Case reports
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Vertebral Fractures as a Manifestation of Phosphaturic Mesenchymal Tumor-Induced Osteomalacia

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Abstract

Background. The rarity of the disease and, in this regard, the lack of doctors awareness about the pathology, late diagnosis and severe complications of the musculoskeletal system emphasize the relevance of clinical case demonstrating. The uniqueness of the case lies in the fact that hypophosphatemia, noted 3 years after the disease debut, was not taken into account. ***Case description.*** A 45-year-old patient with complaints of muscle weakness, gait disorders, torso deformity and multiple vertebral body fractures that appeared against the background of any somatic diseases absence, a differential diagnosis of metastatic vertebral bodies lesions and secondary osteoporosis complicated by vertebral body fractures was carried out for four years in various hospitals, and was even treated with bisphosphonates. Against this background, the chest deformity increased, kyphosis and remodeling fractures of other bones appeared. The assessment of calcium and phosphorus homeostasis was first performed at the 4th year of the disease, but the detected hypophosphatemia was not regarded as a manifestation of hypophosphatemic osteomalacia. ***Conclusion.*** Among adult patients with multiple low-energy fractures, severe muscle weakness and bone pain that appeared against the background of complete health, to exclude hypophosphatemic osteomalacia induced by mesenchymal tumor, it is necessary to include the level of phosphorus in blood and daily urine assessment in the diagnostic algorithm.

Keywords: phosphaturic oncogenic osteomalacia, FGF-23 secreting tumor, phosphaturic mesenchymal tumor, pathological fractures.

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Background

Tumor-induced osteomalacia is also known as phosphaturic oncogenic osteomalacia. In sight of the trauma surgeons, the disease comes due to the fact that its course is complicated by low-energy fractures of various bones. This rare type of osteomalacia causes an incorrect diagnosis — osteoporosis or metastatic lesion. A retrospective analysis of oncogenic osteomalacia 144 cases revealed an initial incorrect diagnosis in 95.1% of cases [1]. According to the literature data [2] and our own observations, the reason for the incorrect diagnosis is the lack of doctors awareness about the pathology.

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With this type osteomalacia, most often the first appear fractures of the vertebral bodies, the condition is regarded for a long time as a metastatic lesion or osteoporosis. Lack of treatment or inadequate therapy leads to the appearance of new fractures, the development of severe deformities of the axial skeleton and bones of the upper and lower extremities, disability, immobility and even death [3]. Diagnosis is difficult due to the fact that the tumor that caused osteomalacia and fractures is small in size and does not cause local pain; not only the doctor, but also, with very rare exceptions, the patient does not know about the tumor existence [4].

We present a case of tumor-induced osteomalacia, when doctors of various specialties for a long time regarded fractures of the vertebral bodies in a patient as a metastatic lesion or as multiple fractures of the vertebral bodies against the background of osteoporosis, which they tried to treat with bisphosphonates. The tumor that caused the paraneoplastic syndrome was noticed early by a patient who did not understand the cause-and-effect relationship between this tumor and the worsening state of the musculoskeletal system, repeatedly tried to draw the attention of doctors who observed him for four years.

Case report

A 45-year-old patient complained of severe and persistent pain in the bones of the axial and peripheral skeleton, decrease in height up to 14 cm, weight loss up to 10 kg, deformity of the trunk, inability to move without additional support due to severe muscle weakness and increased pain in the lower extremities under load.

According to the patient, the first signs of the disease appeared four years ago, when for no apparent reason he began to suffer from pain in his feet and ankle joints, there was a constant "fatigue in the legs". With these complaints, he turned to orthopedist. Flatfoot were diagnosed, the wearing of orthopedic insoles was recommended. The condition did not improve, soon pain in the lumbar and thoracic spine joined, which were regarded as a manifestation of osteochondrosis. For 1.5 years, the patient, on the recommendation of an orthopedist and a neurologist, received non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, repeated courses of B vitamins, massage courses of the back and lower extremities muscles almost without a break. Against the background of treatment, the pain syndrome gradually progressed, weight and height decreased. The course of manual therapy provoked the appearance of pain in the ribs. There was pulmonary tuberculosis in anamnesis (in 2009 the treatment was carried out inpatient in an antituberculosis dispensary for two months, then on an outpatient basis, the patient was removed from the register on 30.09.2013 due to recovery). The loss in weight and height, combined with increasing weakness and bone pain, forced doctors to exclude the tuberculosis diagnosis in October 2018. After that, therapy aimed at relieving pain was resumed: paravertebral blockades, physiotherapy, intravenous administration of glucocorticoids. The lack of effect forced to perform MRI (T1, T2, STIR-WI modes) of the thoracic and lumbar spine (29.11.2018). The revealed fracture of the Th6 vertebra and the dynamic compression of the Th7–12 vertebral bodies in the consolidation stage became the basis for the conclusion: systemic metabolic disorders of bone tissue — osteoporosis (Fig. 1).

There was orchifuniculectomy (29.10.2007) in the patient's anamnesis, followed by radiotherapy of the iliac lymph nodes on the right for a seminoma of the right testicle T2NxM0, which initiated the need to exclude metastatic lesion to the vertebral bodies. During the examination in the oncological dispensary (assessment of tumor markers), relapse and metastases of testicular seminoma were excluded, but multiple areas of hyperfixation of the radiopharmaceutical in the ribs, vertebrae, pelvic bones, right foot and bones forming the

knee joints (more on the right), revealed by scintigraphy (20.12.2018), required the exclusion of myeloma (Fig. 2).

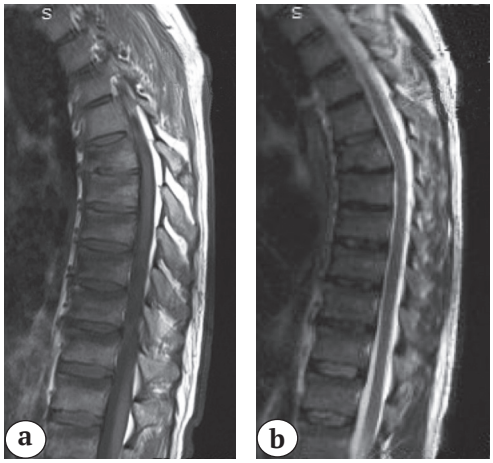

Fig. 1. MRI of the thoracic and lumbar spine:
a — signal intensity from the vertebral column is heterogeneous (severe osteoporosis) by the presence of hemangioma remodeling areas in the Th10 and L1 regions, signs of Th7-12 dynamic compression in the consolidation stage;
b — kyphoscoliotic deformity with its apex at the Th6 level, the Th6 is lower in height, larger in front (wedge-shaped deformity), posterior part minimally prolapsed in the spinal canal (up to 1.0–1.5 mm)

Myeloma was excluded according to the results of biopsy from the iliac bone (11.01.2019). Fractures of the vertebral bodies and changes in the bone structure detected by scintigraphy are again regarded as a manifestation of metabolic disorders associated, most likely, with osteoporosis. With repeated MRI (25.01.2019), performed in the T1, T2, STIR-WI modes, the diagnosis remains: metabolic systemic restructuring of the bone tissue - osteoporosis? Since muscle weakness, gait disorders, bone pain, chest and spine deformity (kyphosis) increased, the patient was examined again. With CT of the abdominal cavity, pelvis, chest and PET/CT with the introduction of 18F-fluorodeoxyglucose (06.02.2019) in addition to multiple compression fractures of the vertebral bodies (Th6, Th8–10) revealed a fracture of the pubic and sciatic bones on the right and a subcapital fracture of the left femur neck (Fig. 3).

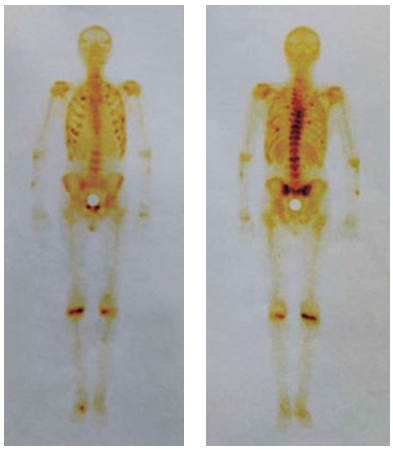

Fig. 2. Scintigraphy of skeletal bones:
multiple sites of radiopharmaceuticals hyperfixation in the ribs, vertebrae, pelvic bones, right foot, and bones forming knee joints (more on the right):
a — front view; b — posterior view

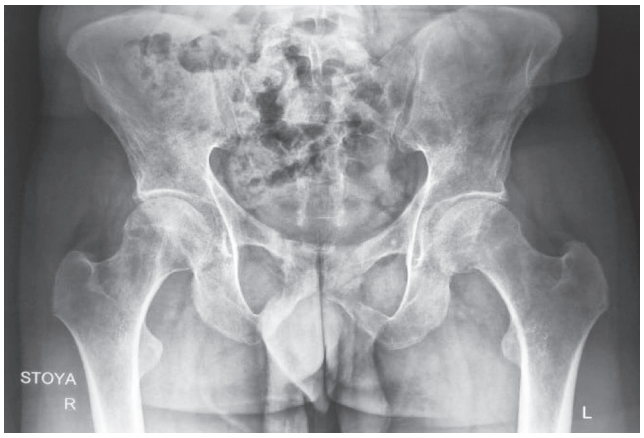

Fig. 3. Pelvic bones X-ray: fracture of the pubic and sciatic bones on the right and subcapital fracture of the left femur neck

The absence of accumulation of radiopharmaceutical in the foci of destruction in the pelvic bones becomes the basis for excluding both the primary tumor and metastatic lesion to the bones, in addition, myeloma is repeatedly excluded. Changes in the bones are finally regarded as a manifestation of osteoporosis, which, as oncologists believe, is associated with previously performed radiation of the lymph nodes. With the diagnosis of "secondary (post-radiation) osteoporosis complicated by fractures of the vertebral bodies and the sciatic bone on the right", the patient was referred to rheumatologist.

Thus, three years after the onset of the disease, the patient began to be treated by a rheumatologist, who for the first time assessed the homeostasis of calcium and phosphorus and revealed hypophosphatemia (according to the patient, the phosphorus level is 0.3 mmol/l, medical documentation is not provided). The rheumatologist diagnosed: generalized osteoporosis (post-radiation), severe course, multiple fractures of the vertebral bodies, ribs, fracture of the ischial ramus on the right, phosphorus deficiency.

The patient is constantly prescribed calcium and phosphorus preparations (dietary supplements) — 500 mg, vitamin D — 2200 IU per day, intravenously (March 2019) zoledronic acid (5 mg). Three months after the introduction of zoledronic acid, due to severe pain in the bones and muscle weakness (he could only move with the help of additional support), the patient again turned to a trauma surgeon at one of the major clinics in Moscow. At the time of the examination, the patient drew the doctor's attention to a small (up to 3.5 cm) painless tumor-like formation in the soft tissues on the inner surface of the left knee joint. The patient did not attach much importance to this formation. Nevertheless, due to the deterioration of his condition, he repeatedly pointed out his formation to doctors who observed or examined him throughout the disease, but the complaint was not taken into account. In 2019, the doctor who examined the patient suspected that this formation could be a tumor that had become a source of bone metastases (the results of the previous examination were ignored, which excluded metastatic lesion). The patient is again recommended to perform an MRI of the whole body. When comparing the MRI data in the DWIBS and STIR modes performed on 20.06.2019 with the results of previous studies, metastatic bone damage was again excluded. Aseptic changes were revealed in the proximal articular ends of the tibia, the neck of the left femur (Fig. 4), linear changes in the hypointensive signal. All this changes were regarded as consolidating reforming fractures against the background of metabolic disorders in the bone tissue. The presence of soft tissues formation of the left knee joint area was confirmed (Fig. 5), and for the first time, tumor-induced osteomalacia was suspected. The patient was sent to the CITO.

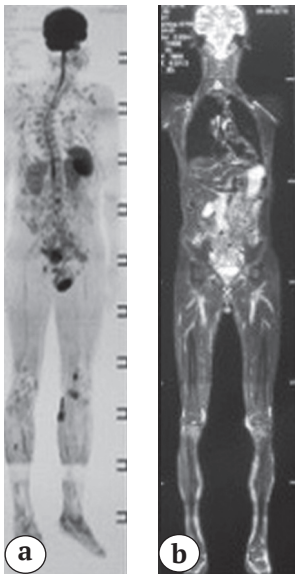

Fig. 4. MRI data:
a — in DWIBS-WI mode the focus of the increased signal 35×30×25 mm is determined in the soft tissues of the left knee joint medial compartment;
b — in STIR-WI mode aseptic changes of the both proximal tibias and the left femur neck are detected with presence of the hypointensive signal linear measurements — consolidating remodeling fractures

Due to the situation with COVID-19, the patient was admitted to the recommended clinic only six months later, that is, four years after the onset of the disease. Blood tests revealed hypophosphatemia (phosphorus – 0.59 mmol/l, norm – 0.81–1.45 mmol/l), decrease in the level of phosphate reabsorption — 73% (norm — 87%) and moderate increase in alkaline phosphatase — 187 U/l (norm — 30-120 U/l). All other indicators remained within the reference values of the norm: total calcium — 2.44 mmol/l (2.20–2.65 mmol/l), creatinine — 61 mmol/l, magnesium — 0.85 mmol/l (0.73-1.06 mmol/l), the trans-

port form of D-hormone — 31 ng/ml (30-100 ng/ml), parathyroid hormone — 33.9 pg/ml (15-69 pg/ml), osteocalcin — 20.03 ng/ml (14-42 ng/ml), the C-terminal telopeptide of type I collagen is 0.457 ng/ml (0.10 — 0.85 ng/ml).

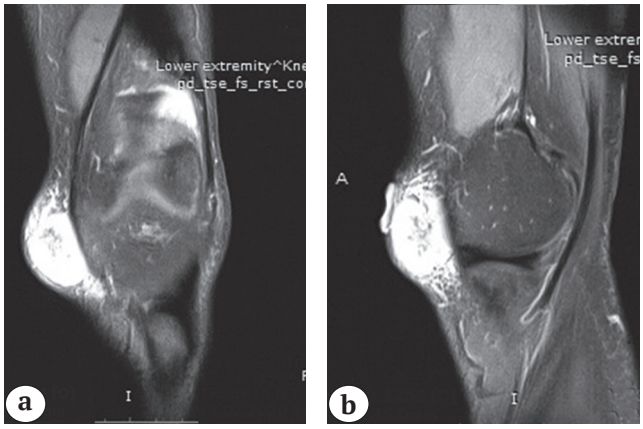

Fig. 5. MRI of the knee:
a — in the DWIBS mode, an additional formation is determined along the medial surface of the joint 30×30×17 mm, heterogeneous intensity on T2 WI, hypointensive on T1 WI and hyperintensive;
b — in the STIR mode and with signs of delineation

Hypophosphatemia and a decrease in phosphorus reabsorption in combination with such clinical signs as pronounced muscle weakness, gait disorder, barrel-shaped deformity of the chest, pronounced kyphosis, dramatic pain during palpation of the ribs, spinous processes of the vertebral bodies, forming varus deformity of the knee joints, decrease in height by 14 cm and a loss of 10 kg of weight, multiple fractures of the vertebral bodies, sciatic bone, reforming fractures of the tibia, became the basis for diagnosis of "hypophosphatemic osteomalacia". Late manifestation (at the age of 45 years) excluded the congenital nature of the disease. It was possible to discuss only the acquired form of osteomalacia: either associated with intoxication and impaired renal function or induced by a tumor secreting fibroblast growth factor-23 (FGF-23). Since the kidney function was not impaired, the patient was diagnosed with phosphaturic oncogenic osteomalacia. Somatostatin-receptor scintigraphy with 99mTc-tectrotide and single-photon emission computed tomography/computed tomography (SPECT/CT) were performed for the diagnostic search for the formation secreting FGF-23, according to the results of which two soft tissue formations with a total size of 34x14x35 mm were identified in the subcutaneous adipose tissue in the area of the left knee joint (Fig. 6). This formation was indicated by the patient.

On 20.02.2020, the surgery was performed under local anesthesia to remove the tumor within healthy tissues with excision of the subcutaneous fat and skin area adjacent to it. The vessels entering the tumor were cut and coagulated. A macroscopically rounded flattened node with a size of 3.5x3.3x1.8 cm is covered with adipose tissue (Fig. 7). On the section there is a tissue of an inhomogeneous red — brown color, shiny, with small dotted grayish inclusions. The boundaries of the tumor are clear, grayish in color.

Histologically, the tumor does not grow into soft tissues, the capsule is well expressed. The tumor consists of fusiform cells fields, around which there are massive deposits of basophilic fields with pronounced dystrophic areas, fields of necrosis (Fig. 8). "lumpy" hyaline-like areas resembling the pathological osteoid were noted in the tumor thickness. Between the lobules of the tumor, there are tumor strands with vascular proliferation, some of them are full-blooded.

To correct metabolic disorders and treat osteomalacia from the first day after surgery, the patient was prescribed alfacalcidol at a dose of 1.0 mcg, an ossein-hydroxyapatite complex (2 tablets 2 times a day) and a diet rich in calcium and phosphorus. The patient was discharged from the hospital on the third day. It should be noted that in such a short time after the surgery, the patient has already noted an improvement in his condition.

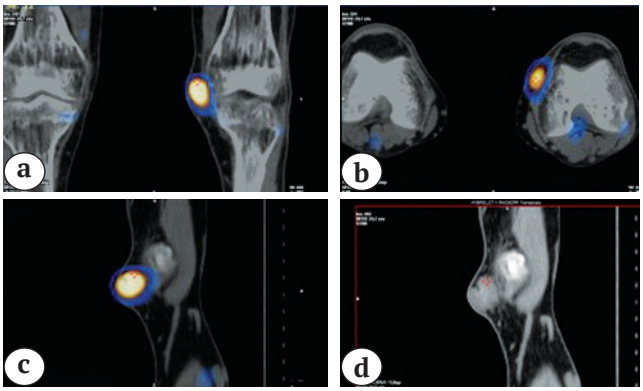

Fig. 6. Somatostatin-receptor scintigraphy with 99mTc-tectrotide and SPECT/CT: in the projection of the left knee joint anteromedial surface in the subcutaneous adipose tissue were determined two closely adjacent soft-tissue ovoid shape formations with clear smooth contours, homogeneous structure, total dimensions of 34×14×35 mm, actively accumulating the radiopharmaceuticals

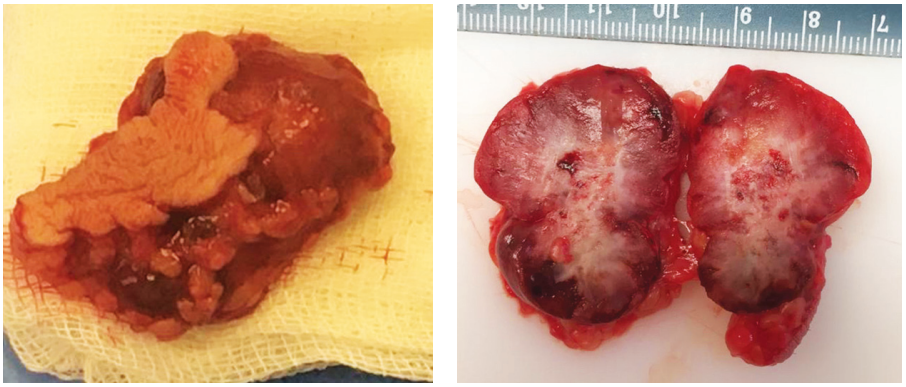

Fig. 7. Removed tumor

A control study of the level of phosphorus and calcium in the blood and urine was performed 16 days after the surgery. In the biochemical blood analysis, the normalization of the inorganic phosphorus level (1.38 mmol, norm — 0.81–1.45 mmol) and alkaline phosphatase (137 U/l, norm — 40-150 U/l) was noted, the daily excretion of phosphorus (15.7 mmol/day, norm — 12.9–40.0 mmol/day) decreased to normal. Blood calcium (total — 2.22 mmol/l, ionized-1.09 mmol/l) of daily urine (0.99 mmol/day, the norm is 2.5-7.5 mmol/day) was reduced, which required an increase in the dose of calcium carbonate to 1000 mg, and alfacalcidol to 1.25 mg. It is recommended to monitor the indicators of calcium and phosphorus homeostasis 3 months after the correction of treatment aimed at restoring bone mineralization.

As for the clinical manifestations, two weeks after the surgery, there was a decrease in weakness and the appearance of muscle strength. After a month, the patient began to move without additional support, after two months, regression of such pathological symptoms as bone pain, muscle weakness was noted, he began to gain weight and returned to his hobby — motorcycle racing.

Thus, in a patient with severe pain in the bones, muscle weakness, impaired weight-bearing ability and the ability to move without support, which occurred for no apparent reason, with multiple fractures of the vertebral bodies, ribs, pelvic bones (the disease began at the age of over 40 years), the osteomalacia phosphopenic form of tumor genesis was confirmed by hypophosphatemia (phosphorus — 0.49 mmol/l), low phosphate reabsorption (73%), increased alkaline phosphatase (164 U/l). Somatostatin-receptor scintigraphy with 99mTc-tectrotide and SPECT were performed for the diagnostic search for the formation secreting FGF-23/CT scans, according to the results of which the formation

in the subcutaneous adipose tissue of the left knee area with a total size of 34x14x35 mm was regarded as most likely a tumor secreting FGF-23. Histological confirmation of the mesenchymal tumor and the reverse development of hypophosphatemia confirmed that the formation in the knee joint was the cause of oncogenic osteomalacia.

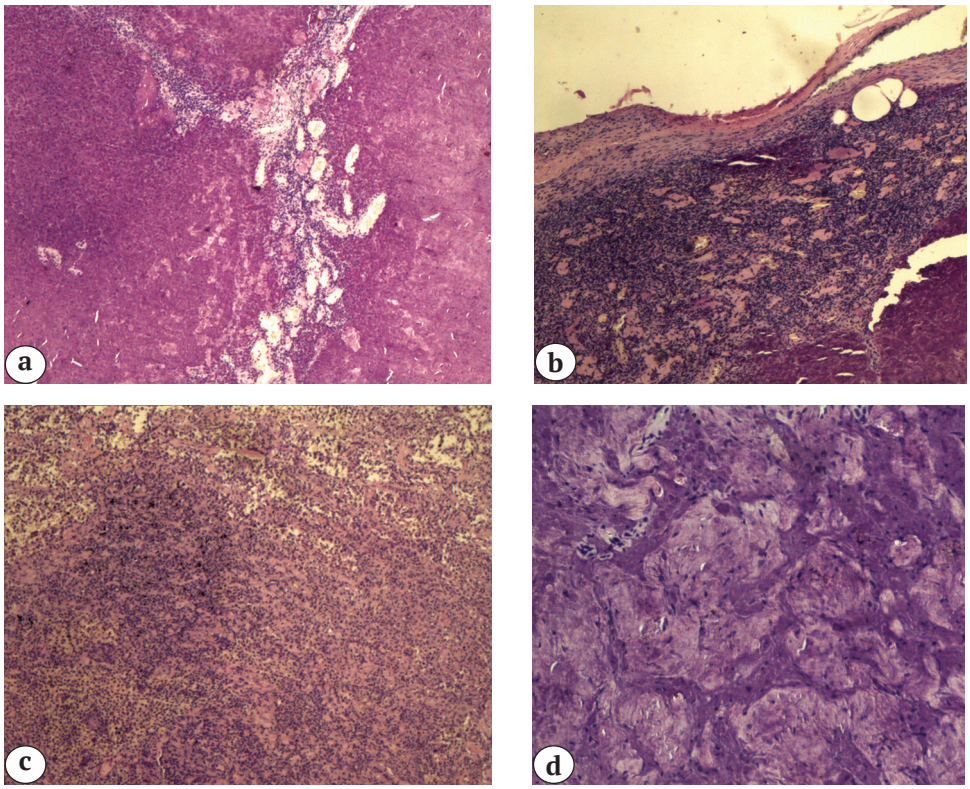

Fig. 8. Micropreparation of the removed tumor:
a — the tumor consists of fusiform cells fields; b — the tumor has a well-defined capsule;
c — dystrophic areas and necrosis fields around fusiform cells clusters;
d — "lumpy" hyaline-like areas that looks like a pathological osteoid.
Stained with hematoxylin and eosin. Mag.: a, b — ×40; c, d — ×100

Discussion

The first case of hypophosphatemic osteomalacia induced by a tumor was described by R.A. McCance in 1947 [5]. However, the connection between the tumor and osteomalacia was revealed only in 1959 by A. Prader [6], and in a child, although the pathology is most often found in adults. To date, about 10 such cases have been described in children, while more than 500 have been described in adults. Judging by the publications of clinical cases, the average age of the disease onset is 40-45 years, which indicates a greater vulnerability of adults [3].

Our patient had a typical age for the onset of the disease and symptoms. A previously published retrospective analysis showed that bone pain and muscle weakness are not only practically common (99.3 and 91.3%, respectively), but also the first symptoms of the disease [1]. However, there is a point of view that the presence of such non-specific symptoms makes it difficult to make a diagnosis, and this is the main reason for the late diagnosis of the disease [7]. However, the analysis of our material (we observed 15 patients with FGF-23 induced osteomalacia) and the literature data indicate that the late diagno-

sis is due to the lack of information about the pathology in a wide range of doctors.

Severe pain in the bones appeared for no apparent reason in an adult, combined with progressive muscle weakness, gait disorders and the appearance of non-trauma-related fractures of various bones requires the exclusion of acquired phosphopenic osteomalacia, since in genetically determined forms of the latter (X-linked hypophosphatemic osteomalacia, autosomal dominant hypophosphatemic lesion of the bones, Fanconi syndrome), symptoms appear in early childhood, they are accompanied by growth retardation, enamel hypoplasia, caries, and multi-plane deformities of the bones of the peripheral skeleton precede the appearance of bone pain and pronounced muscle weakness. A strong sign of hereditary hypophosphatemia can also be a positive family history. If the non-specific symptoms described above occur in an adult patient for no apparent reason, to clarify the diagnosis, first of all, it is necessary to conduct a laboratory assessment of calcium and phosphorus homeostasis, since hypophosphatemia and increased phosphorus content in the urine are absolute symptoms of hypophosphatemic osteomalacia. In this case, FGF-23, which is expressed by the tumor, is responsible for the violation of phosphorus homeostasis [8]. Normally, FGF-23 is also present in the body (synthesized by osteocytes), and its role is reducing the level of serum phosphate in the case of excessive intake of the element with food [9]. In the process of evolution, FGF-23 acquired endocrine functions, therefore, it participates in phosphorus homeostasis and due to the regulation of the active metabolite of vitamin D formation in the kidneys. Under the influence of 1,25-OH D3, the phosphate anion is absorbed simultaneously with calcium. In tumor-induced osteomalacia, hypophosphatemia is due to the fact that an excess of FGF-23, on the one hand, blocks the absorption of phosphorus in the intestine, and on the other hand, reduces the expression of the sodium-phosphate cotransporter NPT2 in the renal proximal tubules, reduces its reabsorption. The patient's blood phosphorus level was first assessed only three years after the onset of the disease, but the marked decrease (0.3 mmol/l, norm — 0.81–1.45), although it served as the basis for prescribing phosphorus and vitamin D preparations, was mistakenly considered as a manifestation of osteoporosis. The latter is a gross mistake, since with osteoporosis (both primary and secondary), the level of phosphorus in the blood remains within the fluctuations of the norm.

Our observation once again confirmed that not all fractures of the vertebral bodies in adults should be considered as a manifestation of osteoporosis. In osteomalacia, including osteomalacia induced by a tumor secreting FGF-23, a violation of bone mineralization is caused by chronic hypophosphatemia. It was possible to suspect a violation of mineralization in the patient and according to the results of MRI (DWIBS and STIR modes), where metabolic disorders in the bone tissue were noted.

In osteomalacia (of any origin), the appointment of bisphosphonates, which are widely used for the treatment of osteoporosis, only worsened the mineralization disorders, which was manifested by increased pain.

Assessment of the FGF-23 level to clarify the diagnosis is possible, but its increase is not specific for the tumor form of osteomalacia, since it can occur both in chronic renal failure and in X-linked osteomalacia [10]. Tumors that secrete FGF-23 are located both in soft tissues and in bones [4].

The search for a tumor is difficult, because it is small and inaccessible (with rare exceptions, such as in our case) for physical examination. There are several functional methods of its visualization, including somatostatin-receptor scintigraphy with tectrotide-Tc99m and SPECT/CT. Although PET/CT with 18F-fluorodeoxyglucose can localize phosphaturic tumors, the study is non-specific, since it also reveals areas of increased meta-

bolic activity, for example, actively healing areas of perestroika fractures [8]. Octreotide scanning can be useful for determining localization, since most phosphaturic tumors express somatostatin receptors [11]. Recent studies have shown that PET/CT with a radiopharmaceutical labeled with gallium-68 (68Ga-DOTA-TATE) has a higher sensitivity and specificity compared to PET/CT with 18F-fluorodeoxyglucose and other functional scans based on somatostatin receptors [12].

Histologically, osteomalacia, including the phosphaturic form, determines an increased content of osteoid or uncalcified bone matrix, while osteoporosis is characterized by loss of mineralized bone, and the amount of osteoid remains normal or even decreases [13]. Only in 1987 it was noted that the tumors associated with hypophosphatemic osteomalacia are a single histopathological formation and are characterized by such common features as low cellularity, myxoid changes, fusiform cells, a characteristic "rough" calcified matrix, the presence of fat, blood vessels, hemorrhage sites and areas of membranous ossification [14]. In 2013 WHO has identified these tumors as "morphologically distinctive neoplasms of soft tissues and bones that cause tumor-induced osteomalacia due to excessive production of FGF-23". Removal of the tumor leads to complete recovery in a short time, and phosphorus homeostasis is normalized within the first week, and in some cases even in the first three days, but it takes at least a year to fully restore mineralization [15].

In a retrospective study of 230 patients performed by X. Li, the frequency of persistent relapses after the first operation was 11.3%, which the authors attributed primarily to non-radical excision of the formation [16].

To confirm the adequate excision of the tumor and the duration of the phosphorus supplements administration , postoperative monitoring of serum phosphorus is recommended. The intake of calcitriol and calcium preparations should be continued until the normal mineralization of the skeleton is restored.

Conclusion

In adult patients with multiple low-energy fractures, severe muscle weakness and bone pain, it is necessary to exclude hypophosphatemic osteomalacia induced by a mesenchymal tumor secreting FGF-23.

Informed consent

The patient gave written informed consent for the publication of this clinical case.

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Conflict of interest:

The authors declare that there is no conflict of interest.