A rare cause of leg pain

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Summary

Sclerosing bone dysplasias (SBD) are skeletal abnormalities characterised by an increase in segmental or generalized bone mass. In this case report, a 76-year-old woman presented right leg pain. The radiological examination revealed a fusiform enlargement of the right femur with marked cortical thickening and narrowing of the medullary canal. A subsequent bone scan reported an intense uptake of radionuclide localised in the same anatomical site. Routine biochemical tests were in the normal range. On suspicion of osteosarcoma, the patient underwent a biopsy of the bone lesion that showed no neoplastic proliferation.
In light of the medical history, laboratory tests and instrumental examinations, the patient was diagnosed with Ribbing disease. She was treated with a low dose of prednisone 5 mg/day and experienced a reduction of pain.

KEY WORDS: leg pain; Ribbing disease; sclerosing bone dysplasias.

Introduction

Sclerosing bone dysplasias (SBD) are skeletal abnormalities of varying severity with a wide range of radiologic, clinical, and genetic features. These disorders can cause an increase in segmental or generalized bone mass and can be classified as primitive or secondary forms and according to genetics in hereditary and non-hereditary disorders (Table 1). Bone alterations depend on a dysfunction of bone remodeling mechanisms, resulting in increased bone mass. Various signals important in maintaining the balance between osteoclastogenesis and osteoblastogenesis are involved in these pathologies, including Wnt beta-catenin signalling, OPG/RANK/ RANKL, TGF-beta, and others (1).
One of the rare SBD of unknown etiology is Ribbing disease, or multiple diaphyseal sclerosis, first described by Ribbing in 1949 (2). It is characterised by sclerosing bone lesions in the diaphyses of long bones in adult patients (2-5). In the literature, only few cases have been reported (4, 5). This disease affects lower extremities, and it is usually asynchronous when multiple bones are involved. Since its occurrence is so rare and due to lack of knowledge of this infrequent disease, diagnosis is often delayed and may be confused with other SBD, metabolic diseases, or even osteomyelitis (4-6). Hence, Ribbing disease is diagnosed by exclusion.

Case report

A 76-year-old woman presented right leg pain and difficulty in walking. Medical history was significant for hypertension, atherosclerosis, ischemic heart disease, and previous cholecystectomy. She had no previous fractures, no family history for bone disease. Pain began 7 years previously and was interpreted as sciatica and treated with anti-inflammatory drugs with partial benefit. In May 2013, due to the persistence of pain, the patient underwent an X-ray of her right leg that revealed a fusiform enlargement of the femur with marked cortical thickening and narrowing of the medullary canal (Figure 1). A CT of the femur showed a diaphyseal-metaphyseal sclerosis and obstruction of the medullary canal. A bone scan reported an intense uptake of radionuclide localised to the right femur (Figure 2). On suspicion of osteosarcoma, the patient underwent a biopsy of the bone lesion that showed no neoplastic proliferation. In light of these tests, the patient was diagnosed with Paget's bone disease and sent to our Center for Metabolic Bone Diseases for specific medical treatment. Serum levels of calcium adjusted for albumin, phosphorus, and alkaline phosphatase were within normal ranges. The patient further underwent magnetic resonance imaging (MRI), which revealed a cortical thickening of the right femur with bone marrow oedema and minimal adjacent soft tissue oedema.
Other biochemical tests were performed. Serum creatinine, complete blood count, erythrocytes sedimentation rate (ESR), and the immunoelectrophoresis of plasmatic and urinary proteins were within normal ranges. The 24-hour urinary calcium concentration was also normal. Concerning bone turnover markers (Table 2), C-terminal telopeptide of type I collagen (CTX) was in the normal range, but we observed an increase in serum levels of total s-Rankl, osteoprotegerin (OPG), and sclerostin.
After evaluating the medical history and clinical, laboratory and instrumental examinations, the diagnosis of Paget's disease was reconsidered, and a new diagnosis of Ribbing dis-

Table 1 - Classification of sclerosing bone dysplasias.

Sclerosing bone dysplasias				
Generalized high bone mass		Segmental high bone mass		
Primitive hereditary	*Secondary*	*Primitive hereditary*	*Primitive not hereditary*	*Secondary*
– Osteopetrosis – Hyperostosis Corticalis Generalisata – FIO – The high bone mass phenotype	– HCAO – Myelofibrosis – DISH – Mastocytosis	– Pycnodysostosis – Osteopoikilosis – Progressive Diaphyseal Dysplasia – Ribbing's disease – Osteopathia Striata	– Melorheostosis – Intramedullary Osteosclerosis – Overlap Syndromes	– Osteoblastic metastases – Mieloma multiple – Paget's Disease of Bone – Erdheim-Chester Disease

HCAO (Hepatitis C-associated osteosclerosis)
DISH (Diffuse idiopathic skeletal hyperostosis)
FIO (Fibrogenesis imperfecta ossium)

Figure 1 - X-ray revealed a fusiform enlargement of the right femur with marked cortical thickening and narrowing of the medullary canal.

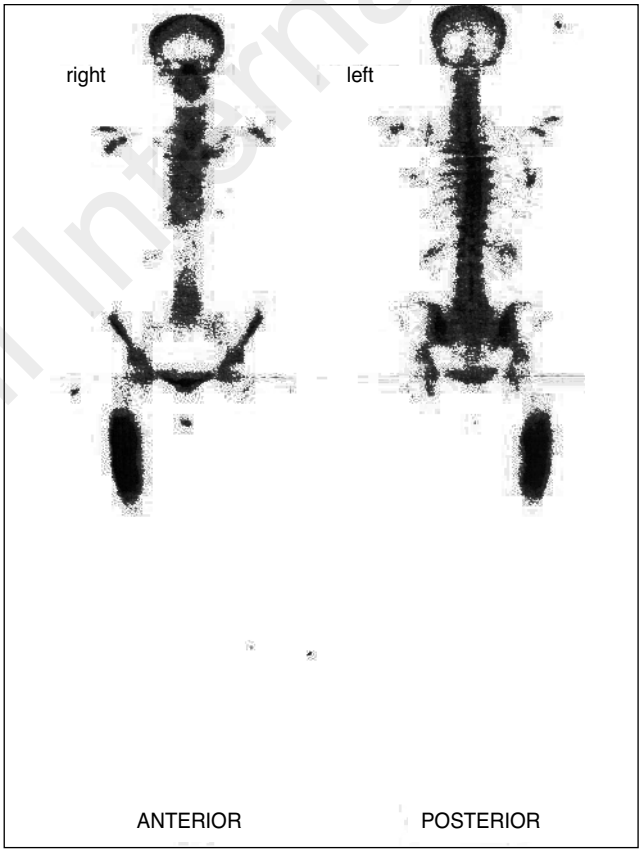

Figure 2 - Bone scan reported an intense uptake of radionuclide localised to the right femur.

ease was made. The patient was treated with a low dose of prednisone 5 mg/day and experienced a reduction of pain.

Discussion

Ribbing disease is a rare sclerosing bone dysplasia of unknown etiology. The disease is characterised radiologically by cortical thickening, involving the periosteal and endosteal surfaces of the diaphyseal portions of long bones. The epiphyses are characteristically spared (1). Bone scintigraphy shows characteristically abnormal tracer concentrations in the involved diaphyses (7). An MRI examination confirms the presence of sclerosis and usually reveals bone marrow oedema in the diaphyses of the affected bones (8, 9). These anatomical and functional alterations are not associated with specific laboratory findings. Ribbing disease has been associated with increased cardiovascular risk (10), possibly due to an altered cytokine pattern. The high values of sclerostin, OPG, and RANKL observed in our patient, as well as being an expression of possible involvement of these signals in the pathogenesis of this disease, may be related to the serious

Table 2 - Bone turnover markers.

Markers		Reference values
CTX (ng/ml)	0.712	0.142-1.351
Total s-RANKL (pmol/l)	**7.41**	3.1-6.9
OPG (pmol/l)	**11.4**	0.6 - 6.9
DKK-1 (pmol/l)	21	25.7- 65.7
Sclerostin (pmol/l)	**56.9**	10.2-48.8

atherosclerotic diseases of the patient, as recently reported by our group and other Authors (11, 12).

Ribbing's disease is considered by some Authors an autosomal recessive variant of Camurati-Engelmann disease (progressive diaphyseal dysplasia). However, contrary to Ribbing disease, Camurati-Engelmann disease is characterised by osteosclerosis of the skull base (56.5% of cases), of the mandible (25% of cases), and symmetry of bone involvement, and the symptoms may start during childhood (2, 4, 5, 13). Camurati-Engelmann disease may show progression into the metaphyses (14) and is associated with neurological abnormalities. Furthermore, Camurati-Engelmann is continuously progressive, whereas Ribbing disease may become static (2, 4, 5). Makita et al. (15) identified the Ribbing disease phenotype in a three-generation Japanese family with Camurati-Engelmann, and subsequently proposed that Camurati-Engelmann and Ribbing diseases represent phenotypic variations of the same disorder. There are other differential diagnoses that should be considered, such as the group of sclerotic bone dysplasias that mainly involve the skull but may also affect the peripheral skeleton (e.g. van Buchem's disease). Paget's bone disease can affect any bone segment, determining enlargement and deformation, but it is generally accompanied by increased alkaline phosphatase concentrations. Chronic multifocal sclerosing osteomyelitis occurs with leucocytosis and elevated ESR values, which are absent in Ribbing disease.

To date there is no specific treatment for this disease. Medications, such as NSAIDs and prednisone, are efficient in reducing pain in most patients, especially at disease onset or as adjunctive therapy when combined with surgery (3, 7, 8, 16). The role of bisphosphonates is very controversial (17). Finally, surgical treatment consisted of intramedullary reaming and fenestration, and it has been proved effective for pain relief in several cases (3, 4).

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