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Patient with Metastatic Process in the Skeleton of Unknown Etiology

Majerníková M*, Sedláček J and Monhart Z

Internal Department, Nemocnice Znojmo, Czechia

*Correspondence: Mária Majerníková, Internal Department, Nemocnice Znojmo, MUDr. Jana Janského 11, 66902 Znojmo, Czechia, E-mail: maria.majernikova@nemzn.cz

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Abstract

Bearing bone involvement is a possible sign of generalization variety of cancers. In many cases the process of bearing skeletal diagnosed at the time when the primary tumor is not obvious. The task of the physician is quickly to determine whether it is a benign process or not, and diagnosis of the primary process by which then determine the further progress of therapy. The search for causative bearing shell process, alternatively the primary tumor, is often common practice in the hands of internist. Departments of Clinical Oncology do not have to have sufficient capacity for complex treatment all of newly discovered deposits skeleton whose nature does not have to be always initially clear. Therefore, in the opinion of the authors in these cases, the role of internist as a significant diagnosis very important In our article, we introduce six case reports of patients who were bearing the ambiguous process of investigation of the skeleton in our department in 2014. In accordance with the literature data were represented kidney tumor, multiple myeloma, chondrosarcoma, and in one case the origo malignant process was not found.

Keywords: Metastasis, Osteolysis, Imaging methods

Introduction

Bone is a mineralized connective tissue. It forms the internal structure of the organism and serves as a support for the body. It is subject to a lifetime rebuilding process, and two basic bone cells maintain its structure. Osteoblasts - bone matrix produce, and osteoclasts - bone tissue breaks down. When the function of these cells fails, the bone structure and the formation of foci in the osteolytic, osteoplastic and mixed lesions consequently occur.

The etiology of the lesion in the skeleton is often very unclear. According to available literature, it is most often a tumor metastasis or a hematological malignancy. It accounts for more than 80% of the deposits, of which about 1% are primary bone tumors. 5-10% of the processes are benign, and in 5-10% of the etiology, we do not find them in autopsy.

Metastases are a manifestation of generalization and complications of cancer. They significantly impair the quality of life of patients. The most common manifestation is pain. It is poorly localized, at rest is worse, often mainly at night time. Pathological fractures with the possibility of spinal cord and spinal nerve compression are common. This can lead to various neurological deficits. These can cause oppression by bone fragments in fracture, or infiltration of nerve tissue by metastasis alone. It is the pain and neurological deficit that are the reasons for the patient's first contact with a doctor. When the skeleton is affected, calcium is often released from the bones into the circulation. Signs of hypercalcaemia - anorexia, polyuria, dehydration, emotional lability, cardiac arrhythmia and failure are common. If a large part of the skeleton is afflicted, hematopoietic oppression may occur [1-10].

The red bone marrow has a very good vascular supply. Therefore, it is a great place to settle malignant...
cells. Therefore, the most common occurrence of bone metastases is in the skeleton. I.e. 80% of metastases are found in the axial skeleton, of which 70% in the thoracic spine, 20% in the lumbosacral landscape and 10% in the cervical. The remaining 20% are found in the pelvic bones, ribs, skull and proximal parts of the long bones [7].

Multiple myeloma (about 70-95%) is the most common malignant disease with skeletal lesions (although it is not a metastasis in the true sense of the word but about localization of the process). Numerous bone metastases have breast and prostate cancer (about 65-75%), lung cancer (30-40%), kidney (20-25%), thyroid (60%), and M. Hodgkin (> 25%) and Non-Hodgkin’s lymphomas (10%) [6,7].

The gastrointestinal tumors (esophagus, stomach, colorectum) also metastasize into the skeleton. But these tumors usually manifest themselves with other problems before disseminating the malignant process. Therefore, we do not diagnose these tumors primarily through bone metastases, likewise, gynecological tumors and malignant melanoma. Heart angiosarcoma almost always forms bone metastases. But it is a very rare tumor.

In our article, we will show in six patients how complex a primary tumor can ever be found. How the investigation depends also on which specialist initiates it. How sometimes a large number of examinations are needed and sometimes we must be lucky.

**Case Report 1**

This is a 61-year-old female patient who has had severe left-sided ribs and back pain for several days. She had no injury; the usual analgesics had no significant effect. We performed an X-ray image of the spine. Here was the compression of the bodies of the seventh and twelfth thoracic vertebrae and the first lumbar, fracture of the fifth rib in the osteolytic terrain, and the brightening was also in the sixth, eighth and ninth ribs. Multiple osteolytic foci were also on CT (computed tomography) examination of the lumbosacral spine (Figure 1). A pathological finding was also on scintigraphic examination of the skeleton.

There was no other pathology besides systolic murmur in physical examination. The patient was treated for hypothyroidism and hypercholesterolemia, after laparoscopic cholecystectomy. She was heterozygous for prothrombin mutation. In medication, the statin and thyroid hormone substitution. Sometimes she used an analgesic, she smoked. There was no cancer in the family history.

Calcium was out of the laboratory, which was repeatedly above the reference range (2.22-2.65 mmol/l). In addition, deficit of IgA (0.58 g/l) and IgM (0.34 g/l) immunoglobulins, and positivity of beta-2-microglobulin (2.29 and 3.89 mg/l) were present. This created a suspicion of hematological malignancy.

However, only a slight anemia (hemoglobin 105-121 g/l, erythrocytes 0.32-0.37 $10^{12}$/l) and thrombocytopenia (123-188 $10^9$/l) were present in the blood count. White blood line was normal.

We added imaging - heart and lung X-ray, abdominal ultrasound examination, CT examination of the abdomen and small pelvis, mammographic and ultrasound examination. The bone scan revealed an uptake of radiopharmaceutical at the T7-T12 vertebrae that was consistent with bone metastases. The diagnosis was confirmed by bone biopsy. The patient was started on a chemotherapy regimen and bone pain was controlled with analgesics.
examination of the breast, gastroscopic (GFS) examination, ultrasound and histological examination of the thyroid gynecological examination. None has brought result.

Therefore, sternal puncture was performed, again with the absence of plasma cells. Flow cytometry (FCM) did not show paraprotein. But serum kappa chains were present. According to FCM, clonality of kappa plasma cells and Bence-Jones protein in urine was present.

All this together with the presence of anemia, hypercalcemia and osteolytic skeletal foci helped to diagnose multiple myeloma.

Case Report 2

We investigated a 68-year-old patient for long-term pain in the lumbar region. Alkaline phosphatase (2.68 µkat/l) was repeatedly elevated in the laboratory. Skeletal scintigraphy was performed, where there were multiple pathological lesions of the right side ribs and the body of the third lumbar vertebra.

It was a polymorbid patient. It has been treated with hypertension, ischemic heart disease, diabetes, hyperlipidemia, chronic obstructive pulmonary disease, chronic renal insufficiency (CKD) IV. Degree and vertebrogenicalgic syndrome.

The patient had several surgeries - amputation of the right lower limb in the lower leg and of the left lower limb in the Chopart joint, surgery of carotid arteries, cholecystectomy and spinal surgery for prolapse of the intervertebral disc. He didn't smoke for forty years.

He used a lot of drugs - loop diuretic, beta-blocker, ACE-inhibitor, acetylsalicylic acid, vasodilator, proton pump inhibitor, statin, bronchodilator, short and long-term insulin, antiemetic, anxiolytic and antidepressant, opioid analgesics. Low-molecular heparin during hospitalization to prevent thromboembolic disease.

He was retreated for infection before hospitalization. However, higher signs of inflammatory activity (leukocytosis 12.2 10^9/l, higher sedimentation FW 70/78 mm, C-reactive protein 131.4-199.3 mg/l) were still present. Mild anemia (Hb 108-115 g/l) developed gradually. Oncomarkers - PSA (1.2 µg/l), TSH (2.65 mU/l) and T4 (15.7 pmol/l) - were within the norm.

We have also added a CT scan of the chest, abdomen and small pelvis. The result was a suspicion of several malignancies: tumor of the lung (infiltrate along the right bronchus), pancreas (suspected caudal lesion), adrenal gland (suspected adenoma diff. dg. metastatis) or intestine (infiltrate in the base of the cecal base). Foci of the 12th thoracic to fourth lumbar vertebrae were also present (Figure 2).

Figure 2: Osteolytic process in vertebral body L3.

We continued the investigation. Abdominal ultrasound, pleural effusion puncture, colonoscopic examination were negative. Only adenocarcinoma suspected cells were present in the cytology of the sample with bronchoscopic examination. However, the patient's health remained worse. No further invasive investigation was possible. Therefore, the origo of malignant disease was not found.

Case Report 3

In another case report, we will present a 60-year-old female patient. We've been investigating her for about two months of subfebris and weight loss. Last week she also reported night sweats and lumbar spine pain and left hip pain.

She was treated only with hypertension and dyslipidemia. She underwent surgery on both hip joints, had total hip replacement and osteosynthesis of the right lower leg. The patient was a smoker. It was a positive oncological family history, the patient's mother had gastric cancer. She regularly used a statin, a beta-blocker, an angiotensin II receptor antagonist, an analgesic, and a diuretic. She had
a second antibiotic from her GP, no effect.

Significant signs of inflammatory activity (CRP 68.6-124.5 mg/l, leukocytes 9.7-14.0 \(10^9/l\), sedimentation 86/90 mm and 90/96 mm) were repeated in the laboratory. The patient had mild anemia (Hb 112-123 g/l). However, procalcitonin was normal (0.02 µg/l). Other laboratory parameters were within the standard. Also, the cultivation of urine, sputum, blood cultures, and throat swabs was negative.

Imaging methods (chest X-ray, paranasal sinuses X-ray with ENT examination, ultrasound examination of the abdomen) had a normal finding. Inflammation in the area of the implanted hip endoprosthesis on the left was not confirmed by RTG. Spondylodiscitis was still suspected. We added neurological examination and magnetic resonance imaging of the spine. Spondylodiscitis was not found. However, multiple metastatic processes of the thoracic vertebrae 1,4,5,9,11 and 12 are visible in the pictures (Figure 3). According to the scintigraphic examination of the skeleton, there were other suspected lesions - in the head of the right humerus, pelvis and right hip.

![Figure 3: MR image of the metastatic process in Th1 and Th9.](image)

Subsequent examinations - protein electrophoresis, gastroscopy, colonoscopy and mammography, skin examination, thyroid ultrasound and CT throat - were negative.

CT scan of the abdomen and pelvis showed a lower left kidney tumor (Figure 4).

![Figure 4: CT image of the left kidney tumor process.](image)

**Case Report 4**

Another patient is a 52-year-old man. He was never ill and had no medication. There was no known cancer in the family history. He wasn't investigated in our department, but we worked on his investigation.

For long-term right hip pain, the patient came to the orthopedic ambulance. Here they made his right hip X-ray. There was irregular clarification in the proximal right femur metaphysis. Further, towards the diaphysis, small sclerotic foci and periostosis of the skeleton. It was a suspected finding.

In the laboratories the input was completely normal - CRP <1 mg/l, 4/10 mm sedimentation, thyroid group (TSH 1.76 mU/l, T4 13.2 pmol/l, T3 4.8 pmol/l), PSA (0.58 µg/l). Also, blood count and coagulation were without significant pathology. Protein electrophoresis was performed on our recommendation. There was only slightly higher albumin (0.681), which was almost normal. Otherwise the electrophoresis was normal. The rectal examination was negative. Ultrasound of the abdomen and the prostate showed only kidney cysts. Chest X-ray was negative, CT scan of the abdomen and pelvis was without significant findings. Pathological findings were on CT and magnetic resonance of the right femur. In the proximal part, osteolytic formation with sclerotic islets was in the bone.
marrow. At the site of the broken cortex, the mass of the femoral contour of the femur was transferred (Figure 5). The deposit also infiltrated the musculus vastus lateralis. Another foci at the site of left fibula and tibia showed skeletal scintigraphy.

**Figure 5:** CT image of chondrosarcoma of the right femur-osteolytic formation in the bone marrow with sclerotic islets, crossing the cortical disorder.

The patient was admitted to the orthopedic department. A probation excision was performed here. Histology confirmed not very common primary tumor of bone - dedifferentiated chondrosarcoma of right femur, high grade, without tumor bone infiltration.

**Case Report 5**

A 77-year-old man had about half a year of left hip pain. Therefore, an X-ray picture of the left hip and pelvis followed by CT was performed. The examination showed osteolysis of the upper left pubic arm, symphysis and acetabulum (Figure 6). Osteoplastic foci were also on the right, the upper arm of the pubis axis was enlarged and filled with a soft tissue density structure (Figure 7).

**Figure 6:** X-ray image of pelvic bone osteolytic on the left.

**Figure 7:** CT-enlarged upper pub arm left, filled with soft-tissue density.

The patient was a diabetic, hypertensive with hyperlipidemia. Six years ago, he had cancer for prostatectomy, currently in remission. He underwent carpal tunnel surgery on the right and orchiectomy on the left for orchiepididymitis. He regularly used oral antidiabetics, a diuretic, an ACE-inhibitor, a calcium channel blocker, a statin. He did not smoke; there was no cancer in his family history.
There was a slight anemia in the lab (Hb 125 g/l). Signs of inflammatory activity were only slightly above normal, or completely normal - CRP 1.2 mg/l, FW 18/37 mm, leukocytes 12.2 10^9/l. Urological and negative PSA (<0.01 µg/l) were negative. Protein ELFOs showed only marginal values - alpha1 (0.053-0.062), alpha2 (0.143-0.176) and reduced gamma (0.045-0.100) fractions, paraprotein not shown.

All other imaging examinations performed (chest X-ray, abdominal and thyroid ultrasound examinations, gastroscopic and colonoscopic examinations, CT chest, abdomen and small pelvis scans and skeletal scintigraphy) showed only a greater extent and dissemination of the process. But origo did not prove it. ORL and skin examinations also did not produce results.

Therefore, due to the exhaustion of possibilities, a biopsy of the lesion was performed. Plasma-type uniform B lymphocytes were found here, clonal proliferation of immature plasma cells, lambda-type, was found. We added sternal puncture and FCM. Lambda IgG paraprotein, significantly increased free light chains, kappa in normal, i.e., multiple myeloma diagnosis, was confirmed.

**Case Report 6**

A 47-year-old female patient was X-rayed. The patient had severe left thigh and proximal lower leg pain that lasted for about a year and a half and progressed. The X-ray image was only the valgus of the neck. Therefore, skeletal scintigraphic examination was supplemented. There was an abnormal finding in the left femur and tibia. Differential diagnosis was very wide.

The patient had an ovarian cyst and varicose cyst of both legs after surgery. She smoked, she had chronic bronchitis. The patient reported weight loss. In medication two days neurotope for pain. She used the analgesics irregularly, she didn't have regular medication. In the family history, there was cancer in the father's stomach cancer.

There were signs of inflammatory activity (CRP 124.4 mg/l) in the laboratory. Leukocytes were normal (7.5 10^9/l). A slight microchromic anemia (Hb 108 g/l) was present, which progressively progressed. Otherwise, there was no significant pathology in the lab. Only minor insignificant variations were present in the ELFO examination.

To exclude infection, we added another examination - swab from the neck, nose, ear and urine cultivation - without finding an inflammatory focus. Gynecological examination was normal.

Both CT and magnetic resonance of the left femur were pathological - multiple focal processes with osteolysis of bone, destructed cortical, soft tissue infiltration (Figure 8). The deposit was also in tibia (Figure 9). The path of the orthopedic department was followed by probation excision of the bearing. Histologically, it was a metastasis of the light-cell tumor - kidney, thyroid or lung cancer was possible within the differential diagnosis. Ultrasound and CT examination of the abdomen brought a definitive diagnosis. There was a left kidney tumor (Figure 10).
Conclusion

Skeletal metastases mean the progression of many cancers. Significantly worsens morbidity and mortality. They are a bad prognostic sign of further development of the disease and the possibilities of its therapy.

In many cases, bone metastases are diagnosed earlier than the original malignant disease. In this case, it is the task of the doctor to determine the origo process. This will then allow for further treatment.

It is important to see if it is a malignant or benign process. The history, including the family, has been taken out of the right importance. This is often forgotten. Next, a thorough physical examination follows, proceeding systematically from head to toe. We use a wide range of laboratory and especially imaging examinations. Combined PET/CT exams have an excellent value. Today, it can be considered basic when searching for origo. The only limitation on its use may be its difficult availability. That is why we did not use this examination in one of the patients mentioned. For a number of workplaces, the availability of this examination is limited by ordering periods of 8-10 weeks. At this time, we were able to diagnose our patients without PET/CT.

As we have shown in several case reports, determining the underlying disease of a patient with a lesion in the skeleton is sometimes a challenging process. Laboratory pathology can sometimes be non-specific. Many benign diseases may have the same laboratory variations. Elderly patients may be near normal, acceptable values. Therefore, it is necessary to interpret them simultaneously with the results of other examinations. Sometimes the biopsy of the bearing itself will help us to diagnose it. Despite all the examinations, however, in 5-10% percent the origo process remains unclear.

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Figure 10: CT image of the left kidney tumor.
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