiroid kanseri (DTK) genellikle iyi prognozlu ve uzun süreli sağkalıma sahiptir. DTK'nin uzak metastaz oranı 5-15%'dir. Major uzak metastaz alanları akciğer ve kemiklerdir. Serebrum, meme, karaciğer, böbrek, kas ve deri metastazları çok nadirdir. Tiroid papiller karsinomasının (PTK) moleküler mekanizmalarının incelenmesi, BRAFV600E gen mutasyonunun bu hastalık sürecinde önemini ortaya koymuştur. Tiroid papiller kanserlerindeki bu mutasyonlar, ekstrasitroidal yayılım, lenf nodu metastazı, tümör rekürrensi ve mortalite ile ilişkilidir. Biz bu olguda akciğer, kemik, karaciğer, adrenal ve serebellar metastazı olan, BRAF mutasyonunun pozitif, PTK'li 55 yaşında erkek hasta sunduk. DTK'de serebrum metastazı oldukça nadir görülmektedir. Uzak metastazlar tutulan alana göre farklı semptomlar gösterebilir. Pozitif BRAFV600E gen mutasyonu PTK'li hastalarda agresif seyir açısından fikir verebilir.

Anahtar kelimeler: Diferansiye tiroid kanseri, metastaz, BRAF mutasyon, serebrum

Introduction

Differentiated thyroid cancers (DTCs) account less than 1% of all cancers and more than 90% of endocrine cancers. DTC mostly occurs in 3rd-4th decades of life. The local recurrence rate is 5-20% and distant metastasis rate is 5-15%. DTC is generally associated with good prognosis and long survival. Specific histological variants of papillary thyroid carcinoma (PTC) include tall cell, columnar cell, diffuse sclerosing and insular variants that are considered to be more aggressive forms with worse prognosis.

In recent years, a study investigating the the molecular mechanisms of PTC has demonstrated that the BRAFV600E gene mutation is a significant event in the process of this disease. A large number of studies have demonstrated that the BRAFV600E gene mutation is associated with pathological features, including extrathyroidal invasion, lymph node metastasis and tumor stage which aid

in determining the patient prognosis (1). DTC most commonly metastasizes to the bones and lungs. Cerebellar metastasis is extremely rare. In this report, atypical multiple metastases including the brain (cerebellum), bone, lung, liver, and adrenal gland due to PTC will be discussed.

Case Report

A 55-year-old male patient was admitted to our endocrinology clinic with the complaint of swelling of the neck. He was examined and multinodular goiter was identified. Thyroid fine needle aspiration showed malignant cytology. Total thyroidectomy and neck dissection were performed. Pathological examination was consistent with PTC (follicular variant); the tumor diameter was 4.5 cm. There were vascular and perineural invasion; 13 lymph nodes were removed, 11 of them had PTC infiltration. Right and left lateral cervical lymph

nodes, upper and lower mediastinal lymph nodes, an area in the right lower lobe of the left lung, multiple areas in lower lobe basal segment, bilaterally and C4-C5 cervical vertebrae had increased fluorodeoxyglucose uptake on positron emission tomography/computed tomography (CT) one month after the first surgery. Two months later, bilateral second look neck dissection was performed. 33 of 46 lymph nodes had PTC infiltration. 200 mCi of radioactive iodine (RAI) ablation therapy was given as a treatment three months after the second look surgery. Before RAI treatment, the thyroid-stimulating hormone (TSH) level was 82 μ U/mL (0.34-5.6), thyroglobulin (Tg) was 38817 ng/mL (1.15-35) and anti-Tg was 107 IU/mL (0-115). On whole body scanning, radioactivity was detected around the neck, in the region of the mediastinal area and both sides of the chest after 10 days of RAI ablation therapy. Three months after the first RAI ablation, he received radiotherapy for cervical bone metastases. 30 Gy external beam radiotherapy was administered to the cervical vertebra in the multiple fractions. After 1 year of RAI ablation treatment, the laboratory findings were: TSH: 0.8 μ U/mL (0.34-5.6), Tg: 38933 ng/mL (1.15-35), anti-Tg: 116 IU/mL (0-115). Due to the high levels of Tg, second RAI ablation treatment was planned. When L-thyroxine replacement treatment was stopped, laboratory findings were: TSH: 150 μ U/mL (0.34-5.6), Tg: 135511 ng/mL (1.15-35), and anti-Tg: 234.3 IU/mL (0-115). RAI ablation was given at the dose of 250 mCi. On whole body scanning, radioactivity was detected in the mediastinal region, axillary area, hemithoraxes and the liver after 10 days of RAI ablation therapy. After treatment, the patient did attend follow-up visits approximately for one year, then, he was admitted to the emergency department with severe headache, nausea and vomiting ongoing for 3 months. A mass was detected on cranial magnetic resonance imaging (MRI) (Figure 1). The patient was referred to the neurosurgery clinic. Chest CT showed multiple lymph nodes with pathological dimension in both axillary and mediastinal areas and multiple metastatic foci less than 1 cm in diameter in the right and left segments of the lower lung lobes. Multiple metastatic foci less than 1 cm in diameter in the liver, 8x5 cm in the left adrenal gland and 3.5 x2.5 cm in the right adrenal were consistent with the abdominal metastases on abdominal CT (Figure 2) that was performed before brain surgery. On cranial MRI, a 37x47 mm soft tissue mass with solid and cystic components in the right side of the cerebellum, besides, bilateral cerebellar contrast-enhancing multiple foci were detected.

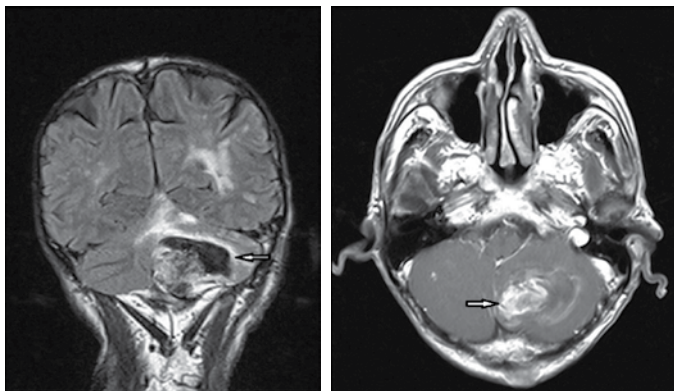


Figure 1. Views of magnetic resonans imaging of the brain which demonstrated a ring-enhancing lesion in the cerebellum accompanied by surrounding edema and compression of the fourth ventricle

The cerebellar mass was excised. Papillary carcinoma infiltration was reported (Figure 3) and BRAFV600E mutation was analyzed in the cerebellar metastatic mass. polymerase chain reactions were carried out in a volume of 25 μ L containing 100 ng genomic DNA, 10 pmol of each primer, 250 μ M each dNTP, 0.5 U of Taq polymerase and the reaction buffer was provided by the supplier (Qiagen, Hilden, Germany). Samples were denatured for 5 min at 94 °C in MWVG AG Biotech Primus 96 Plus Lab Thermal Cycler (SVC Asset Management Inc., CA, USA) and then amplified by 35 cycles of 94 °C for 30 s, 55 °C for 30 s and 72 °C for 1 min, with a final elongation of 10 min at 72 °C. The patient exhibited the BRAFV600E (codon 600, Val → Glu, GTG → GAG, exon 15). Laboratory tests during that period showed the following results: TSH: 0.35 μ U/mL (0.34-5.6), Tg: 39100 ng/mL

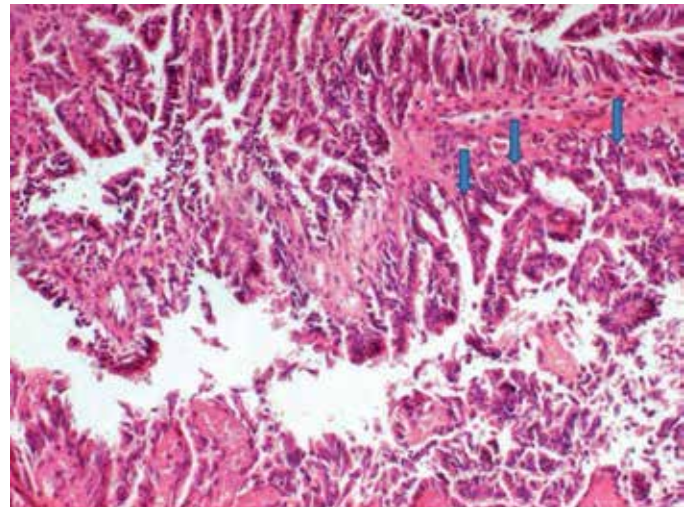


Figure 2. Hematoxylin-eosin stain of the tumor showing complex, branching, randomly oriented papillae with fibrovascular cores (hematoxylin-eosin, original magnification x100)



Figure 3. Adrenal and liver metastases in computer tomography of the abdomen

(1.15-35), and anti-Tg: 20 IU/mL (0-115). The patient was transferred to the oncology department for chemotherapy.

Discussion

We have reported a patient who had multiple distant metastatic DTC in whom BRAFV600E mutation was detected. Ten-year survival rate in DTC is 80-95%. The disease is usually limited to the thyroid gland. Commonly, local recurrence and regional lymph node metastasis may be seen. Distant metastases in DTC are much rarer, but the most common localizations are the lung and bone (2). Brain, breast, liver, kidney, muscle and skin metastases are much rarer than lung and bone metastasis.

In this case, the patient with PTC had lung, bone, liver, adrenal and cerebellar metastases. Brain metastases are extremely rare, occurring in 0.15-1.3% of all cases of thyroid carcinoma (3). Brain metastases occur more frequently in the cerebral hemispheres. Cerebellar metastases from PTC are exceptional and only few cases have been reported in the literature. Aguiar et al. (4) reviewed the literature and found 75 cases of central nervous system metastasis of PTC and only 12 cases of solitary brain metastases. Carcangiu et al. (5) and Tanaka et al. (6) noted a case of metastasis in the cerebellopontine angle and Pazaitou-Panayiotou et al. (3) reported cerebellar metastasis four years after initial diagnosis (7). Previous case reports revealed neurological deficit as a result of brain metastasis after surgery to primary thyroid cancer (3,5,6). Similarly, the patient had symptoms of cerebral edema and cerebral surgery was preferred. There is no clearly defined treatment protocol for patients with intracranial metastatic tumors from primary thyroid carcinoma and therapy must be individually modified for each patient. Several treatment modalities, including surgical resection, external radiation and RAI therapy, have been used.

Surgery is the primary mode of therapy for patients with PTC. This operation should be performed by an experienced thyroid surgeon to minimize the risk of hypoparathyroidism, recurrent laryngeal nerve injury and reappearance of the disease. In this case, first neck dissection was not performed successfully. Therefore, he needed a second surgery.

After initial thyroidectomy, L-thyroxine therapy is required for all patients to prevent hypothyroidism and to minimize potential TSH stimulation of tumor growth. As recommended by the American Thyroid Association guidelines, for initial thyroid hormone suppression therapy for intermediate- or high risk patients, initial TSH should be maintained below 0.1 mU/L (8). It has been reported that lowering TSH levels aggressively was associated with improved overall survival in high-risk differentiated cancer patients (9,10). Our patient had high risk features, but TSH suppression could not be achieved. The reason might be noncompliance to treatment.

RAI [¹³¹I-iodine] ¹³¹I-I) is the most effective adjuvant treatment for PTC. ¹³¹I causes cytotoxicity by the emission of short path-length (1 to 2 mm) beta radiation. RAI treatment of residual disease and metastatic disease may reduce the risk of recurrence and mortality, especially in small volume disease that is RAI avid. The 5-year survival rate in patients treated for ¹³¹I-concentrating pulmonary metastases, which occur in about 5 percent of cases of DTC (11), is higher than in patients with those do not concentrate (12). Skeletal metastases are often

seen on ¹³¹I scans, but do not concentrate ¹³¹I very well; complete resolution of disease occurs in less than 10 percent of treated patients, and partial remission in only 35 percent (13). In this case, RAI uptake was increased in the lung, especially in the mediastinal area after the first and second RAI ablation treatments. We thought that, the condition was progressing day by day, despite a total of 450 mCi RAI ablation treatment. These treatments were not effective in the patient. We consulted the oncology department for possible administration of tyrosine kinase inhibitors, a new class of medication for thyroid cancer.

External beam radiation should be used in the management of unresectable gross residual or recurrent cervical disease, painful bone metastases, or metastatic lesions in critical locations likely to result in fracture, neurological, or compressive symptoms that are not amenable to surgery (e.g., vertebral metastases, central nervous system metastases, selected mediastinal or subcarinal lymph nodes, pelvic metastases) (8). In this case, external beam radiotherapy was administered to the cervical vertebra because of bone metastasis.

BRAF gene mutations in papillary carcinoma may be present at the rate of 53%. 90% of the V600E mutations in exon 15 seen in BRAF-positive patients (3). Among the various histological subtypes of PTC, conventional and tall-cell variants are most commonly associated with the mutation (67-68% and 80-83%, respectively); the mutation is least associated with the follicular variant (12-18%) (14). In this case, follicular variant PTC and BRAFV600E mutation were defined in the preparation of the cerebellum and BRAFV600E mutation was reported. It is still controversial whether BRAFV600E mutation correlates with aggressive clinicopathological characteristics or not. Lupi et al. (15) performed a retrospective study in 500 patients with PTC 43% of whom had the mutation, and found that those patients had a higher incidence of extrathyroidal extension, nodal metastasis, multicentricity, and advanced tumors than patients without the mutation. Kebebew et al. (16) followed 314 patients with thyroid cancer prospectively for a median of six years and found that the BRAFV600E mutation was independently associated with recurrent and persistent PTC. Kim et al. (7) reported in a prospective study that the mutation was associated with a higher clinical recurrence of disease in low-risk patients with conventional PTC. Choi et al. (17) have shown that the prevalence of the BRAFV600E mutation was 71.3% in 101 papillary thyroid microcarcinoma patients in their study and the BRAFV600E mutation was not associated with prognostic factors in patients with metastatic PTC (17).

In conclusion, we report a BRAFV600E gene mutation-positive PTC case with metastasis to cerebellum, lymph nodes, bone, lung, liver and adrenals. The clinical management of this case was discussed. The patient progressively worsened, although he was treated with surgery and I-¹³¹ RAI ablation. Distant metastasis may show different symptoms, according to region. Especially in a BRAFV600E gene mutation positive-PTC patient, we must be careful in terms of disease aggressiveness.

Ethics

Informed Consent: Informed consent was obtained from our patients for being included in this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Elif Turan, Ahmet Kaya, Mustafa Kulaksızoğlu, Ayşe Gül Zamani, Sümeyye Kozacıoğlu, Concept: Elif Turan, Ahmet Kaya, Mustafa Kulaksızoğlu, Design: Elif Turan, Ahmet Kaya, Mustafa Kulaksızoğlu, Data Collection or Processing: Elif Turan, Ayşe Gül Zamani, Sümeyye Kozacıoğlu, Analysis or Interpretation: Elif Turan, Ahmet Kaya, Mustafa Kulaksızoğlu, Literature Search: Elif Turan, Writing: Elif Turan.

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