Symptomatic Infundibulum Metastasis from Breast Cancer and Resolution of Symptoms Following CyberKnife® Fractionated Stereotactic Radiotherapy: Case Report

Meme Kanserinin Semptomatik İnfundibulum Metastazı ve CyberKnife® Fraksiyone Stereotaktik Radyoterapiden Sonra Semptomların Rezolüsyonu

Mehtap COŞKUN,[a]
Ela DELİKGÖZ SOYKUT,[a]
Yıldız GÜNEY,[a]
Ebru KARAKAYA,[a]
Dinçer YEĞEN,[a]
Mehmet Metin ŞEKER,[b]
Nazan ÇİLEDAĞ GÖKBAKAR[c]

Departments of
[a]Radiation Oncology,
[b]Radiology,
Dr. Abdurrahman Yurtarslan
Ankara Oncology Education and
Research Hospital,
[c]Department of Medical Oncology,
Ankara Numune Education and
Research Hospital, Ankara

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Yazışma Adresi/*Correspondence:*
Ela DELİKGÖZ SOYKUT
Abdurrahman Yurtarslan
Ankara Oncology Education and
Research Hospital,
Department of Radiation Oncology,
Ankara,
TÜRKİYE/TURKEY
eladelikgoz@gmail.com

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ABSTRACT While metastasis to the brain is a well known and common complication of breast cancer, metastatic spread to the pituitary gland, specifically to the area of infundibulum is a rare presentation. In symptomatic cases, the most common manifestation of an infundibular metastatic lesion is diabetes insipidus (DI). Management of lesions in this area is controversial. Here, we presented a patient with symptomatic solitary infundibulum metastasis originating from breast cancer and the results of fractionated stereotactic radiotherapy (FSRT). The tumor size regressed and her symptoms decreased after the delivery of FSRT. The patient died due to the progression of systemic disease seven months after the FSRT.

Key Words: Pituitary gland, posterior; diabetes insipidus; breast neoplasms; radiosurgery

ÖZET Meme kanserinde beyin metastazı yaygın ve iyi bilinen bir komplikasyon olup, hipofiz bezine özellikle de infundibuluma metastaz hayli nadirdir. Semptomatik olgularda, infundibulum metastazı en sık diabetes insipitusa (DI) bağlı klinik belirtilerle kendini gösterir. Bu bölgedeki metastatik kitlelerin tedavisi tartışmalıdır. Bu olgu sunumunda, semptomatik infundibulum metastazlı bir meme kanseri olgusunda fraksiyone stereotaktik radyoterapi (FSRT) uygulamasının sonuçları sunulmuştur. FSRT uygulamasından sonra, tümor boyutunda ve DI'ya bağlı klinik belirtilerde belirgin gerileme görülmüştür. Hasta, primer hastalığın progresyonu nedeniyle FSRT uygulamasından yedi ay sonra kaybedilmiştir.

Anahtar Kelimeler: Pituiter bez, posterior; diabetes insipidus; meme tümörleri; radyocerrahi

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Metastasis to the pituitary gland is a relatively uncommon complication. The majority of pituitary metastases are clinically asymptomatic and too small to cause radiological changes.[1-5] They can mimic a variety of sellar area benign or malignant lesions, complicating the diagnosis, especially when it is the first presentation of an unrecognized primary disease.[1,5-8]

However, in the last decades, with the improved survival rates of cancer patients, pituitary metastases have been noted increasingly by means of advanced imaging technologies.[7,9] In symptomatic cases, the most common presentation of a pituitary metastasis is diabetes insipidus (DI).[3,10] While many types of cancer can metastasize to the pituitary gland, breast and lung cancers are the most likely primary neoplasms to metastasize to the pituitary

gland.[3,11] There are different treatment options, such as symptom relief with desmopressin, whole-brain radiotherapy (WBRT), craniotomy for resection, radiosurgery and fractionated stereotactic radiotherapy (FSRT).[2,6,7] Local therapy for the relief of symptoms is beneficial; however, prognosis is determined by the primary tumor.

CASE REPORT

A 35-year-old pre-menopausal woman was initially diagnosed with invasive ductal carcinoma of the right breast (T3N3M0, ER 90%+, PR 90%+, CerbB2 10%+, Grade 3) in July 2007. After undergoing right modified radical mastectomy and axillary dissection, she received chemotherapy consisting of six cycles of docetaxel and epirubicin. Following chemotherapy, she received locoregional radiotherapy. She agreed to proceed with tamoxifen and leuprolid acetate therapy starting after radiotherapy. However, at the end of the third cycle of hormone therapy, she developed a palpable lump in the left breast. A tru-cut biopsy revealed invasive ductal carcinoma with moderate differentiation (ER < 5%, PR-, CerbB2-, Grade 3). After neoadjuvant chemotherapy, she underwent left modified radical mastectomy in January 2009. Then, she received four cycles of capecitabine followed by tamoxifen therapy. In September 2009, while she was on the fifth month of her tamoxifen hormone therapy, she presented with increased thirst, excessive desire for liquids, and nocturia. On physical examination, no neurological deficits were found. Unfortunately, the patient was not tested for diabetes insipitus with urine and plasma osmolality or serum hormone or cortisol levels except for serum electrolytes, which showed normal serum sodium concentration (141.6 mmol/l).

Magnetic resonance imaging (MRI) of the brain demonstrated thickening of the pituitary infundibulum to 8 mm, compressing the posterior optic chiasm (Figure 1). It was consistent with a solitary pituitary infundibulum metastasis from the primary breast cancer based on clinical and radiological findings. No other metastatic sites were evident within the brain. Subsequently, multiple liver metastases were also detected. Given the status of the systemic disease, and tumor location, size and nature, FSRT was considered the best option. After the first cycle of the salvage chemotherapy including paclitaxel and gemcitabine, on November 3, 2009, the patient underwent FSRT with CyberKnife® (Accuray Incorporated, Sunnyvale, CA).

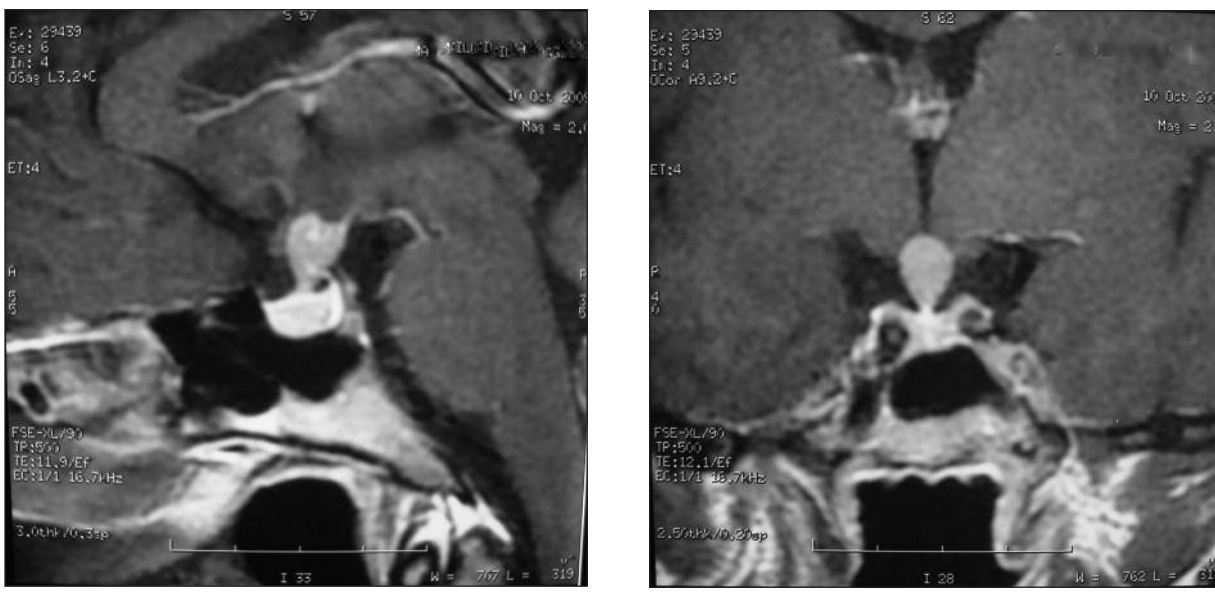

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FIGURE 1: Pretreatment magnetic resonance imaging (MRI) of the pituitary stalk.

The potential risks and benefits of CyberKnife FSRT were explained to the patient and informed consent was obtained.

Immobilization was achieved using a thermoplastic mask. Thin slice, computed tomographic scans with 1.5 mm slice intervals were acquired along the length of the skull and upper neck from which digitally reconstructed radiographs were derived to facilitate skull tracking for stereotactic treatment guidance. MRI scans with 3 mm slice intervals, obtained after intravenous administration of gadolinium, were used to plan treatment. The Accuray Multiplan Treatment Software 3.5.2 was used to fuse those images to better visualize the tumor and critical structures (Figure 2). The relevant critical structures including the optic chiasm, optic nerves, eyes, brainstem and the tumor volume were then outlined.

The treatment plan consisted of 172 beams given from 103 nodes with a fixed collimator to cover a gross tumor volume of 613 mm^3. A total dose of 18 Gy was prescribed to the 80% isodose line in 5 fractions. The limiting factor for radiosurgery of the pituitary lesion is the radiation dose to the optic apparatus. The tolerable dose for the optic chiasma and optic nerves is set to 10 Gy.[12] Thus, we used FSRT instead of radiosurgery to minimize the dose delivered to the optic chiasm adjacent to the infundibulum. The maximum calculated dose delivered to the tumor and the optic chiasm was 22 Gy, and 16,7 Gy, respectively. The patient tolerated radiation without any acute incident and was followed-up clinically and by MRI three months after treatment. After the FSRT procedure, she continued to receive paclitaxel and gemcitabine. Polyuria and nocturia started to releive starting from the first few days of treatment. The prescribed dose was completed without the development of any acute morbidity. The three-month follow-up MRI revealed a 70% contraction in tumor size, accompanied by disappearance of the symptoms and the laboratory findings associated with DI (Figure 3). Serum electrolytes, cortisol, and thyroid hormone levels were within normal reference ranges. Unfortunately, the rapid progression

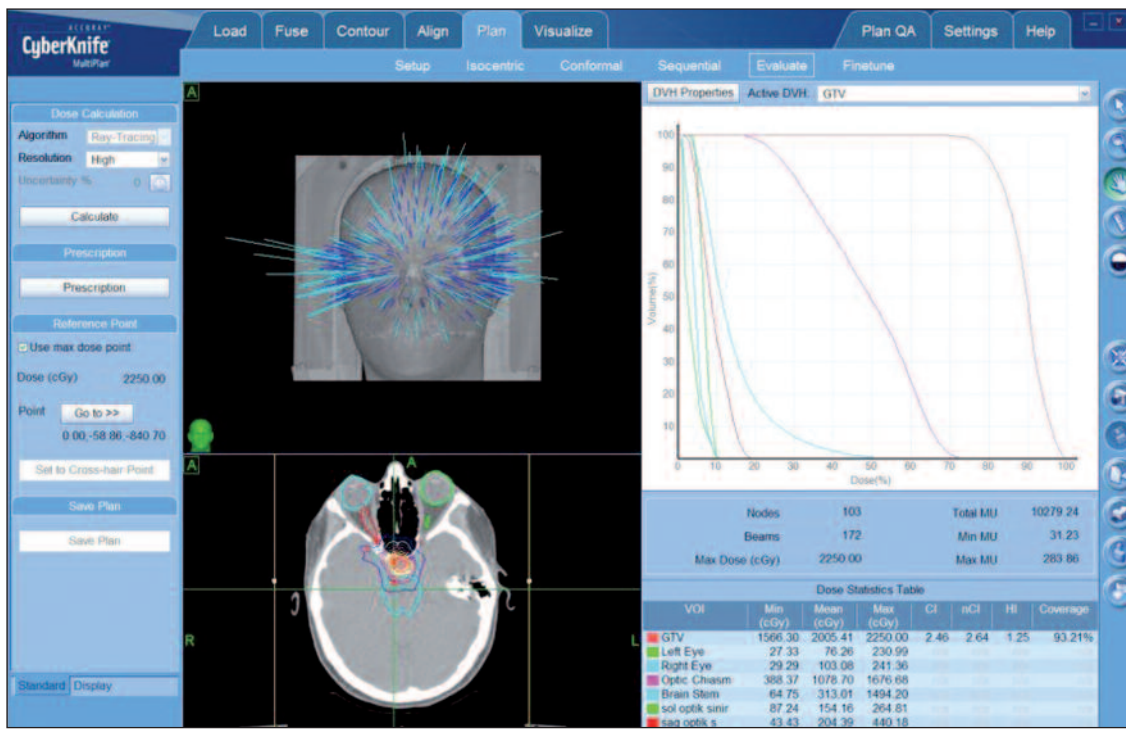

FIGURE 2: CyberKnife treatment planning images.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

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FIGURE 3: Posttreatment magnetic resonance imaging (MRI) of the pituitary stalk.

of the metastatic breast cancer continued and the patient died of her systemic disease seven months after the FSRT.

DISCUSSION

The incidence of pituitary metastases in large surgical series of patients who have undergone transsphenoidal surgery for sellar or parasellar tumors is less than 1%.[2,4,5,10,13-15] Pituitary metastases may be associated with all kinds of cancer, but lung and breast cancers are the most common causes for men and women, respectively.[4,16] Breast and lung cancers account for approximately 65% of all pituitary metastatic autopsy series.[17] In breast cancer patients, incidence of pituitary metastasis is 17.6%, while this percentage is approximately 5% for all patients with any known malignancy in different autopsy series.[2,4,5,10,13-15]

There are different ways for metastatic tumor deposits to reach the sellar or the parasellar region. Direct hematogenous spread to the pituitary parenchyma, spread through hypothalamo-hypophyseal vessels, infundibulum metastasis through portal vessels, extension of skull base metastasis, and meningeal spread are the major routes.[4,18-20] Authors of early series have reported that posterior pituitary metastasis is more frequent than anterior pituitary metastasis.[2,10,13] Infundibular involvement with metastatic tumor deposits is much rarer than any anterior or posterior lobe involvement. Teears et al. has reported in their review that only two out of 88 pituitary metastases had pituitary infundibulum involvement.[2]

Extraocular nerve palsies, visual field defects, headache, and anterior pituitary dysfunction symptoms are other clinical manifestations of hypothalamic pituitary region metastases. Although cavernous sinus invasion and suprasellar extension can cause painful ophthalmoplegia and visual disturbances, all are less common than DI.[4,9,15,21-23]

In addition, 53-100% of all pituitary metastatic cases are accompanied by widespread organ metastases at the time of diagnosis.[4,9,10,24] Differential diagnosis of a pituitary tumor can include pituitary adenomas, meningiomas, and granulomatotic disease.[25] It remains a diagnostic challenge to distinguish pituitary metastases from benign pituitary adenomas. Magnetic resonance imaging is more successful than a CT scan in the distinction of those lesions.[3]

There are multiple treatment modalities for pituitary metastases including resection, radiation

therapy, and chemotherapy.[2,6,7,26] In a review of 36 patients with symptomatic pituitary metastases, Morita et al. performed trans-sphenoidal surgery in 16 patients and transcranial resections in five patients.[9] They found no statistically significant difference in the survival of the 21 patients who underwent surgery. Length of survival was not different between patients who underwent surgery and those who did not. However, local tumor control ratio was higher in the surgery group. They also found an improvement in symptoms in the surgery group. Some studies showed that resection combined with WBRT could prolong survival of patients with metastatic brain tumors.[10,22] However, surgery has a high risk of mortality when used for lesions in that region and it is not cost-effective.

Mori et al. reported 623 patients with brain metastases treated with Gamma Knife ® (Elekta AB, Stockholm, Sweden) radiosurgery, 4 located on the pituitary gland, 5 located on the cavernous sinus, and 4 located on both the sella and the cavernous sinus.[27] Treatment doses for metastases located on the piutitary gland ranged between 12 and 12.3 Gy. The median follow-up time was 4 months (range, 2-12 months) 9 out of 13 patients. While the tumor size was stable in three patients, the tumor size decreased or the tumor disappeared with resolution of symptoms in 6 cases.

Iwai et al. reported seven patients with pituitary gland metastases treated with Gamma Knife radiosurgery, one treated with surgery initially.[28] Mean radiosurgery dose was 11.9 Gy (range, 10-14 Gy). Mean optic pathway exposure doses were 9.5 Gy (range, 8-10 Gy). During the follow-up time, one patient died 10 days after treatment, five patients remained stable at radiological imaging, one patient recurred 18 months after radiosurgery, and required surgery. Despite stable tumor size, symptomatic improvement has been observed in five patients.

Stereotactic radiosurgery with Gamma Knife has been shown to yield comparable results to those with surgery combined with WBRT.[29-31] Whole brain radiotherapy alone has not been sufficient for the control of DI symptoms.[3]

Currently, two phase-III randomized trials comparing WBRT alone versus WBRT plus Stereotactic Radiosurgery (SRS) for brain metastases were published. The Radiation Therapy Oncology Group (RTOG) 9508 trial showed survival benefit for single brain metastases and increased local control without survival advantage for 2-3 brain metastases. This study also emphasized that with WBRT plus SRS, all patients had improved performance status and decreased steroid use.[32] The other study from Kondziolka et al. reported that combined therapy with WBRT and SRS improved local control for 2 to 4 brain metastases significantly.[33]

Three randomized controlled trials have tried to assess the role of SRS alone versus WBRT plus SRS for 1-4 brain metastases. There was no difference in overall survival in both arms, but local control and distant brain control significantly improved in the WBRT plus SRS arm. Neurocognitive functions and performance status ameliorated in the SRS alone arm.[34] The idea of deferring WBRT in order to avoid its adverse effects on healthy brain tissue such as deteriorated neurocognition and decreased performance status, and implementing SRS alone should be considered a new approach for selected patients.[35,36] Owing to the good performance status of our patient with single brain metastasis, we decided to delay WBRT until the development of new brain metastases.

Radiation-induced optic neuropathy is significantly correlated with total dose and fraction size and requires more attention for its prevention.[37] Effectiveness of radiotherapy is limited because high doses are excluded to avoid complications. SRS with Gamma Knife must be delivered in single fraction due to its invasive nature and the limited tolerable dose of the optic pathway between 8 to 10 Gy limits its prescription dose.[37,12] Fractionated stereotactic radiotherapy with CyberKnife® treatment may be delivered in single to five fractions; increasing number of fractions increases the tolerable dose of the optic pathway enabling the clinician to achieve high radiation doses close to the target volume while protecting critical structures.

Fractionated stereotactic radiotherapy delivered in single to five fractions with a total dose of 18 to 36 Gy has well established efficacy for brain metastases, but total dose and number of fractions differ according to tumour location, tumour size, number of lesions, performance status of patients and combination of FSRT with WBRT.[38-41] Killory et al. reported 20 pituitary adenoma patients whose tumour was located within 3 mm of the optic chiasm so that they were not candidate for radiosurgery; they were treated with FSRT with a prescribed dose of 25 Gy in 5 fractions.[42] The preliminary results showed that the optic nerve and the optic chiasm tolerated this treatment. In our case, the infundibular lesion pushed the optic chiasm, so we chose FSRT instead of SRS to maximize the protection of the optic chiasm and to provide visual preservation and we prefered a prescribed dose of 18 Gy in order to combine the treatment with WBRT. The maximum point dose of the optic pathway was found 16,7 Gy.

CyberKnife® (Accuray Incorporated, Sunnyvale, CA) is a frameless stereotactic radiosurgery system and is noninvasive.[43] The technology of CyberKnife® depends on image guidance and also allows for intensity-modulated therapy.[44-47] This new technology is especially useful for the treatment of small lesions close to critical structures.[43] Delivery of high doses to target volume, and limiting the dose exposure to the adjacent normal tissues by rapid dose fall-off, CyberKnife FSRT is a very effective and safe advanced radiotherapy technique.[12] Abundant clinical data has established the feasibility and utility of CyberKnife FSRT in the treatment of brain metastases.[47-50] With our case, we demonstrated the feasibility of this technology in the treatment of a pituitary infundibulum metastasis, which was near the critical optic pathways. We did not encounter any acute or subacute toxicity and achieved a significant improvement. Our patient had received chemotherapy previously and after the diagnosis of the pituitary infundibulum metastasis, but she never needed to take desmopressin at any time during her treatment. Chemotherapy alone can suppress brain metastases from breast cancer, but it is not successful in reversing DI symptoms.[51,52] In contrast, desmopressin treatment can control DI symptoms but can not hinder intracranial tumor progression.[52] In conclusion, CyberKnife ® FSRT alone or in combination with WBRT is the treatment of choice for pituitary infundibulum metastases of breast cancer.

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