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## **Differentiation of metastatic lesions to the bones and multiple myeloma – a case study**

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## **Summary**

Bones are one of the most common locations for cancer metastasis. Foci, which are in the most cases osteolytic, are located in the spine, ribs, pelvis, long bones. The etiology of changes varies widely as they can be observed in the course of breast, prostate or lung cancer and multiple myeloma.

The aim of the study is to present the case of a 72-year-old female patient after right nephrectomy due to clear cell carcinoma with the presence of disseminated osteolytic foci in the bones located in the ribs, sternum and femur and the existence of calcified pulmonary nodules on diagnostic computed tomography (CT). Basing on the clinical data and imaging results, metastatic bone disease of kidney carcinoma was diagnosed. Despite the treatment, no clinical improvement was observed. In addition, general symptoms such as weakness, weight loss, bone pain appeared. Osteolysis and diffuse osteopenia with hypercalcaemia increased. Further diagnostics – a histopathological examination of the bone marrow combined with laboratory results allowed to make the correct diagnosis - multiple myeloma in stage III in Durie and Salmon classification, in stage 3 according ISS scale. The appropriate treatment was introduced. Patient received bortezomib-thalidomide-dexamethasone chemotherapy regimen and achieved very good partial response (VGPR).

On the grounds of the case given, the key to successful treatment is to carry out detailed differentiation and to make an accurate diagnosis. Coexistence of another cancer should be always considered. A biopsy of pathological lesions is often the only way to diagnose disease.

**Key words: multiple myeloma; osteolytic lesions; bones; metastases.**

## **Introduction**

Metastases and multiple myeloma (MM) are common malignant disease involving bone marrow. The typical symptoms are pain, pathological fracture and compression of the spinal cord [1,2].

Bone metastases are the most common in tumours of breast, prostatic gland, lung, thyroid, kidney, melanoma and appear in various forms of lytic or sclerotic bone lesions. Among these, the most frequent location of metastases is vertebral column, pelvis, femur, cranium and upper extremity [1]. Renal cell carcinoma gives metastases to the bone system in 20–25% of the cases [3].

The incidence of MM is increasing in recent years. It accounts for about 1% of all neoplasms and about 10 % of all hematological malignancy. It occurs in elderly population, the median age of patients in diagnosis is 72 years [4]. MM is characterised by pathological proliferation of monoclonal plasma cells. Symptomatic MM is characterised by hypercalcaemia, renal failure, anemia and bone lesions [5]. Bone changes emerge as a result of increasing activity of osteoclasts stimulated by cytokines, especially interleukin-6 (IL-6). On skeletal radiography CT or positron emission tomography - computed tomography (PET–CT) there are commonly osteolytic lesions visible [4].

### Case description

A 72-year-old female patient, in condition after strumectomy in 2005 due to nodular goiter and right-sided nephrectomy due to clear cell renal cell carcinoma (CCRCC) in 2012, was admitted to the hospital in 2017 on account of weakness and weight loss accompanied by bone pain.

CT showed multiple osteolytic lesions located in vertebral bodies, ribs, sternum and femurs as well as existence of calcified nodules (3-5 mm diameter) in both lungs, whereas no pathological structures in postoperative bed was observed. The laboratory tests revealed mild anemia (Hb=10g/dl), leucopenia (WBC=3200/ $\mu$ l), hypokalaemia and elevated serum concentration of urea, creatinine and uric acid. Metastasis of CCRCC to the bones was diagnosed. Therefore, sunitinib monotherapy for metastatic renal cell carcinoma was started and palliative radiotherapy directed at the thoracic part (T<sub>5</sub>-T<sub>12</sub>) of spinal column were undertaken.

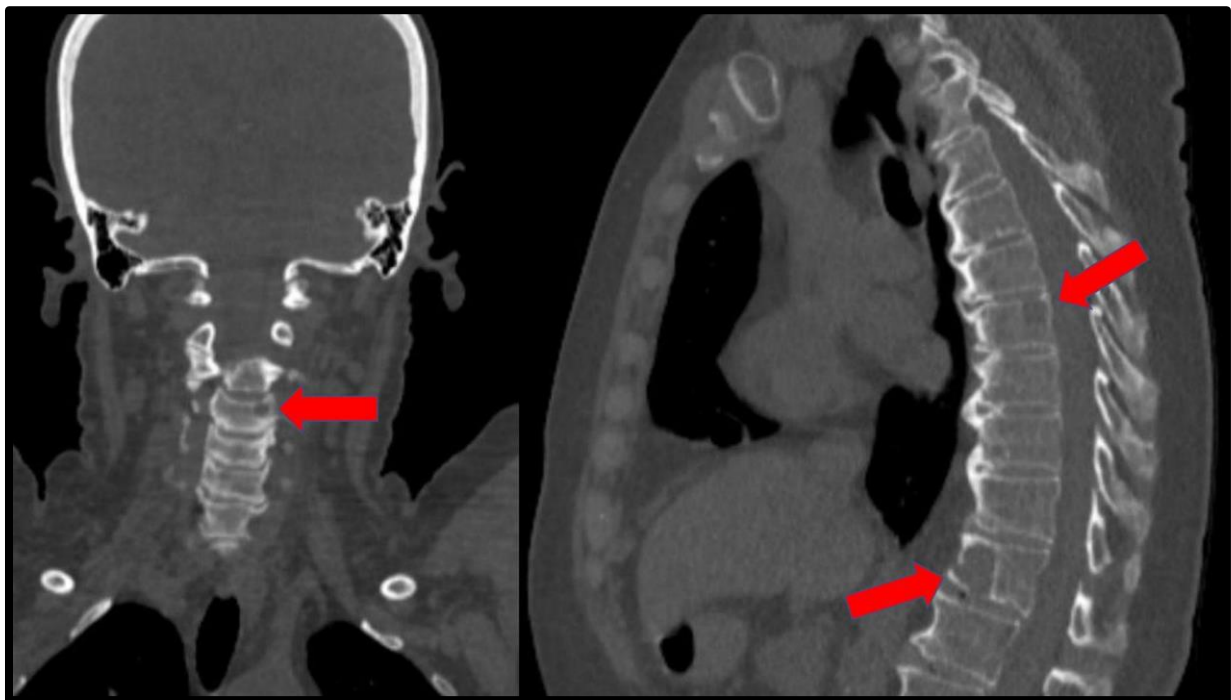


Figure 1. Lesions in vertebral column – CT

During the treatment, the complications were observed. Patient required a hospitalisation. Impaired tolerance of treatment, features of liver damage (elevated liver enzymes), leucopenia and elevated C-reactive protein (CRP) and ESR (erythrocyte sedimentation rate) were noted. Conservative treatment and improvement of patient's condition enabled continuation of chemotherapy.

Due to the outcome of routine PET-CT multiple myeloma (MM) was suspected. Nodules in the lungs without intensified metabolism of 18F-fluorodeoxyglucose (18-F-FDG), lymph nodes in mediastinum and hilum of both lungs as well as postoperative bed were not pathologically metabolic active lesions. These were only found in bones mentioned above.

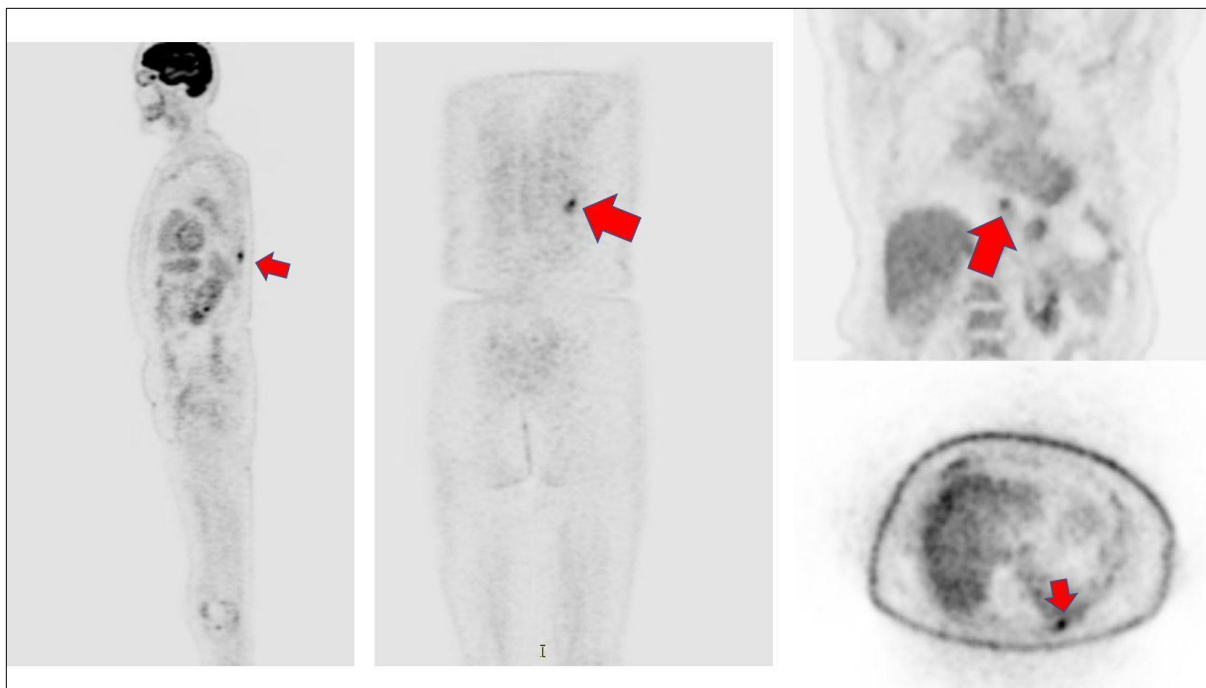


Figure 2. Lesions in PET-CT

The patient was redirected for further diagnosis to Department of Hematooncology. Lab tests revealed mild anemia (hemoglobin 11g/dl), hypogammaglobulinemia and increase of creatinine to 1,5mg/dl. Electrophoresis with immunofixation detected IgA kappa with additional line on the kappa path; free light chains (FLC) kappa (6331,24 mg/L), FLC kappa/FLC lambda ratio (1017,88). In trepanobiopsy of the bone marrow, interstitial monoclonal plasmocytes infiltrations (CD138 +; FLC kappa+) accounting about 30% of bone marrow cells were observed. Finally, a proper diagnosis of MM stage III according Durie and Salmon scale, ISS 3 was established. The patient underwent 6 cycles of VTD (bortezomib-thalidomide dexamethasone) chemotherapy and achieved VGPR (very good partial response). The progression free survival (PFS) was 12 months.

## Discussion

The presented case is an example of the difficulty of differential diagnosis of pathological bone lesions. Initially, they were recognised as metastatic bone disease in the course of previous malignant carcinoma – CCRCC. However, as it turned out later, the lesions were misdiagnosed, resulting in ineffective therapy, which probably contributed to morphological and organic complications of the patient.

The diagnosis of renal cell carcinoma (RCC) metastases should be differentiated with other diseases which emerge with similar symptoms like weakness, weight loss, bone pain, osteolysis or diffuse osteopenia with hypercalcaemia. The disease corresponding the most to above features is MM, but it is important to remember that also parathyroid adenoma with primary hyperparathyroidism may give similar symptoms. The one of laboratory result's difference between MM and RCC metastases is the level of alkaline phosphatase (ALP), which is usually normal in MM (it mirrors the inhibition of bone formation activity of osteoblasts), while in metastases ALP is elevated [6].

Having analysed several publications of similar cases, that is RCC and subsequent MM, it seems that the association between these two diseases is significant and is far from a mere

coincidence. This issue brought our attention to the factors that could give possible explanations of this phenomenon. In the case reports we based on, the time span between the RCC eradication and MM diagnosis took form 1 year up to 25 years, which does not give any significant information. Notably, according to Ozturk and colleagues, there is a tendency of RCC to precede MM in majority of cases (10 of 14 cases, 71 %). Another fact is that 11 of 14 (78%) metachronous cases were male, hence they are more susceptible than women [7].

The publications highlight the crucial role of IL-6 in the coincidence of both malignancies. IL-6 is a B-cell differentiation factor, which “causes proliferation of plasmoblastic cells and induces terminal differentiation of B cells into antibody-producing cells” [7]. Herein it needs to be mentioned, that MM is characterised by monoclonal plasma cells, which are the final differentiation stage of B cells [8].

Furthermore, it was also confirmed that IL-6 is produced by some RCC cells *in vitro* and has been found in high concentration in serum of patients with advanced RCC. On the other hand, myeloma cells also produce IL-6 and some of them express substantial levels of IL-6 receptors. Therefore, IL-6 can act as an autocrine growth factor produced by RCC, which may possibly contribute to progression of MM [8]. Other authors point that not only IL-6, but also different tumor stimulating hormones like TNF $\alpha$ , produced by primary malignancy may considerably increase the risk of subsequent neoplastic disease [8,9].

In the light of this hypothesis, it seems to be evidenced that subsequent coexistence of RCC and MM can not be explained by chance only, but still needs to be researched whether other factors may contribute to it. On the common etiology of both diseases indicates also the fact that the prevalence of MM was 1.51 times higher in RCC patients than in the general population. Another important matter is shared risk factors, which include obesity, smoking and hypertension, but this point is questionable [10]. According to the previous literature review published in 2009 by Ozturk and co. there are no common risk factors, “pathogenetic mechanisms or chromosomal abnormalities seen in either RCC or MM” [7].

Further studies on the risk factors, immunological and genetic background to better understand the pathobiology of coexistence of both cancers needs to be carried out.

## **Conclusions**

The base of the effective treatment is to make an accurate diagnosis. A mistake made during diagnostic process may result in incorrect, ineffective treatment and deterioration of patient's condition. A biopsy of pathological lesions and specific laboratory tests should be used for differential diagnosis between metastases to the bones and myeloma.

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