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Giant-cell tumour of bone with lung metastases — case report

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ABSTRACT

Majority of giant-cell tumours of bone are benign with locally malignant potential. In some patients, the clinical course may be more aggressive, and treatment is not always effective. An individual therapeutic approach may then be of benefit, including bone remodelling agents, chemotherapy, radiotherapy, and possibly immunotherapy, in a future perspective.

Key words: tumour gigantocellularis, giant-cell tumour, lung metastasis, denosumab, chemotherapy, radiotherapy, abscopal effect

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Introduction

Giant-cell tumour of bone is a neoplasm of some locally malignant potential. In some patients, the clinical course may be more aggressive, which necessitates a more intensive management, that might not be effective. An individual therapeutic approach, with multimodal treatment protocols, may then be of benefit

The authors present herein a case report of a patient with lung metastases of giant-cell tumour of bone, in whom sequential application of systemic and local therapy resulted in a significant clinical benefit and disease control.

Case report

A 26-year-old male patient presented in September 2009 to the surgical outpatient clinic of the Lower Silesian Oncology Centre (DCO, Dolnośląskie Centrum Onkologii) in Wrocław because of sensory symptoms and the presence of a tumour in the left upper limb. The patient reported numbness and paraesthesia in the fingers of his left hand supplied by the left ulnar nerve, which had begun in May that year. He was referred to an orthopaedic surgeon in August.

On admission, physical examination revealed a tumour in the lower part of the left forearm, painful to palpation. X-ray picture showed a five-centimetre-long osteolytic dilatation of the left distal ulnar bone, with thinned and locally disrupted cortex, periosteal thickening, and soft tissue engagement.

There were no signs of disease dissemination on radiological staging (T1N0M0).

Open biopsy of the ulnar tumour was performed on October 30th, 2009. Histopathological investigation identified giant-cell tumour of bone (GCT). The patient was qualified for elective surgery, and the tumour was resected with distal 1/3 of the ulnar bone on December 2nd, 2009.

Postoperative histopathological report confirmed the diagnosis of GCT with low proliferative activity. Focal necrosis and haemorrhages were found in the sample, which could suggest some malignant potential and risk of recurrence. Adjuvant radiotherapy (RT) was first considered but not undertaken given the radical excision, and active follow-up was chosen instead.

In March 2010, the patient observed a centimetre-long thickening of the distal part of postoperative

scar. Radiological investigation showed no pathological lesions, and further follow-up was scheduled.

Control X-ray performed in February 2011 revealed a local lesion of uncertain character, and computed axial tomography (CAT) was decided. CAT scans showed findings consistent with local postoperative lesions of $3.3 \times 3 \times 6$ cm, with no contrast enhancement. Magnetic resonance imaging (MRI) was decided to perform but the patient did not attend. The investigation was performed in January 2012, and a 5-cm tumour was found in the previously operated area.

Chest X-ray disclosed multiple bilateral pulmonary metastases of up to 2.6 cm, and upper left limb MRI showed a local tumour recurrence of $7.3 \times 6.5 \times 13$ cm. The patient was referred for consultation to the Maria Skłodowska-Curie Institute of Oncology in Warsaw, where tumour recurrence was confirmed on histopathological reexamination. The patient was then qualified for the clinical study involving denosumab.

Treatment with denosumab was carried on from May 2012 until February 2013, when progression of lung lesions was observed radiologically. As sarcomatous transformation was suspected, the patient discontinued treatment within the study, and chemotherapy (CT) was initiated (AP3 protocol: doxorubicin 20 mg/m^2, cisplatin 30 mg/m^2 on days 1–3, repeated every 21 days).

Chemotherapy was continued in Wrocław, and the patient received three courses of treatment between April 10th and May 25th, 2013. Under treatment, progression of both the limb tumour and the lung lesions (increasing number and size of lesions) was observed. The tumour in the forearm was then $11 \times 8 \times 7$ cm in size, the lesion was soft to palpation, fixed, causing progressive spasticity of left hand fingers and pain. In June 2013, the chemotherapy protocol was changed to ifosfamide (IFO 5,000 mg/m^2 every 21 days) combined with palliative RT due to progression of lesions and symptoms.

Between June and July 2013, the patient received 30 Gy in 10 fractions to the tumour site, which resulted in a marked symptom decrease. As multiple bilateral lung lesions persisted and the patient's performance status was good, palliative chemotherapy using IFO was continued.

A total of 32 chemotherapy cycles were administered between June 2013 and August 2015 and treatment was well tolerated with the exception of single transient ischaemic attack (TIA), that caused a short pause in therapy. Treatment resulted in an improved local status and stabilisation of lung lesions. However, from February 2015 both the lesion in the forearm and lung metastases began to progress again. Chemotherapy was stopped, and RT was reintroduced, with administration of 30 Gy in 10 fractions to the limb recurrence in November 2015.

At that time, chest X-ray revealed slowing down of the disease progression (with lung lesions up to 46 mm in diameter). Consecutive CAT scans, taken between November 2015 and October 2016, pointed to tumour stabilisation, with gradual decrease of the dimensions of lung lesions.

Episodes of transient left-sided hemiparesis were observed in July and September 2016. Head MRI scans excluded central nervous system (CNS) dissemination. The patient was from then on followed by a neurologist and controlled in a chemotherapy outpatient clinic.

A chest X-ray from October 3rd, 2016 demonstrated further shrinking of metastatic lesions (the greatest of 37 mm in diameter). The disease had been stable for 1.5 years at that time, and the neurologist suggested portacath removal, which was performed in December 2016. Control chest X-ray (March 7th, 2017) showed stable lung lesions as compared to the previous investigation.

The patient remains under clinical supervision, has a good performance status, with no signs of local or distant lesion progression.

Summary and discussion

Giant-cell tumour of bone is rare neoplasm, with slight predominance in women, occurring mainly in limbs and more rarely in axial skeleton and pelvis. European and US statistics show that GCT represents 5% of all bone tumours and 21% of benign skeletal neoplasms.

Data from the National Cancer Institute (NCI) show that the prevalence of GCT in the USA is 1.6 per 10,000 inhabitants per year, with slightly increased number of cases in patients between 20 and 44 years of age [1]. The authors could not retrieve prevalence figures for the Polish population.

Giant-cell tumours most often have benign character and confer good prognosis but may progress locally in up to 65% patients and cause local bone destruction [2].

The tumours may, however, transform or produce distant metastases. Less than 5% of recurrent GCTs harbour lung metastases, that occur on average 3–5 years from diagnosis. Pulmonary lesions tend to grow slowly — sometimes are referred to as "tumour deposits" and may regress spontaneously under follow-up. In a small proportion of cases, sarcomatous cells may be identified in tumour tissue, which suggests a higher malignancy potential. Such tumours may demonstrate an aggressive growth and lead to patient death [3].

Localised disease is treated by radical surgical excision, preceded by open biopsy. Radiotherapy may be considered in cases of uncertain malignant potential, non-radical excision when wider resection is not possible, in non-operable locations, and when surgical

treatment cannot be carried out, e.g. due to concomitant diseases [4, 5].

Inoperable GCT may be treated with denosumab, humanised monoclonal IgG2 antibody, binding to the receptor activator of nuclear factor kappa-B ligand (RANKL), thus preventing its interaction with RANK.

Stromal cells of GCT express RANKL and thereby interact with osteoclast-like giant cells, which are in turn positive for RANK. This binding impairs the balance between bone formation and tumour-induced resorption and destruction.

The beneficial effect of denosumab in patients with GCT is related to the reduction of the number or elimination of osteoclast-like giant cells, caused by RANKL binding. This results in osteolysis inhibition, and the proliferating tumour stroma is replaced by proliferation-quiescent compact, differentiated bone tissue. Disease progression is stopped, performance status is improved, and pain reduction is observed in up to 80% of patients. The agent is administered for GCT therapy subcutaneously, 120 mg every four weeks, with additional doses on day 8 and day 15 of the first treatment cycle [6–8].

Optimal treatment of distant metastases includes surgical resection, which may be considered if the primary lesion is well controlled.

Chemotherapy plays a marginal role in the treatment of GCTs, and is applied in cases of suspected local sarcomatous transformation. Single reports of attempted interferon alpha treatment in disseminated disease can be found in literature [9, 10].

The presented patient was not suited for resection of secondary lesions, which were multiple and located in both lungs. Besides, progression of the primary limb tumour was observed.

Denosumab modulates bone metabolism, and in the presented patient led to control of disease that had been disseminated for nine months. Doxorubicin-based chemotherapy is most commonly used in the treatment of sarcomas but could not inhibit disease progression in the presented patient. Ifosfamide was well tolerated and efficient for more than 13 months. After completion of chemotherapy and repeated local radiotherapy, an eighteen-month' progression-free survival was achieved.

Several case reports of spontaneous regression of GCT metastases can be found in literature. This would be highly unlikely in the presented patient, given the quite aggressive initial course and progressive disease character. Local therapy seemed most efficient in this case. Regression of the primary lesion was obtained after two courses of RT with a total dose of 60 Gy, which could also have an impact on distant metastases.

This might be explained by the so-called "abscopal effect" (*ab* — away from, *scopus* — target), a term used to describe regression of secondary lesions in cases of disseminated disease after local RT applied only to the primary tumour focus.

This phenomenon was described in malignancies strongly affecting the immune system, including lymphoma, melanoma, and renal tumours [11]. Some authors explain this effect by the impact of radiotherapy upon the tumoural microenvironment, where infiltration by activated T-cells is stimulated. These lymphocytes in turn stimulate immune response focused on tumour cells, resulting in their destruction.

This hypothesis gave the grounds to attempt to combine radiotherapy and immunotherapy, particularly using CTLA4 and PD1 inhibitors. The strategy is undertaken currently in various clinical trials and might become a valuable therapeutic option in tumours poorly responding to conventional chemotherapy [12].

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