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Abscopal effect of radiotherapy in a patient with metastatic diffuse-type giant cell tumor


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To the Editor,

A 19-year-old male presented in 1999 with anemia, increased inflammatory parameters and knee complaints, based on diffuse-type giant cell tumor (DGCT). In 2010, a low femoral amputation was performed after several functional joint sparing surgeries and a short unsuccessful period of imatinib 400 mg once daily (OD) therapy [1]. Histopathology showed destructive DGCT with secondary changes due to imatinib treatment, but no signs of malignancy.

Four years later, he presented with fever, sweating, anorexia, weight loss, palpitations and anemia. FDG-pozitron emission tomography (PET)-computed tomography (CT) scan showed new pulmonary lesions and mediastinal lymphadenopathy. A cytological lymph node biopsy proved metastatic DGCT. Imatinib 400 mg OD and predisolone 30 mg OD were started. No other immune-modulating therapy has been administered. Two months after start of imatinib and prednisolone, his clinical condition deteriorated with weight loss, fever and inflammation (Table 1). FDG-uptake showed increased metabolic activity of metastases. To prevent atelectasis, the highly metabolically active right hilar metastasis was irradiated (30 Gy in 10 fractions; Figure 1(a)). During radiotherapy, his condition rapidly deteriorated with high fevers, profound anemia, hypoalbuminemia, decreased sodium, hyperglycemia and pulmonary infection (Table 1). Unexpectedly, within two weeks after completing radiotherapy, he clinically improved and his inflammatory laboratory values decreased (Table 1). FDG-PET-CT showed response of the right irradiated hilar lesion, volumetric and metabolic response of left-sided non-irradiated pulmonary metastases and an increase of uptake in one mediastinal lymph node (Figure 1(b) and (c)). This phenomenon is called abscopal effect. It persisted for six months, after which he progressed and died from disease three months later.

Discussion
The abscopal effect induced by radiotherapy is rare and is mostly reported in tumor types considered immunogenic such as melanoma, lymphoma and prostate cancer [2]. Even rarer is the abscopal effect of a systemic therapy, such as imatinib [3]. A possible mechanism could be the immune-modulating properties of imatinib. In agreement with this, a case report [4] describes a patient with a highly immunogenic melanoma response to treatment with ipilimumab and continued to respond to radiotherapy alone, implying enhanced antigen presentation and response by imatinib. It is plausible that such mechanisms also lead to the observed abscopal effect of radiotherapy and imatinib in this patient.

REFERENCES

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as melanoma, but has to our knowledge never been described in mesenchymal malignancies [2]. The immune system has been proposed as the key component of this abscopal effect [3]. Local radiotherapy induces cell death and release of immunogenic factors, leading to host immune responses. Damage-associated molecular patterns trigger dendritic cells, resulting in improved antigen presentation to T cells [2,4]. Pharmacological modification of the abscopal effect has been suggested for immune checkpoint inhibitors and granulocyte-macrophage colony-stimulating factor [4–7].

Here we report a patient with malignant DGCT with marked inflammatory symptoms and laboratory parameters, who demonstrated a systemic benefit from local radiotherapy by an abscopal effect. Tenosynovial giant cell tumors are rare mesenchymal lesions that arise from the synovial lining of articular spaces, bursal sacs, and tendon sheaths. The diffuse-type is an aggressive multifocal proliferation of synovial-like mononuclear cells with inflammatory infiltrates. Metastases of DGCT are extremely rare. The current treatment strategies have recently been reviewed [8]. The inflammatory nature and the observed abscopal effect plea for considering immunotherapeutic approaches in this disease.

**Disclosure statement**

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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LETTER TO THE EDITOR

The relative biological effectiveness of carbon ion irradiations of the rat spinal cord increases linearly with LET up to 99 keV/μm

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To the Editor,

Based on preliminary work at the Lawrence Berkeley Laboratory [1], carbon ion beams developed to a mature technology in radiotherapy, which has now been applied successfully in patients for two decades [2–4]. As in proton radiotherapy, the depth-dose profile (Bragg peak) of carbon ions allows for highly conformal irradiations of the tumor. However, the rise of the relative biological effectiveness (RBE) with penetration depth towards the distal end of a spread-out Bragg peak (SOBP) is much more pronounced for carbon ions than for protons [5]. Quantitatively, the RBE is given by the ratio of a photon and an isoeffective carbon ion dose at a defined endpoint. However, the RBE is a complex quantity depending on particle type, linear energy transfer (LET), dose, and also on biological properties of the irradiated tissue. To consider the increased effectiveness of carbon ions, the RBE is calculated by bio-mathematical models. In Europe, clinical treatment planning is done using the local effect model (LEM), which is presently available in two versions (LEM I [6] and IV [7]). Although LEM I has been used for all patients so far, LEM IV was extended by including information on the spatial DNA double stand break density. It is, however, an open question, which version is more accurate.

To validate the LEM in vivo, the RBE for radiation-induced myelopathy in the rat spinal cord has been determined in several studies [8–11] and comparisons with LEM predictions were made. In these studies RBEs were calculated for the tolerance doses at 50% complication probability (TD50) determined from dose-response experiments. Although initial studies [8,9] demonstrated a strong dose-dependence of the RBE, the LET-dependence was not investigated in detail.

This was the starting point of a second series of experiments, where the rat spinal cord was irradiated with single and split doses at six different positions of a 6 cm SOBP covering a LET range from 16 to 99 keV/μm [10,11]. These data showed a linear increase of RBE with LET, where the slope of the curve increased with decreasing fractional dose [11]. For the single fraction experiment at 99 keV/μm, however, an inconsistently low RBE combined with a shallow dose-response curve was found. As this was only observed in the single but not in the split dose experiments, we repeated the 99 keV/μm single dose experiment and report here on the results.

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