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Radiation-induced myelopathy after hypofractionated radiotherapy in women with spinal metastases from breast cancer — a case report

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ABSTRACT

Hypofractionated radiotherapy, with a single dose of 8 Gy or 20 Gy given in 4–5 fractions, remains a standard treatment of bone metastasis, including spine lesions. Hypofractionated radiotherapy is also used during re-irradiation. These schedules are associated with an increased risk of severe complications, and their differentiation from local tumour progression can be difficult. We describe a 55-year-old female with breast cancer, who underwent palliative radiotherapy with a dose of 20 Gy in four fractions to the Th6–Th10 spine levels. After four months the patient was referred for re-irradiation due to progression of neurological symptoms. MRI examination suggested local tumour progression. Due to rapid deterioration she did not receive re-irradiation, and died due to systemic fungal infection. Autopsy revealed extensive radiation myelopathy in previously irradiated thoracic spine, without the presence of cancer at the site.

Key words: breast cancer, bone metastases, hypofractionated radiotherapy, re-irradiation

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Introduction

Breast cancer is the most frequent neoplasm diagnosed among women in the majority of countries, as well as in Poland. Bone metastases are very common in patients with breast cancer and are typically located in the axial skeleton (including spine) [1]. Palliative radiotherapy together with surgery is the standard modality of local treatment of bone metastases. Beyond its analgesic effect it decreases the risk of some complications, including neurological changes due to the presence of tumour mass and deformation of surrounding tissues, which result from bone destruction. Furthermore, in some cases radiotherapy can prolong survival [2].

Various protocols of hypofractionated irradiation are used during palliative radiotherapy of bone metastases, most commonly with a single dose of 8 Gy or total dose of 20–25 Gy divided into 4–5 fractions [3]. This is supported by short treatment duration, and lower patient burden and cost. Comparable analgesic efficacy of single dose of 8 Gy and total dose of 20 Gy in five fractions was confirmed in randomised controlled trials [4, 5]. Hypofractionated radiotherapy is also used in patients with local progression of cancer in previously irradiated areas [6]. Administration of a fraction dose that is higher than a conventional one (2–2.5 Gy) is associated with higher risk of complications, particularly with reference to tissues of low α/β ratio, including spinal cord (it is assumed that the α/β ratio for spinal cord amounts to 1–2 Gy, depending on the part).

Differentiation between post-irradiation changes and local progression of cancer in a previously irradiated site could be very difficult. We present the case of patient eligible for re-irradiation of metastases in thoracic spine, which during autopsy turned out to be a necrosis after previous palliative hypofractionated radiotherapy.

Case report

A 55-year-old female patient with metastatic ductal breast cancer was admitted to the Clinic of Oncology and Radiotherapy of the Medical University of Gdańsk in October 2013 for re-irradiation of metastases in the spine. No major concomitant diseases were revealed. In January 2012 right mastectomy was carried out due to breast cancer pT2N1M0 with subsequent adjuvant hormone therapy. During the course of adjuvant treatment bone metastases were diagnosed. In September 2012 the patient had palliative radiotherapy with irradiation of thoracic part of spinal cord (Th6–Th10; area of 6 cm × 10 cm) with dose of 20 Gy divided into four fractions (one fraction per day) specified to a depth of 9 cm from skin, using 2D technique and single photon beam with energy 6 MV. During hospital admission for re-irradiation the patient was in a moderately severe general condition with signs and symptoms of pneumonia. The medical history revealed compassing abdomen pain, radiating to lower extremities, which progressed during the previous two months, and loss of bladder and bowel control of two weeks' duration. Patient received dexamethasone (daily dose of 24 mg). Neurological examination revealed symmetrical lemniscus disturbances of sensation from the level Th6, mainly in proximal parts, muscle weakening, and bilateral pyramidal symptoms of lower extremities. All those signs and symptoms indicated transverse interruption of the spinal cord on the level Th6. Magnetic resonance imaging (MRI) showed numerous lytic and sclerotic focuses in vertebrae trunks of the thoracic and lumbar part of the spine, with no loss of vertebral height. T2 imaging showed increased signal of spine from Th2 to Th11, which could correspond to post-irradiation changes. Additionally there was visible band-like area of contrast spinal cord enhancement on the level Th9–10–11 with a length of 54 mm and width of 8 × 9 mm that showed no abnormal signals in T1 imaging before intravenous contrast medium administration and was of potential concern due to secondary infiltration. In order to distinguish cancer invasion from post-irradiation changes positron emission tomography–computed tomography (PET-CT) — was done with administration of fluorodeoxyglucose, but due to technical issues it was non-diagnostic.

Concomitant pulmonary invasive aspergillosis was diagnosed. Despite targeted antifungal and antibacterial treatment, the patient died. The autopsy revealed numerous, partially fungal pulmonary abscesses and necrosis of neural tissue in specimens of spinal cord, involving central the thoracic part and nearly the whole area of spinal cord cross-section. Necrosis was accompanied by thickening and vitrification of the walls of arterioles in spinal cord. There were numerous metastases in bones, ovaries, and bone morrow although there were no cancer cells in the spinal cord.

Discussion

Post-irradiation necrosis of spinal cord is an uncommon serious complication of palliative radiotherapy of cancer metastases to the spine [7, 8]. As patients with advanced breast cancer are continuously living longer this issue could have increasing importance [9].

Neurological signs and symptoms of post-irradiation necrosis of spinal cord may appear months to years after radiotherapy [10]. Some authors described short time to spinal cord involvement — 3 to 8 months with median of 5 months [9]. The intensity of symptoms increases in time and, depending on the injury level, involve numbness and hyperesthesia of distal parts of limbs, constrictor dysfunctions, and progressing muscle weakening, most commonly leading to para- or tetraplegia [11].

The damage of endothelial cells and oligodendrocytes has a crucial role in the pathophysiology of post-irradiation necrosis of the spinal cord [12]. Studies conducted on the spinal cords of rats with use of conventional doses of irradiation showed the loss of myelin commencing two weeks after radiotherapy cessation and progressing during subsequent months [12].

There are many different factors, besides total and fractional dose, that impact the risk of post-irradiation necrosis of the spinal cord [13, 14]. Total duration of irradiation, intervals between fractions, the extent of the irradiated area of spinal cord, and individual – mostly unpredictable – susceptibility to irradiation are of significant importance. Diabetes and vascular diseases as well as concomitant chemotherapy additionally may increase the risk of post-irradiation injuries. The risk of post-irradiation necrosis significantly grows after exceeding the biological dose expressed as an equivalent dose in 2 Gy fraction (EQD2) amounting to 50 Gy and is estimated at 0.2%, 6%, and 50% after administration of an EQD2 dose of 50 Gy, 60 Gy, and 69 Gy, respectively [15]. In the case of re-irradiation the risk of post-irradiation necrosis significantly increases and depends mainly on the sum biological dose. The time since first irradiation has additional importance with respect to repairing processes of post-irradiation damage. Those processes go fastest during first eight weeks after irradiation; approximately 50% of post-irradiation damage regenerates after six months, but they are observed even 1–3 years after radiotherapy [16]. In the presented patient the isodose curve capturing spinal cord accounted for approximately 120% of the requested dose. Assuming that the α/β ratio for spinal cord amounts to 2 Gy, the EQD2 dose given to the spinal cord was approximately 48–49 Gy.

The main goal of differential diagnosis of post-irradiation necrosis of the spinal cord is the exclusion of other reasons for neurological symptoms, particularly local progression of cancer, which could be an indication for re-irradiation. However, magnetic resonance

imaging, which is the method of choice, typically reveals only unspecific changes, including strong signal in T2 imaging, oedema of spinal cord in T1 imaging, and annular focuses in spinal cord after contrast medium administration [17]. PET-CT imaging is more specific in differentiating post-irradiation myelopathy [18]. Contrary to cancer infiltration, which intensively uptakes fluorodeoxyglucose, the necrotic changes do not show such an uptake of radiotracer. However, a case of post-irradiation damage of spinal cord with enhanced uptake in PET-CT was described, interpreted as being the result of a lack of myelin in neural fibres in the irradiated area [19]. Use of 11C-choline as a radiotracer increases the specificity and sensitivity of PET-CT in the differentiation of cancer relapse and post-irradiation in the central nervous system [20].

Therapeutic options in post-irradiation necrosis of spinal cord are limited. In some cases objective improvement could be achieved after administration of steroids, hyperbaric oxygen, alpha-tocopherol, deferoxamine, warfarin, and heparin as well as bevacizumab [21].

In the presented article we described the difficulties in diagnosis of post-irradiation necrosis of the spinal cord. In the presented case this severe complication occurred after hypofractionated radiotherapy with a dose of 20 Gy given in four fractions, which corresponded to a biological dose of relative safety. The reasons for the described fatal myelopathy remain unknown; one possibility is specific individual sensitivity of the patient to ionising radiation.

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