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Article

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Multilevel "fish vertebrae" in a patient with tumor-induced osteomalacia

D. Adam[1,2], D. Iftimie[1], Gina Burduşa[1], Cristiana Moisescu[1]

[1]Department of Neurosurgery, "Saint Pantelimon" Clinical Emergency Hospital, Bucharest, ROMANIA
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, ROMANIA

Abstract: *Background and importance*: "Fish vertebra" is an uncommon anomaly of vertebral body shape, consisting of central depression of the superior and inferior vertebral surfaces. It has been associated with various conditions: osteoporosis, osteomalacia, hyperparathyroidism, Paget disease, sickle cell disease, multiple myeloma and systemic lupus erythematosus. *Clinical presentation*: A 29-year-old male patient, previously treated for ankylosing spondylitis (with NSAIDs and TNFα inhibitor), without any clinical improvement, was admitted to our Neurosurgical Department. He complained of difficult gait, possible only with the aid of a cane, low back pain and bilateral hip pain, but without leg pain. He denied any history of recent trauma. Neurological examination was normal. Plain thoracic and lumbar spine X-rays revealed multilevel "fish vertebrae". Lumbar spine MRI and contrast thoraco-abdominal CT scan showed fractures of multiple structures: left L4 pedicle, right L4 lamina and pars interarticularis, right II-VII costal arches, left I-V costal arches and bilateral sacral alae. We performed extensive laboratory tests that detected low seric phosphorous and PTH levels, with increased alkaline phosphatase, indicating a possible endocrinological cause for this condition. Subsequently, we decided to transfer the patient to an Endocrinological Department. A diagnosis of hypophosphatemic osteomalacia was established and increased FGF23 levels, later determined, suggested it was tumor-induced osteomalacia. Whole-body MRI was unable to locate the tumor, but Gallium-68 DOTATATE PET/CT revealed a small (15 mm in diameter), hyperfixating mass in the head of the right femur. The patient was treated with oral calcitriol and phosphate, with alleviation of symptoms. Surgical excision of the tumor was recommended, but the patient decided to postopone the operation. *Conclusion*: Modern medical imaging and biochemical testing have made the leap from merely observing vertebral biconcavities to diagnosing their cause and, consequently, the possibility to adequately treat uncommon causes of "fish vertebra", such as neuroendocrine tumor-induced osteomalacia.

Key words: fish vertebrae, hypophosfatemic osteomalacia, tumor-induced osteomalacia (TIO), multiple fractures, FGF23, Gallium-68 DOTATATE PET/CT

Clinical presentation

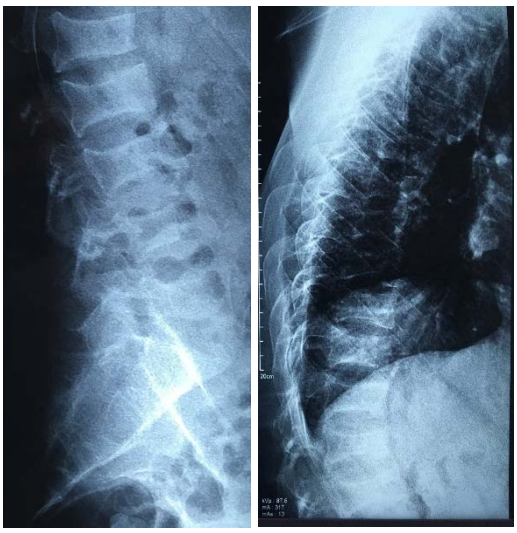
A 29-year-old male, former cocaine user (until 2010), with a negative family history for neoplasia or osteomalacia, was previously diagnosed with ankylosing spondylitis at an University Hospital in Great Britain, approximately a year prior to his presentation at our Neurosurgical Department. He had been treated with NSAIDs and subsequently TNFα inhibitor (Adalimumab), without alleviation of symptoms. At that time, a contrast thoraco-abdominal CT scan revealed modified thoracic and lumbar vertebral bodies, with a biconcave aspect and no other focal bone lesions, an aspect suggestive for a congenital metabolic or endocrine disorder.

At admission to our Department, he presented a difficult gait, possible only with the aid of a cane, low back pain, bilateral hip pain, but without leg pain. He mentioned a fall from approximately 2,5 meters approximately 7 years ago, but denied any history of recent significant trauma.

General physical examination revealed a patient with normal weight, generalized muscle atrophy, thoracolumbar kyphoscoliosis and rigidity of thoracic and lumbar spine. Neurological examination was normal.

Plain lumbar and thoracic spine X-rays revealed a symmetrical biconcave deformity of all visualized vertebral bodies, an aspect also known as "fish vertebrae" (Figures 1A, 1B).

Lumbar MRI confirmed the "fish vertebra" appearance of lumbar vertebral bodies (Figure 2A) and additionally showed a recent left L4 pedicle fracture (Figure 2B). However, lumbar vertebral alterations suggestive for ankylosing spondylitis were absent.



A B

Figure 1 - Lumbar (A) and thoracic (B) spine X-ray revealing a symmetrical biconcave aspect of all vertebral bodies ("fish vertebrae")

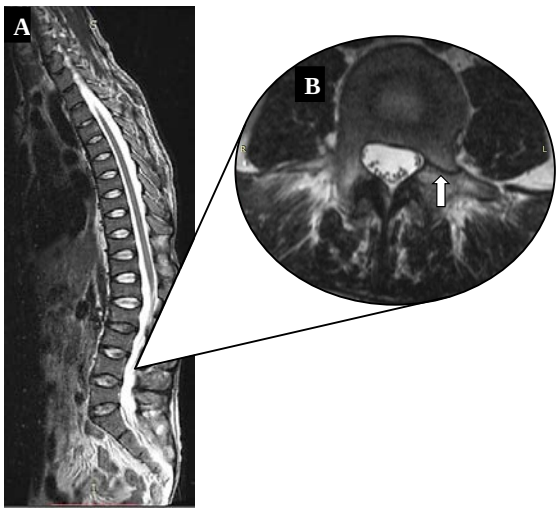


Figure 2 - (A): Lumbar MRI (T2-weighted) confirming the "fish vertebrae" appearance of vertebral bodies. (B): Axial slice (T2-weighted) of lumbar MRI showing a recent left L4 pedicle fracture

We performed a thoraco-abdominal contrast CT scan, which revealed the "fish vertebra" aspect of all thoracic and lumbar vertebral bodies (Figure 3.A, 3.B) and, in comparison with the previous CT scan and lumbar MRI, fractures of multiple additional structures:

•right L4 lamina and pars interarticularis; type A0 spinal fractures according to the AO Spine Classiffication (Figure 3.C),

•right II-VII costal arches and left I-V costal arches

•bilateral sacral alae

The patient's routine blood tests were unremarkable. Therefore, we performed extensive laboratory test in order to determine the cause of the patient's "fish vertebra" and multiple spontaneous fractures. Inflammation markers were within normal ranges. We ruled out sickle cell disease because the patient's hemoglobin levels and peripheral blood smear were normal. Available tests for autoimmune diseases, such as HLA-B27, rheumatoid factor, anti-Ro, Anti-dsDNA, c-ANCA, p-ANCA, anti-mitochondrial antibodies, were also within normal ranges.

The abnormalities that caught our attention were the low blood phosphate and parathyroid hormone (PTH) levels, with an increased alkaline phosphatase (Table I). We strongly suspected an endocrinological condition and therefore decided to transfer the patient to an Endocrinology Department of a neighboring hospital.

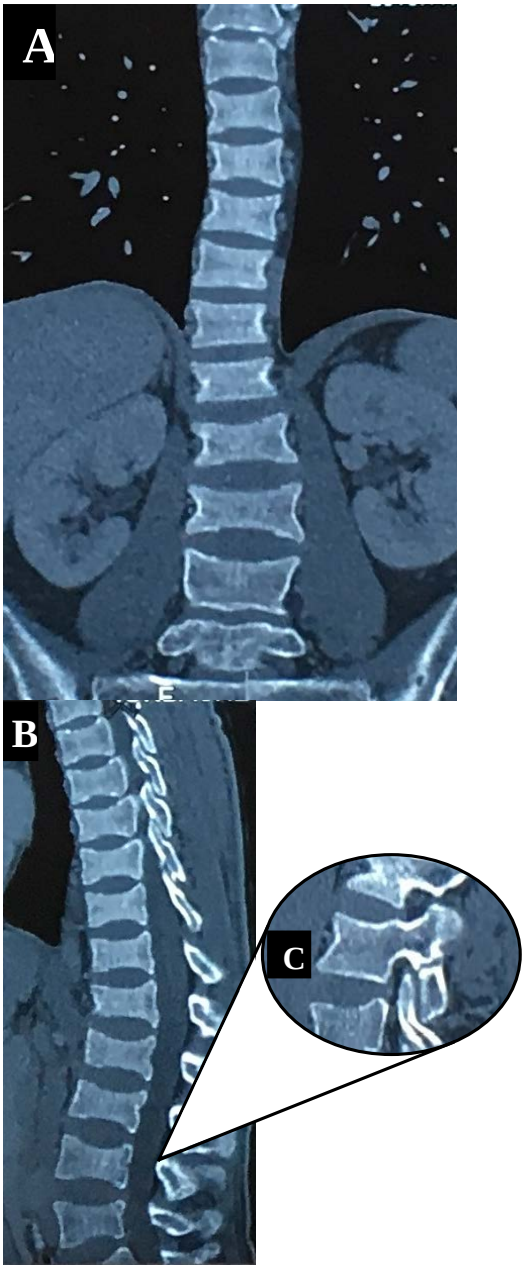


Figure 3 - Coronal (A) and sagittal (B) CT slices of the thoraco-lumbar spine showing the multilevel "fish vertebrae" aspect. (C): Sagital CT image revealing a L4 lamina and pars interarticularis fracture

TABLE I

Blood test anomalies that suggested an endocrinological condition

Investigation	*Result*	*Normal range*
Seric phosphorus	**1,43** ⇩	*2.7 – 4.5 mg/dl*
PTH	**9,83** ⇩	*15 – 65 pg/ml*
Alkaline phosphatase	**335** ⇧	*35 – 129 UI/l*

Endocrinologists continued investigations, revealing osteoporosis on DXA scan, increased bone turnover markers (β-crosslap and P1NP) suggestive for increased bone resorbtion, low 25-hydroxy-vitamin D, hyperphosphaturia, proteinuria and glycosuria (Tabel II). They established the diagnosis of hypophosphatemic osteomalacia with adult onset, considering that the differential diagnosis should be made between acquired Fanconi syndrome, congenital hypophosphatemic rickets with adult onset and tumor-induced osteomalacia.

TABLE II

Additional tests performed by endocrinologists

Investigation	*Result*	*Normal range*
Seric phosphorus	**1,7** ⇩	*2,3 – 4,7 mg/dl*
Alkaline phosphatase	**306** ⇧	*38 – 129 UI/l*
24-hour urine phosphorous	**1,54** ⇧	*0,3 – 1 g/24 h*
24-hour urine glucose	**5.8** ⇧	*0 – 0,5 g/24 h*
DXA lumbar spine	**T = -4,3** ⇩	*Osteoporosis = T≤ -2,5*
DXA left hip	**T = -3,9** ⇩	*Osteoporosis = T≤ -2,5*

The patient was treated with oral calcitriol and phosphates (potassium dihydrogenphosphate/sodium monohydrogenphosphate dihydrate) under phosphatemia control and recommended a dairy-rich diet. One month later, he presented slight alleviation of symptoms and partial correction of hypophosphatemia.

FGF-23 levels (a test not widely available), later determined, were increased (383 pg/ml, with a normal range of 26-110 pg/ml), highly suggestive for oncogenic osteomalacia. The next step was locating the causative tumor. The patient underwent a whole body MRI that was unable to detect a tumor, showing only bone alterations compatible with osteomalacia. However, a Gallium-68 DOTATATE PET/CT subsequently performed revealed a small, hyperfixating lesion in the right femoral head (15 mm in diameter), with a high expression of somatostatin receptors, which suggested a neuroendocrine tumor (Figure 4A, 4B).

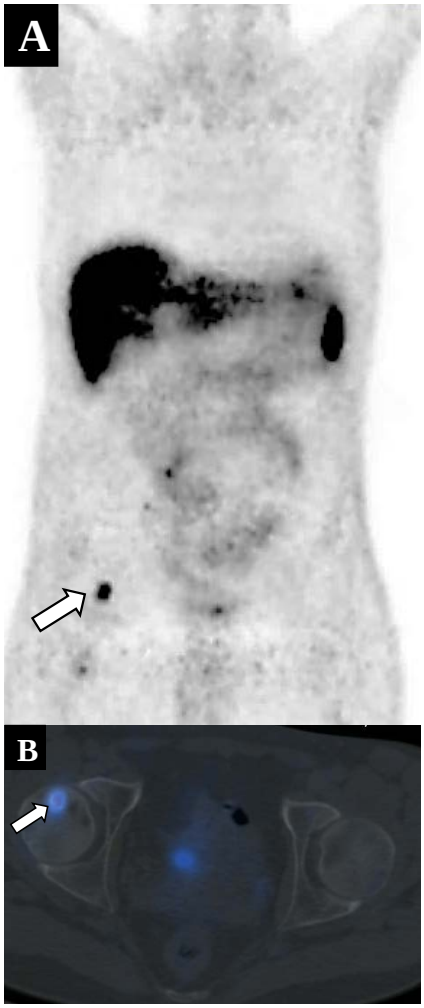


Figure 3 - Coronal (A) and axial (B) slices of the Gallium-68 DOTATATE PET/CT, showing a small (15 mm in diameter) hiperfixating lesion located in the right femoral head

Surgical excision of the tumor was recommended, but the patient decided to postpone surgery. His symptoms continued to alleviate under treatment. Unfortunately, due to a lack of histopathological analysis of the tumor, a definitive diagnosis could not be established.

Discussion

Classical radiological investigations and modern imagistic techniques of the spine can reveal vertebral bodies with altered shape. An uncommon type of modified vertebral body is called "fish vertebra". These particular vertebrae present a biconcave aspect determined by the depression of the central area of the superior and inferior vertebral surfaces. The changes in normal vertebral body shape can be limited to a single vertebra or extend to several levels.

Biconcave vertebrae, an abnormal shape for human vertebrae, were called "fish vertebrae" due to the resemblance with the normal vertebrae of fish, described by Albright, Resnick or Rexroad in codfish, tuna or salmon, respectively. The biconvex appearance of the disc between two "fish vertebrae" is similar to a fish mouth, hence the alternative term of "fish mouth vertebrae". (1, 2)

The earliest reports of this spinal anomaly were published in the first half of the 20th century, on the basis of their radiological appearance. The first description of a biconcave vertebra belongs to Schmorl. In 1926, he reported it in a patient with osteomalacia, stating that the vertebra resembled "the silhouette of a fish vertebra"3. The intraosseous herniation of the intervertebral disc causes disruption of the subchondral bone.

"Fish vertebrae" are most prominent in the lower thoracic and upper lumbar regions of the spine.

This biconcave aspect of vertebrae has been described in various conditions: osteoporosis,

osteomalacia, hyperparathyroidism, Paget disease, sickle cell disease, multiple myeloma and SLE (lupus). (1, 2, 4–7)

"Fish vertebrae" have been frequently encountered in patients with age-related osteoporosis. A single vertebral body can be affected with an unequal concavity of the superior and inferior surface of the vertebra. Furthermore, an emphasis of the subchondral bone and of the vertical trabecular pattern can be seen on plain spine X-ray. However, the most frequent shape alteration of an osteoporotic vertebra is represented by a compression fracture, with the characteristic wedge-vertebra aspect.

In the case of osteomalacia, all vertebral bodies can present a "fish vertebra" aspect with the two endplates equally depressed.

In 1932, Leivy (8) first described the biconcave appearance of vertebrae in patients with sickle cell disease (SCD), considering it pathognomonic for this condition. Due to the fact that the same radiological aspect also appears in other diseases, distinctive radiological features (for the cup-like depression of vertebrae in patients with SCD) were searched. Caroll et al (9) considered that "cupping of the vertebral end plates… is manifest in about 30% of the adults with this blood dyscrasia". This form of endplate distortion is considered to be a defect in development and not an acquired lesion, as in the case of osteoporosis.

In the case of patients with sickle cell disease, the floor of central depression is flat, not rounded, and the concavity of the two vertebral surfaces is almost identical in shape and depth, i.e. simetrical. The development of these shape alterations is caused by stasis of regional circulation, anoxia and ischemia associated with this chronic hemolytic anemia. (10) The cartilaginous endplate is the equivalent of the growth cartilage of long bones, the metaphysis. Ischemia manifests itself significantly more in the middle portion because the periphery is also vascularized by short perforating vessels from the periosteal circulation. Thus, the central part of the vertebral growth plate is the one predominantly affected by circulatory alterations, determining a local inhibition of bone growth. Pathological changes appear in the first year and continue throughout the patient's life, but the radiological features become apparent in their teens.

The first descriptions of "fish vertebra" using classical radiological examinations only noted that the sign appears in several conditions. Speculations were made regarding the mechanism of similarly development of this particular shape in such different disorders.

Although the "fish vertebra" aspect has attracted the attention of radiologists, rheumatologist and endocrinologists, there are only a small number of published cases.

Modern imagistic techniques have allowed not only the confirmation of biconcave vertebral bodies, but also establishing the causes of these alterations.

In our patient, CT and MRI scans revealed the uncommon fish vertebra aspect, but also multiple fractures that impaired his locomotion and were an explanation for his pain.

Absence of family history, blood test markers and radiological changes associated with autoimmune diseases (such as ankylosing spondylitis) were suggestive for a different type of disorder.

The correlation between hypophosphatemia and hyperphosphaturia with a DXA test positive for osteoporosis oriented the differential diagnosis to osteomalacia, possibly caused by an endocrine tumor, i.e. oncogenic osteomalacia. This diagnosis was supported by high levels of FGF23, which is secreted by osteocytes in response to elevated calcitriol levels and overproduced by some types of tumors, such as benign mesenchymal neoplasms. (11, 12)

Tumor induced osteomalacia is considered a paraneoplastic syndrome. (13) The main role of FGF23 is the regulation of plasmatic phosphate concentration. It decreases the reabsorption and increases excretion of phosphate in the proximal renal tubule. Also, it inhibits production and stimulates the breakdown of calcitriol.

Tumors secreting FGF23 are often small and difficult to find with conventional imaging. (14) In our case, a whole body MRI was unable to detect the tumor. Gallium (68Ga) DOTA-TATE (GaTATE) was used for tumor diagnosis with PET/CT. (15) DOTA-TATE is an amide of the acid DOTA which acts as a chelator for a radionuclide and (Tyr3)-octreotate, a derivation of octeotride, which binds to somatostatin receptors found on the cell's surface of some neuroendocrine tumors. Thus, the tumor was found in the right femoral head, presenting a diameter of only 15 mm.

Conclusion

"Fish vertebra" or biconcave vertebra represents an uncommon anomaly of the vertebral body, initially revealed by roentgenologic investigation. It is associated with several conditions (osteoporosis, osteomalacia, sickle cell disease etc.), with minor variations in aspect of the concavities.

Modern medical imaging and biochemical testing have made the leap from merely observing vertebral biconcavities to diagnosing their cause and, consequently, the possibility to adequately treat uncommon conditions such as neuroendocrine tumor-induced osteomalacia.

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