



Cyberknife Radiosurgery for Cranial Plasma Cell Tumor

Kraniyal Plazma Hücreli Tümör İçin Cyberknife Radyocerrahisi

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ABSTRACT

Cranial and intracranial involvement by myelomatous disease is relatively uncommon. Furthermore, systemic manifestations of multiple myeloma are present in the majority of these cases at the time of symptom onset. The authors report the case of a patient with serial appearance of multiple intracranial plasma cell tumor localizations as the first manifestations of a multiple myeloma. The patient was treated with CyberKnife radiosurgery for a lesion localized at the clivus and sella turcica with complete local control. With such a technique, based on high-dose conformality, the tumor was centered with an ablative dose of radiation and, at the same time, with a low dose spreading to the surrounding critical structures. The radiosensitivity of plasma cell tumors renders this treatment modality particularly advantageous for their localized manifestation. A technical description of this case is provided. To our knowledge, this is the first case of successful Cyberknife radiosurgery of multifocal intracranial plasmacytoma.

KEYWORDS: Radiosurgery, Cyberknife, Plasma cell tumor

ÖZ

Myelomatöz hastalık nedenli kraniyal ve intrakraniyal tutulumu nispeten sık rastlanır. Ayrıca multipl myelomun sistemik bulguları belirtilerin başlangıcında bu olguların çoğunluğunda mevcuttur. Yazarlar multipl myelomun ilk bulguları olarak çok sayıda intrakraniyal plazma hücreli tümör lokalizasyonlarının arka arkaya ortaya çıktığı bir hastayı belirtmektedir. Hasta klivus ve selladaki lezyonlar için tam lokal kontrol sağlanacak şekilde Cyberknife radyocerrahisiyle tedavi edilmiştir. Yüksek doz konformalite temelinde kullanılan böyle bir teknikle tümör ablatif bir doz radyasyonu ile ortalandı ve aynı zamanda çevre kritik yapılara sadece düşük bir doz yayıldı. Plazma hücreli tümörlerin radyosensitivitesi bu tedavi modalitesini lokalize manifestasyonlar için özellikle avantajlı hale getirmektedir. Bu olgunun teknik bir tanımı verilmiştir. Bildiğimiz kadarıyla bu multifokal intrakraniyal plazmasitomun ilk başarılı Cyberknife radyocerrahisidir.

ANAHTAR SÖZCÜKLER: Radyocerrahi, Cyberknife, Plazma hücreli tümör

INTRODUCTION

Plasma cell tumors include a variety of clinico-pathologic entities that are categorized as localized or diffuse.

Solitary plasmacytoma of the bone and its extramedullary localization are known to be solitary lesions with an histopathological appearance of plasma cell tumor in absence of clinical and systemic disease (10). Multiple myeloma is a monoclonal neoplastic proliferation of plasma cells of bone marrow derivation that involves extraosseous tissues in a multifocal fashion.

Multiple myeloma is a disseminated malignancy of plasma cells and is thought to represent the endpoint in disease progression for patients with the localized disease. Cranial or intracranial involvement by myelomatous disease is not frequent and the majority of these cases have typical systemic manifestations of multiple myeloma (12). Here, we report a

case of a patient with multifocal cranial localizations as the first manifestation of multiple myeloma. The patient was treated with CyberKnife radiosurgery with successful local control and complete disappearance of the treated tumors. To our knowledge this is the second published case of intracranial plasma cell tumor treated with cyberknife radiosurgery.

CASE REPORT

A 65-year-old man was referred to our neurosurgical department with a diagnosis of a non-functional pituitary macroadenoma. He reported a 2-month history of headaches and progressive diplopia. On physical examination, right proptosis and a mild hypoesthesia on the right side of the face were detected. The patient did not present with systemic symptoms and all hematological parameters were normal except for a slight increase in prolactin which was 36.7 ng/ml. The patient underwent brain magnetic resonance imaging (MRI) scan which showed a homogeneously enhancing mass into the cli-

vus with intrasellar extension (Figure 1). A biopsy of the lesion was performed by the transphenoidal approach. Specimens were analyzed and revealed an highly cellular neoplasm with mature plasma cells including binucleate forms. Immunocytochemistry showed that all the tumor cells were positive for CD-138 and the kappa light chains suggested a diagnosis of a plasmacytoma. Further investigations were carried out. 13q14 deletion was detected in more than 15% of the nuclei by interphase fluorescence in situ hybridization combined with cytoplasmic light chain fluorescence (probe LSIRB1-Vysis). p53 deletion (LSIp53 probe Vysis + 17- CEP alpha DNA centromeric probe), and a monoclonal cytoplasmic expression of kappa light chains were found in malignant plasma cells.

The features of the biopsy prompted further investigations such as serum and urine protein electrophoresis and bone

marrow biopsy without revealing any evidence of an occult myelomatous disease.

Serum beta-2 microglobulin was normal.

The patient received 1.3 mg of bortezomib per square meter of body-surface area twice weekly for 2 weeks, followed by 1 week without treatment, for up to four cycles. After treatment, the patient showed very good partial remission so he underwent radiotherapy (RT). The patient was referred to the radiation oncology department for treatment. External beam radiation was taken into consideration but a radiosurgical strategy was chosen because of the vicinity of critical structures including the brainstem, cavernous sinuses, eyes and the optic pathway, together with the absence of evidence of a diffuse disease.

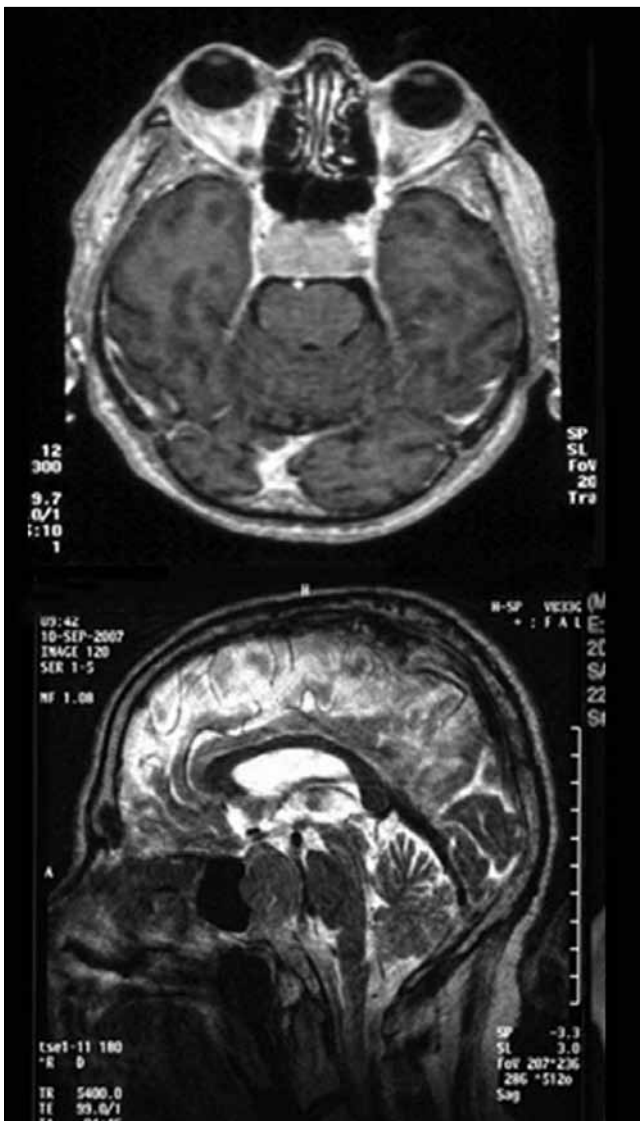


Figure 1: Pre-operative MRI in axial view (up) and sagittal view (lower) showing a lesion causing the enlargement of the clivus and extending into the sellar area.

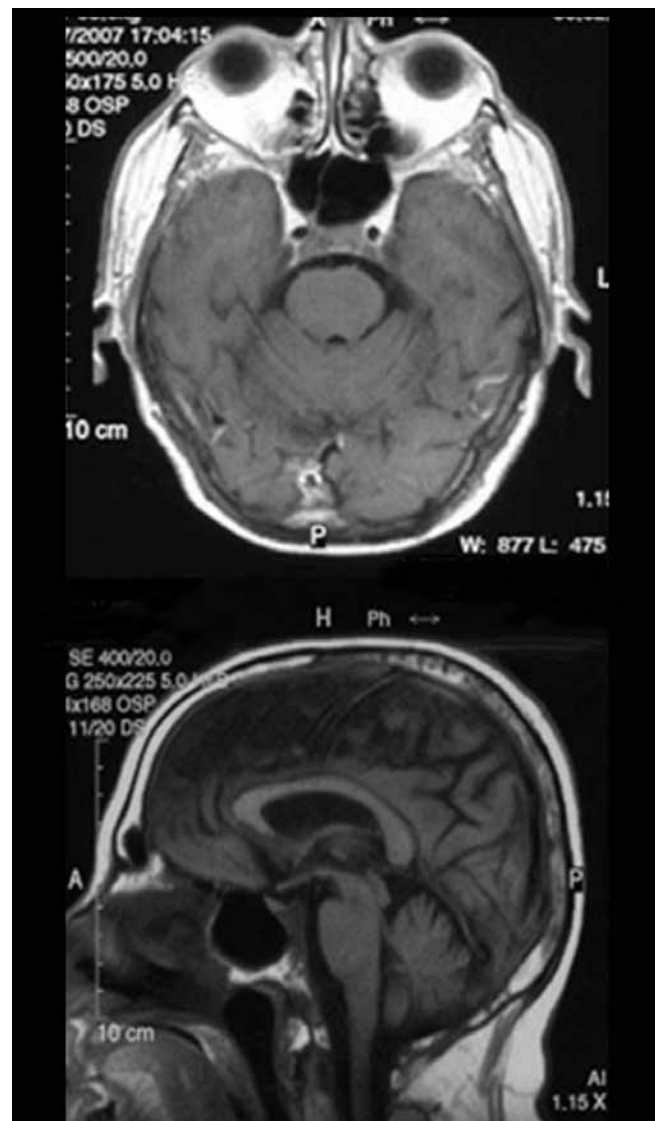


Figure 2: Post-treatment MRI in axial view (up) and sagittal view (lower) showing the disappearance of the tumor.

CyberKnife Treatment: The clival lesion (volume: 3353 mm³) was treated with 2100 cGy in three fractions at the isodose line of 80%, with 208 beams and a target coverage of 97%. The conformality index was 1.40 and the homogeneity index 1.25. The maximal dose to the chiasm was 1009 cGy, the maximal dose to the brainstem was 1263 cGy in three fractions (Figure 2). The patient tolerated the treatment well with no adverse side effects. The follow-up MRI obtained 6 months after radiosurgery demonstrated complete tumor disappearance (Figure 3). The patient underwent new investigations for a myelomatous disease including serum and urine protein electrophoresis, a bone survey and a bone marrow biopsy showing evolution to a diffuse disease. Chemotherapy was undertaken with 1.3 mg of bortezomib per square meter of body surface area twice for 2 weeks, followed by 1 week without treatment for up to four cycles. After treatment the patient had very good partial remission so he underwent radiotherapy.

DISCUSSION

The treatment of isolated lesions differs from the treatment of multiple myeloma. Solitary plasmacytomas of bone and extramedullary plasmacytomas are well treated with complete surgical resection followed by external radiation therapy (7). A dose of 5000 cGy is recommended and is given as 200 cGy in 25 fractions. Nevertheless, it has been reported that complete treatment can be achieved with biopsy and radiation therapy, while others suggest the possibility of complete surgical resection without radiation therapy (7, 9). Radical surgery is less of an option for patients with multiple myeloma. Symptomatic patients affected by multiple myeloma can be managed with chemotherapy or bone marrow transplantation. Palliation can be accomplished by radiation therapy with a total dose of 3000 cGy, given in 10 fractions (300 cGy per fraction), for pain relief and to prevent pathological fractures. Chemotherapy includes C-VAD chemotherapy (cyclophosphamide, vincristine, adriamycin, and dexamethasone) (8) combined with autologous peripheral blood stem cell transplant and interferons. Melphalan and prednisolone can be given orally

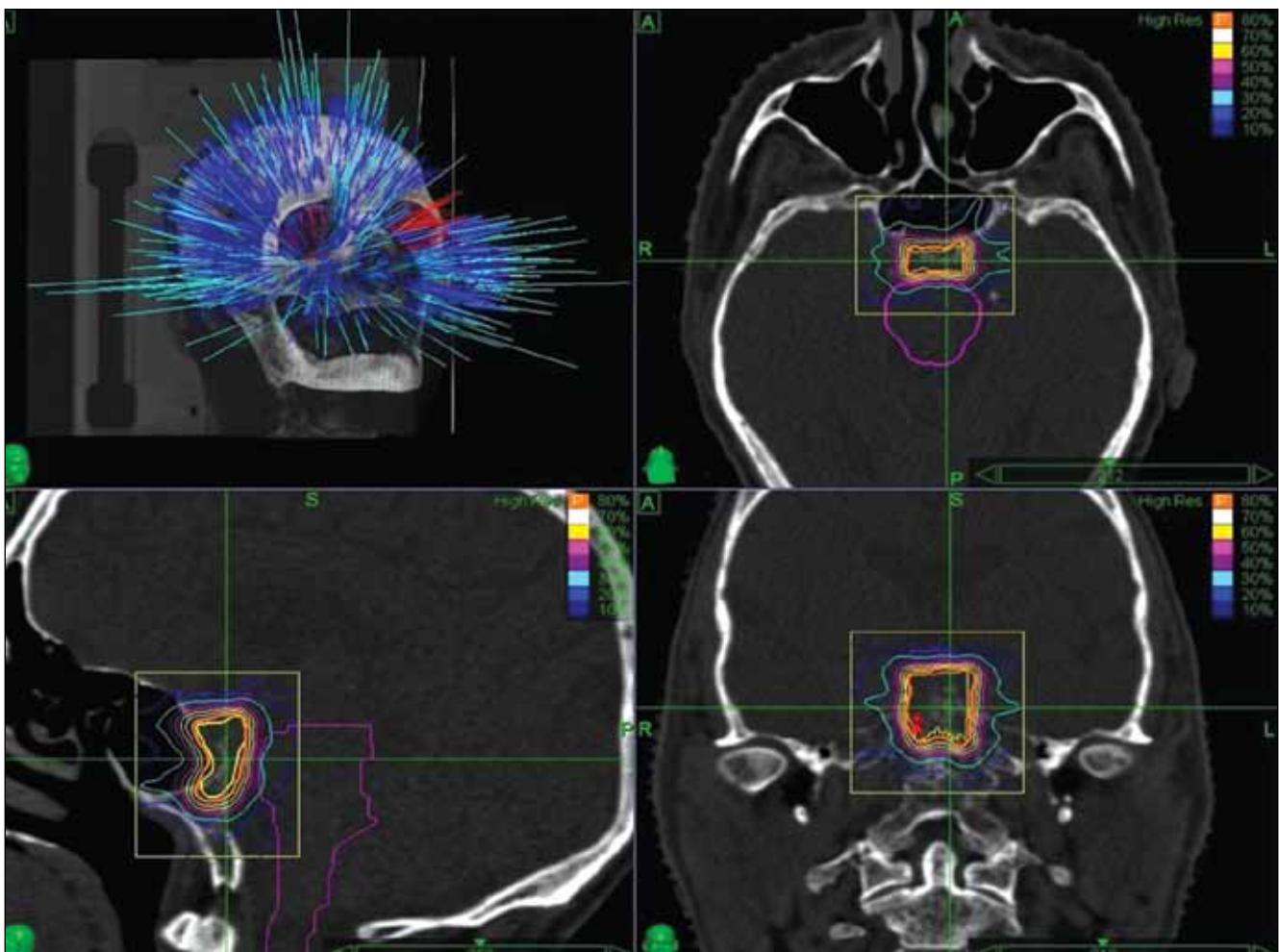


Figure 3: Treatment planning showing isodoses distribution around the clivus, 3D rendering of bony anatomy and distribution of beams delivered by the robotic device during treatment, and dose- volume histograms of tumor site, brainstem and optic chiasm showing reduced dose delivery to the critical areas.

(4). Thalidomide and dexamethasone (5) or high-dose dexamethasone (1) are used in refractory cases or in cases with relapse while undergoing the above regimens. Autologous and allogeneic stem cell transplantation is a new treatment modality in the treatment for multiple myeloma (2). In our case, there was no evidence of systemic disease at the diagnosis. A transphenoidal biopsy allowed a diagnosis of plasmacytoma. Radical surgery was prevented by the diffusion to the entire clivus and sella lesions. External beam radiation was considered, but the vicinity of critical structures including the brainstem, eyes and the optic pathway, together with the absence of a systemic illness favored a radiosurgical approach with the Cyberknife technique. The Cyberknife (Accuray, Sunnyvale, CA) is a frameless LINAC-based system constructed on a non-isocentric single-beam radiation delivery and a high number of penetration trajectories (up to 1600) allowed by a robotic delivery system (13). Real-time image guidance, based on digitally reconstructed skull radiographs, provide an accurate tool to localize and treat the target without need for a rigid frame, thus offering the unique opportunity for hypofractionated radiosurgical treatment.

The system also possesses submillimeter accuracy and highly conformal dosimetry, and was therefore reasonable option to control our patient's tumors without causing undue radiation-induced toxicity (6). According to previous experiences with the GammaKnife, we choose 1400 cGy to treat the lesions (3). A biologically equivalent dose was used for hypofractionation. Concerning the lesion of the clivus, the direct contact with the brainstem and optic chiasm favored a hypofractionated approach. Three fractions for a total of 2100 cGy were delivered to this target. The maximal dose to the chiasm was therefore maintained at about 300 cGy per fraction, whereas the maximal dose to the brainstem was about 400 cGy per fraction, well within the tolerance margins. Despite the clear advantages with a similar approach, the rationale for this choice should be discussed. Plasmacytoma involving the skull base is rare (7, 12). When such a pathology is found, histological grade should be established and extensive evaluation for multiple myeloma should be performed. This approach can provide important prognostic information and can lead to optimal treatment. Surgical resection should be reserved for selected lesions and should be followed by radiation.

The Cyberknife system should be considered for its ability to tightly target the tumor with an ablative dose of radiation and a corresponding minimal dose to the surrounding critical structures. This approach, together with the radiosensitivity of plasma cell tumors, makes this treatment modality particularly advantageous. There is also evidence that high conformal radiosurgery offers advantages over surgery and conventional external beam radiation for all lesions widely involving the clivus and the sella (11). Those lesions have a high probability of being metastases or tumors amenable to radiosurgical treatment. This area needs further exploration, as it may prove better for the patient to undergo a biopsy to

confirm tumor diagnosis before proceeding with a surgical resection.

REFERENCES

- Alexanian R, Barlogie B, Dixon D: High-dose glucocorticoid treatment of resistant myeloma. *Ann Intern Med* 105(1):8-11, 1986
- Alyea E, Weller E, Schlossman R, Canning C, Mauch P, Ng A, Fisher D, Gribben J, Freeman A, Parikh B, Richardson P, Soiffer R, Ritz J, Anderson KC: Outcome after autologous and allogeneic stem cell transplantation for patients with multiple myeloma: Impact of graft-versus-myeloma effect. *Bone Marrow Transplant* 32(12):1145-1151, 2003
- Peker S, Abacioglu U, Bayrakli F, Kilic T, Pamir MN: Gamma knife radiosurgery for cavernous sinus plasmacytoma in a patient with breast cancer history. *Surg Neurol* 63(2):174-176, 2005
- Raje N, Anderson KC: Multiple myeloma. *Curr Treat Options Oncol* 1(1):73-82, 2000
- Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, Geyer S, Iturria N, Fonseca R, Lust JA, Kyle RA, Witzig TE: Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 20(21):4319-4323, 2002
- Ryu SI, Chang SD, Kim DH, Murphy MJ, Le QT, Martin DP, Adler JR Jr: Image-guided hypo-fractionated stereotactic radiosurgery to spinal lesions. *Neurosurgery* 49(4):838-846, 2001
- Schwartz TH, Rhiew R, Isaacson SR, Orazi A, Bruce JN: Association between intracranial plasmacytoma and multiple myeloma: Clinicopathological outcome study. *Neurosurgery* 49(5):1039-1044, 2001
- Segeren CM, Sonneveld P, van der Holt B, Baars JW, Biesma DH, Cornellissen JJ, Croockewit AJ, Dekker AW, Fibbe WE, Lowenberg B, van Marwijk Kooy M, van Oers MH, Richel DJ, Schouten HC, Vellenga E, Verhoef GE, Wijermans PW, Wittebol S, Lokhorst HM: Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma. *Br J Haematol* 105(1):127-130, 1999
- Singh AD, Chacko AG, Chacko G, Rajshekhar V: Plasma cell tumors of the skull. *Surg Neurol* 64(5):434-438, 2005
- Weber DM: Solitary bone and extramedullary plasmacytoma. *Hematology / the Education program of the American Society of Hematology*. American Society of Hematology 373-376, 2005
- Weilbaecher C, Patwardhan RV, Fowler M, Willis BK, Nanda A: Metastatic lesions involving the sella: Report of three cases and review of the literature. *Neurol India* 52(3):365-368, 2004
- Wein RO, Popat SR, Doerr TD, Dutcher PO: Plasma cell tumors of the skull base: Four case reports and literature review. *Skull Base* 12(2):77-86, 2002
- Yu C, Main W, Taylor D, Kuduvali G, Apuzzo ML, Adler JR Jr: An anthropomorphic phantom study of the accuracy of Cyberknife spinal radiosurgery. *Neurosurgery* 55(5): 1138-1149, 2004