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Case report

A case report of stereotactic radiosurgery in a patient with Ehlers–Danlos syndrome

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ABSTRACT

In this report, we outline the case of a patient who has Ehlers–Danlos Syndrome (EDS) who received two courses of CyberKnife stereotactic radiosurgery (SRS) for metastatic non-small cell lung cancer. Patients with EDS have increased blood vessel fragility, and therefore are subject to increased risk of bleeding. There are no published data regarding the risks of hemorrhage associated with SRS for intracranial metastases in this patient population. The patient described in this case report had two courses of SRS for two sites of brain metastases. She tolerated treatment well, with no acute toxicity and good local control to date. We have also included a discussion of published literature regarding toxicity of intracranial radiation in patients with EDS.

DD is a 71-year-old woman with a past medical history significant for Ehlers–Danlos syndrome (EDS) and tobacco abuse who presented to her primary care physician with cough and mild hemoptysis. Chest X-ray and CT scan demonstrated an abnormality in the lower lobe of the left lung. A PET scan showed mildly FDG avid left hilar lymph nodes and a 6.8 cm × 12 cm left lower lobe mass abutting the aorta; there was no extrathoracic disease. Endobronchial ultrasound guided biopsy of a subcarinal lymph node was positive for adenocarcinoma. Staging brain MRI revealed a 7 mm ring enhancing lesion in the anterior right frontal lobe consistent with metastasis.

Approximately 5 years prior to her cancer diagnosis, the patient was evaluated by a clinical geneticist at our institution and diagnosed with hypermobility type EDS. She also has a history of EDS-related medical problems, including Raynaud's syndrome, subarachnoid hemorrhage, infra-renal abdominal aortic aneurysm, hypertension, and lower GI bleeding.

For management of her lung cancer, she received concurrent chemotherapy and external beam radiation therapy. She initially received carboplatin and paclitaxel, but due to severe myalgia and arthralgia was switched to carboplatin and pemetrexed for subsequent cycles. After the completion of chemoradiotherapy, she was evaluated for consideration of CyberKnife stereotactic radiosurgery (SRS) for a solitary right frontal brain metastasis. At that time, the patient denied any neurologic symptoms. Physical exam did not reveal any focal neurologic deficits or other abnormalities. Treatment options for her intracranial disease were discussed, which included observation, surgical resection with or without adjuvant radiation therapy (whole brain or SRS), whole brain radiation therapy, and CyberKnife SRS.[1] As part of this discussion, the patient was informed that she may be at higher risk for severe complications from SRS, including life-threatening intracranial hemorrhage, given her diagnosis of EDS. We explained

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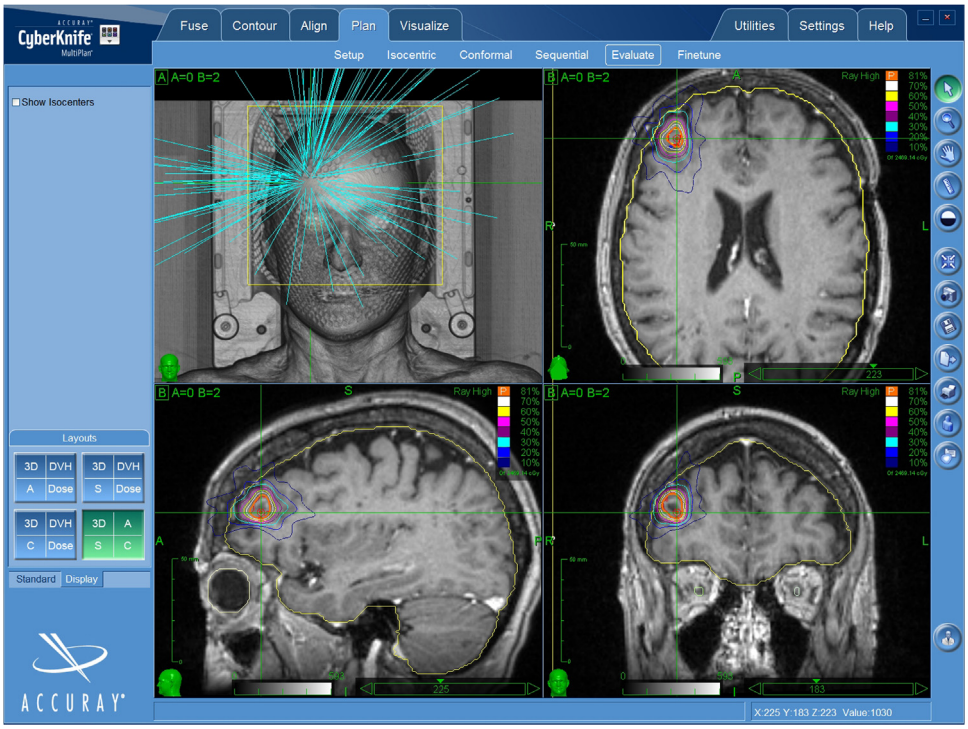

Fig. 1 – Treatment plan for first SRS treatment.

that there were no published data evaluating the safety of CyberKnife SRS in patients with EDS. The patient elected to proceed with CyberKnife SRS.

She was treated with a single fraction of CyberKnife SRS to her right frontal brain metastasis. She received a prescription dose of 20 Gy prescribed to the 81% isodose line. The maximum dose was 24.6 Gy which occurred within tumor volume. The conformity index was 1.25 and 97.1% of the tumor volume received the prescription dose or higher (see Fig. 1). The patient tolerated SRS well and had no acute toxicity from treatment. Approximately 3 months later, the patient was seen in Radiation Oncology clinic for ongoing oncologic surveillance. A repeat MRI demonstrated stability of the right frontal metastasis that was treated, with no evidence of new intracranial metastases.

She returned for repeat brain imaging approximately 6 months after her course of CyberKnife SRS. A brain MRI demonstrated a new 1 cm metastasis in the left frontal lobe, as well as interval decrease in the size of the previously treated right frontal lobe metastasis. Her extra-cranial disease remained stable. At this time, she did complain of occasional symptoms of imbalance while walking and difficulty with word-finding. These symptoms were said to occur several times per week. She otherwise denied any other neurologic or focal complaints. Physical exam showed some mild gait unsteadiness but did not demonstrate focal weakness or any new neurologic deficits.

We again discussed treatment options with the patient, and she elected to proceed with a second course of CyberKnife SRS to the new metastatic lesion. Her left frontal lobe metastasis was treated with a prescribed dose of 20 Gy to the 83% isodose line. The maximum dose was 24.1 Gy and occurred within the tumor volume. The conformity index was 1.23 and 100% of the tumor volume received the prescription dose or higher (see Fig. 2). The dose to the previously treated right frontal radiosurgical bed was limited to 28 cGy. She tolerated the procedure well and had no acute toxicity from treatment.

1. Discussion

Ehlers–Danlos syndrome refers to a heterogeneous group of inherited connective tissue disorders that are caused by various defects in the synthesis of type I or type III collagen. The nomenclature for types of EDS has evolved over the years, and was simplified in 1997 to six major types: (1) hypermobility, (2) classical, (3) vascular, (4) kyphoscoliosis, (5) athrochalasis, and (6) dermatosparaxis.[2] Vascular EDS (previously known as Type IV EDS) is inherited in an autosomal dominant fashion and is caused by a defect in the synthesis of type III collagen. One important clinical characteristic of this defect is the association with blood vessel fragility, which causes affected patients to have above-average risk for blood vessel rupture.[3] This can manifest as spontaneous rupture of cerebral arteries, easy skin bruising, and aortic aneurysm. Hypermobility type EDS, such as that seen in our patient, is a much more common albeit less severe form of this disease.[4] Given our patient's history of EDS-related gastrointestinal as well as intracranial bleeding, it is reasonable to assume that she may have an increased risk of bleeding related to CyberKnife SRS treatment of intracranial metastatic disease.

To the authors' knowledge, there are no published data regarding the risk of acute or late toxicity associated with CyberKnife SRS in patients with EDS. Holodny et al. reported

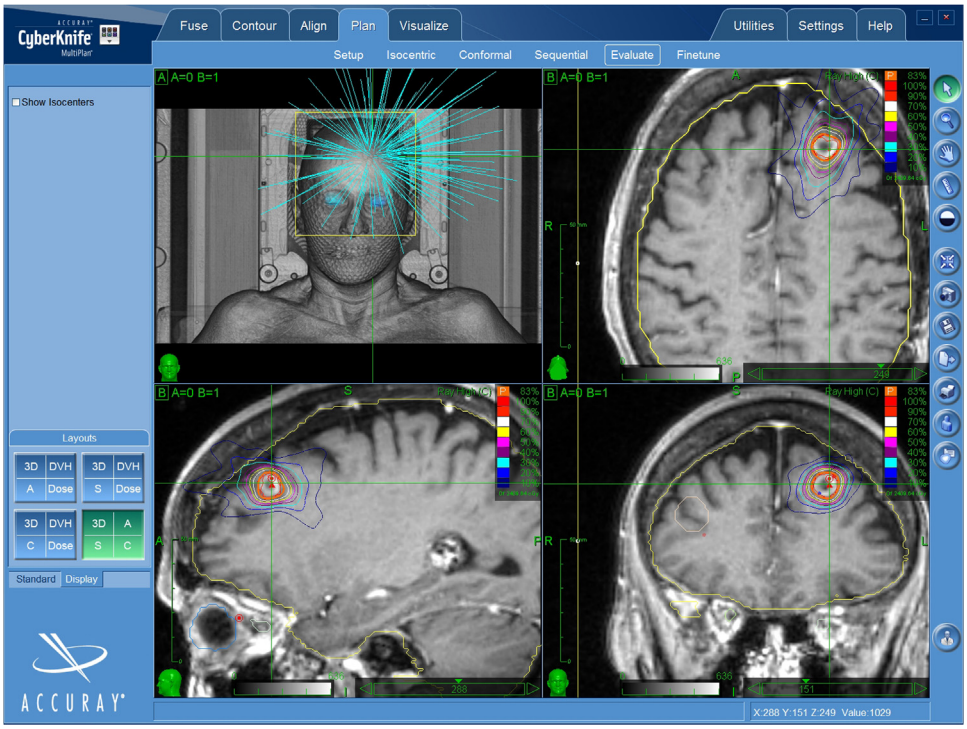

Fig. 2 – Treatment plan for second SRS treatment.

a patient with a presumptive diagnosis of Vascular EDS who received whole brain radiation therapy for breast cancer metastatic to the brain.[5] She received 21 Gy and four months later was treated with an additional 10.8 Gy. Both courses of radiotherapy were tolerated without any acute toxicity. Three months after the second treatment, the patient had a generalized seizure and died shortly thereafter. Her autopsy revealed seven aneurysms in or near the Circle of Willis, one of which had ruptured. All other intracranial vessels were found to be normal at autopsy. Interestingly, an MRI performed prior to intracranial radiation therapy did not show any abnormalities in the vessels of the Circle of Willis.

In vitro studies have shown that there is an increase in collagen biosynthesis in cells that are exposed to ionizing radiation at doses comparable to what is used for therapeutic whole brain radiation.[6] The formation of intimal fibrosis may prevent the formation of an aneurysm.[7] Patients with EDS are at above average risk for blood vessel aneurysm and rupture because of deficiencies in the collagen supporting these vessels. Furthermore, Holodny et al. hypothesize that patients with Vascular EDS are more sensitive to blood vessel damage caused by high doses of ionizing radiation due to the inability to generate a protective intimal fibrotic response.[5] This might lead one to be leery of administering high-dose radiosurgery to patients with EDS. However, at this time our patient continues to be without symptoms from her treatment.

Although we are unaware of published literature regarding toxicity of SRS in patients with EDS, Lowell et al. recently published a series examining the toxicity of SRS in patients with mixed connective tissue disease (MCTD).[8] In this retrospective series, 14 patients with MCTD were treated with Gamma Knife Radiosurgery (GKRS) for intracranial tumors. No patients were reported to have suffered vascular injury or aneurysm related to GKRS. Despite the different mechanisms underlying vascular abnormality and weakness between EDS and MCTD, it is notable that patients with a nominally increased risk of vascular injury were able to tolerate high dose radiosurgery with no vascular complications.

In summary, we report the case of a patient with Vascular EDS who was treated with two courses of CyberKnife SRS for intracranial metastatic disease. To date, the patient has not experienced any significant treatment related toxicity and has shown satisfactory local control. The two lesions treated in our patient were located in the frontal lobe and were not in close proximity to the Circle of Willis. This case demonstrates that CyberKnife SRS can be safely administered and effective in patients with EDS.

Disclaimer

None.

Conflict of interest

None declared.

Financial disclosure

None declared.

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