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LETTER TO THE EDITOR

Recall radiation myelitis after stereotactic radiation and dabrafenib in metastatic melanoma

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To the Editor,

About 50% of all cutaneous melanomas have an activating mutation in the BRAF gene – 80–90% of those being V600E mutations, resulting in increased proliferation. The BRAF inhibitors like vemurafenib and dabrafenib have resulted in increased overall survival [1]. The interaction with radiotherapy is not yet well explored. We present a case of a possible late radiation recall phenomenon.

A 48-year-old Caucasian woman was diagnosed with metastatic melanoma in 2013. First line treatment was seven courses of nivolumab. In autumn 2014, the patient received four courses of ipilimumab due to progression. A partial response was obtained. Concomitant with ipilimumab the patient received stereotactic radiotherapy in November 2014 to a large central, left-sided pulmonary lung metastasis. Treatment was given with 56 Gy in 8 fractions; 4 fractions per week. The dose to the organs at risk was in concordance with our general practice; the dose to the spinal cord did not exceed 33.5 Gy (Figure 1(a) and (b)). In March 2015, a restaging computed tomography (CT)-scan showed progression. Third line treatment was dabrafenib, initiated March 2015 and with addition of trametinib from April 2015. A follow-up CT-scan showed complete remission by June 2015.

In June 2015, seven months after stereotactic body radiotherapy the patient described a skin rash on her back in the same volume where she received radiotherapy, located below the third thoracic vertebra. The rash was interpreted as a radiation recall phenomenon, caused by dabrafenib. A month later the patient developed back pain in the same site as the rash was seen. A positron emission tomography (PET)-CT showed unspecified activity in the former radiation-treated volume of the spinal cord. Between July and November 2015, the patient's back pain intensified and paresthesias in the lower body and extremities was registered. Magnetic resonance imaging (MRI) showed radiation-induced myelitis in the thoracic spine from TH2 to TH9 (Figure 1(c) and (d)), described as edema. We assume this to be caused by radiotherapy followed by radiosensitization by dabrafenib.

The patient was treated with prednisolone 25 mg/day for one week, tapering off over six weeks. A PET-CT from January 2016 showed no sign of malignant disease in the volume, previously receiving radiotherapy. However, disease progression was found in other sites and dabrafenib and trametinib was reintroduced, without worsening of the myelitis.

In this case, a patient developed radiation recall myelitis after receiving a BRAF inhibitor. Radiosensitization and radiation recall skin toxicity have been reported in relation with treatment with another BRAF inhibitor vemurafenib [2]. Newer case reports describe the same phenomena with dabrafenib [3], but presumably with a lower frequency. To our knowledge this is the first reported case of radiation recall

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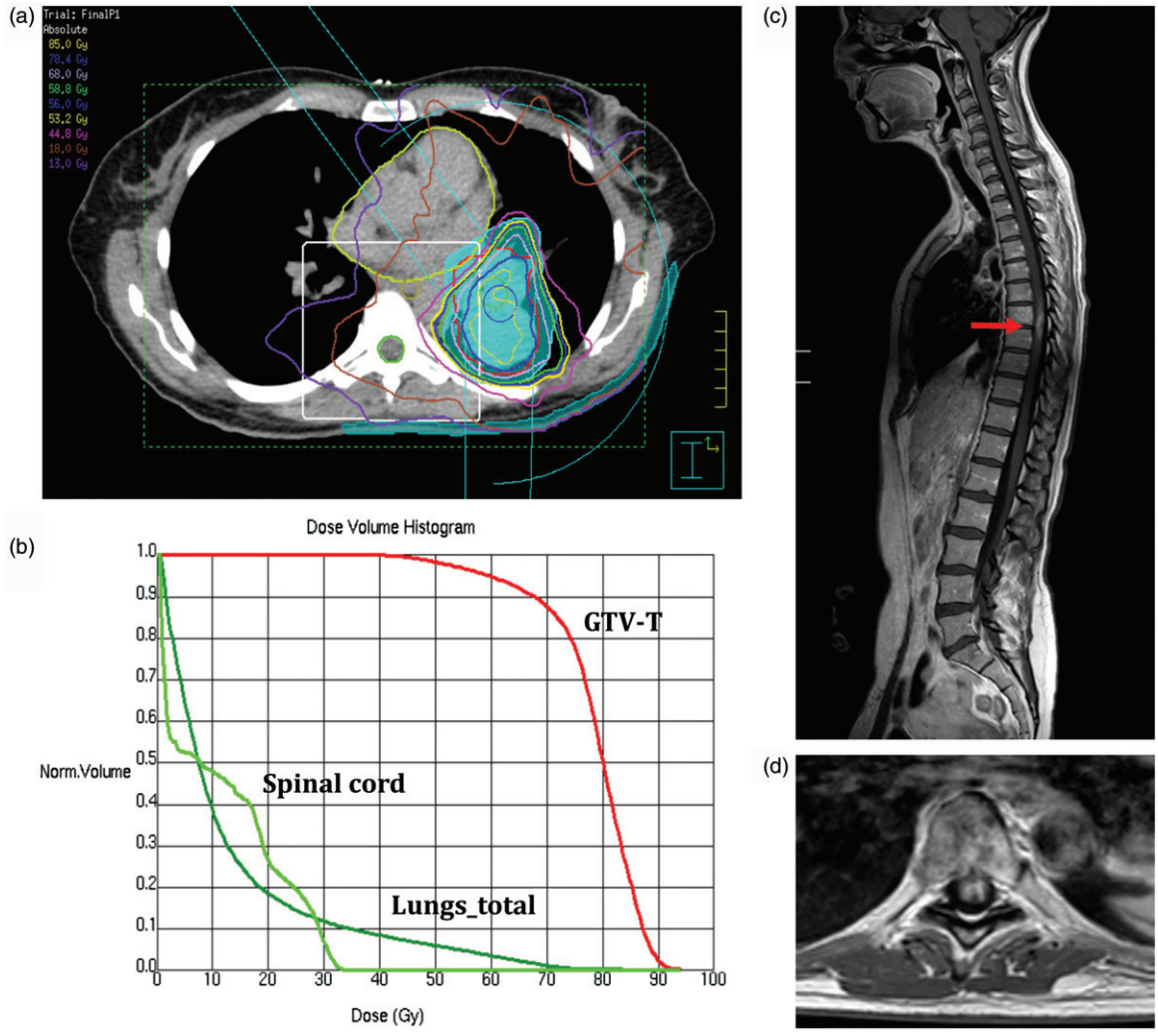

Figure 1. The CT-based plan of stereotactic radiotherapy showing isodoses (a), along with the dose-volume histogram – the pale green line showing absorbed dose by the spinal cord (b). Also, MRI after radiotherapy sagital plane – arrow marking the affected area (c) and in the axial plane showing myelitis (d).

myelitis described with a BRAF inhibitor, in this case dabrafenib [3,4].

The frequency of radiation recall phenomena with drugs targeting BRAF and MEK is unknown [5]. Radiation recall is best described as an acute inflammatory reaction in previously irradiated volumes – the reaction is triggered by systemically given drugs, in this case a BRAF inhibitor. This case is challenging due to the long time interval between radiotherapy and the severe reaction. There are, at the moment, no evidence-based guidelines for patients who are at risk of developing radiation recall phenomena during treatment with BRAF inhibitors [6].

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