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CASE REPORT

Diffuse, fracturing systemic skeletal histiocytosis of unknown type: a novel metabolic bone disease

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Abstract

We describe a novel disease of diffuse skeletal histiocytosis associated with multiple fragility fractures and high osteoclast activity. Clinical, radiographic, biochemical, genetic, and histopathological investigations were performed to characterize the diagnosis of an Asian man who presented with hip fracture and diffuse skeletal lytic lesions. After excluding malignancy and other common metabolic bone diseases, open bone biopsy yielded several pathological samples all showing extensive skeletal histiocytosis likely to explain the diffuse axial and appendicular lytic lesions. Rare disorders such as Langerhans histiocytosis, Erdheim-Chester disease, and diffuse cystic skeletal angiomatosis were excluded through careful pathological examination and lack of CD1a and S-100 staining. Whole exome sequencing did not yield diagnostic findings to explain this likely acquired disease. High markers of osteoclast activity suggested excessive focal bone resorption but normalized after zoledronic acid treatment. A novel disease of skeletal histiocytosis with high bone turnover is differentiated from other histiocytic and lytic skeletal diseases.

Keywords Histiocytosis · Lytic lesions · Metabolic bone disease · Osteoporosis

Introduction

The most common causes of diffuse skeletal lytic lesions are metastatic bone disease and multiple myeloma. Other uncommon etiologies with a similar radiological presentation include Langerhans cell histiocytosis, hyperparathyroidism, and diffuse cystic skeletal angiomatosis [1–3]. Most of these disorders may be diagnosed using clinical history, biochemistry, and radiology. Bone biopsy may also confirm the diagnosis of metastatic bone disease and uncommon diseases such as diffuse cystic skeletal angiomatosis. Here, we present a case of fracturing bone disease linked to diffuse skeletal histiocytosis of unknown cause which has not been previously described.

Case report

In 2010, a 59-year-old gentleman from Hong Kong sustained a spontaneous fracture on his right hip after several months prodrome of hip pain. He was treated in Hong Kong with internal fixation of the right intertrochanteric fracture. At surgery, an abnormal appearance of the bone was noted and biopsy reportedly performed. The patient reported having been told that the diagnosis was Paget's Disease, but there was no corresponding biochemistry, and no specific treatment offered. He emigrated to Canada in 2012.

In 2015, he was referred for evaluation of incidentally noted radiological changes, which were interpreted as possible metastatic malignancy. Signed consent was obtained for investigation and publication of his case. He denied bony pain or systemic complaints suggestive of a chronic medical disorder or malignancy. He had a past history of beta thalassemia

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trait and Barrett's esophagus. He was a non-smoker and did not drink alcohol. There was a family history of colon cancer (mother and sister) but no history of bone disease or recurrent fractures.

On examination, his weight was 60 kg and height was 161.5 cm. Sclerae were white. There were no bony deformities or tenderness. Thyroid exam was unremarkable. Wall-occiput distance and rib-iliac crest distance were normal. There was no peripheral edema, no skin lesions, and no organomegaly. Examination of joints was also normal.

The skeletal survey demonstrated the presence of lytic lesions in the parietal and occipital bones along with multiple lytic lesions in the thoraco-lumbar spine. Vertebral anterior compression fractures at T9 (30%) and L1 (10%) were noted, with old healed rib fractures bilaterally, many ribs also showing lytic lesions. The pelvis and proximal femur had mixed osteolytic and sclerotic changes (Fig. 1).

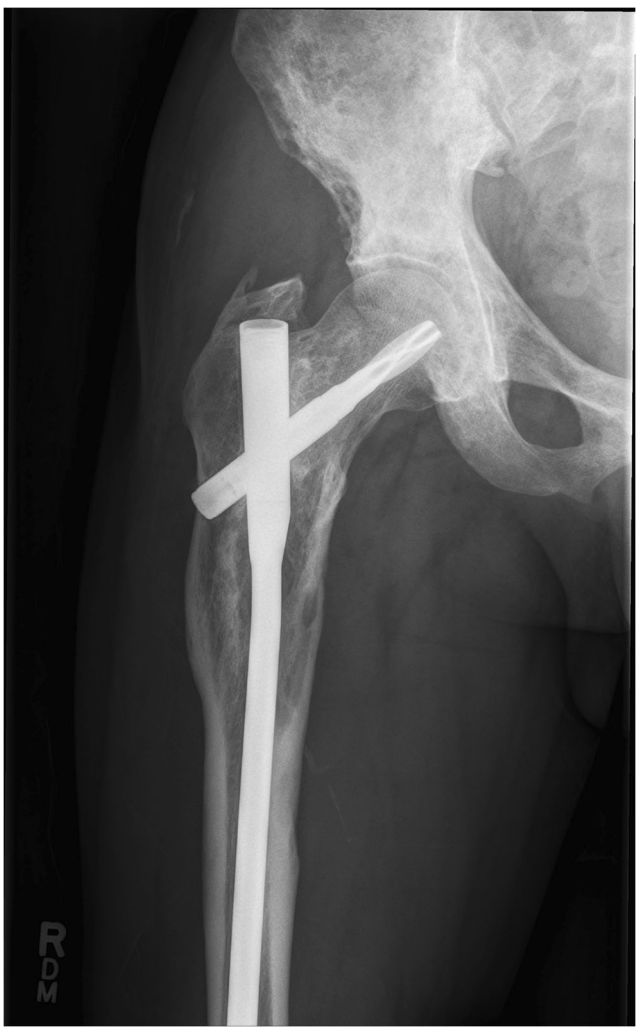

Fig. 1 Pelvis radiograph showing the mixed osteolytic and sclerotic changes in pelvis and proximal femur along with nail in situ used for fixation of right intertrochanteric fracture

There was no CT evidence of primary malignancy identified within the chest, abdomen, and pelvis and no involvement of visceral organs. CT scan did confirm areas of mixed sclerosis and lysis in the pelvic bones, femoral heads, and proximal femoral shafts. There was no cortical thickening. The rib lytic lesions were accompanied by small extra-pleural soft tissue masses. The radiological findings were not typical of multiple myeloma as it is usually associated with well defined, "punched out" lytic lesions of uniform size and not associated with sclerotic changes.

Technetium-99 m MDP bone scan demonstrated a diffuse heterogeneous uptake in the vertebral bodies, multiple ribs, pelvis, and bilateral proximal femora, potentially consistent with extensive bony metastatic disease. However, metastatic prostate cancer was ruled out by normal prostate examination and normal levels of prostate-specific antigen, and there was no evidence of primary malignancy on history, examination or CT scan survey. Bone mineral density showed a *T* score of + 0.1 in the lumbar spine and + 0.6 at the hip with 1/3 radius *T* score of − 2.6 (*Z* scores of 0.6, 1.0 and − 1.5 respectively).

Blood work showed microcytic anemia (hemoglobin 116 g/L) with beta thalassemia trait. The level of fasting, morning serum beta-C-telo-peptide (BCTX) was high (814 ng/L normal < 400), suggesting abnormally high bone remodeling/resorption (measured at least 2 years after discovery of the vertebral fractures) but with normal alkaline phosphatase (127 U/L, normal 30–145). Serum 25-vitamin D level was 52 nmol/L. Serum calcium and parathyroid hormone levels, ESR, CRP, liver enzymes, protein electrophoresis, thyroid stimulating hormone, testosterone, serum phosphate, serum magnesium, and urinalysis were within normal limits. He had negative fecal occult blood test and normal colonoscopy. Plasma IL-6 was normal as was tryptase to exclude mastocytosis; normal T cell glucosidase activity ruled out Gaucher's disease. Whole exome sequencing (Blueprint Genetics Whole Exome Test version 2, February 9, 2018, Helsinki, Finland) did not detect mutations in any genes known to be associated with congenital bone dysplasias/osteoporosis.

Histopathology

Open iliac crest biopsy was performed and three irregular pieces of brown-yellow, gritty, cortical, and cancellous bone were retrieved, measuring 1.3 × 1.2 × 1.1, 1.9 × 1.3 × 0.5, and 1.9 × 1.4 × 0.6 cm, respectively. Following decalcification, 6 μm sections were cut and stained with hematoxylin and eosin and examined under light microscopy by a pathologist with expertise in bone pathology (LD).

Sections showed a diffuse proliferation of histiocytes, confirmed by positive CD68 and negative CD45, and pooled cytokeratin staining in the lesional cells with use of appropriate positive and negative immunohistochemical staining

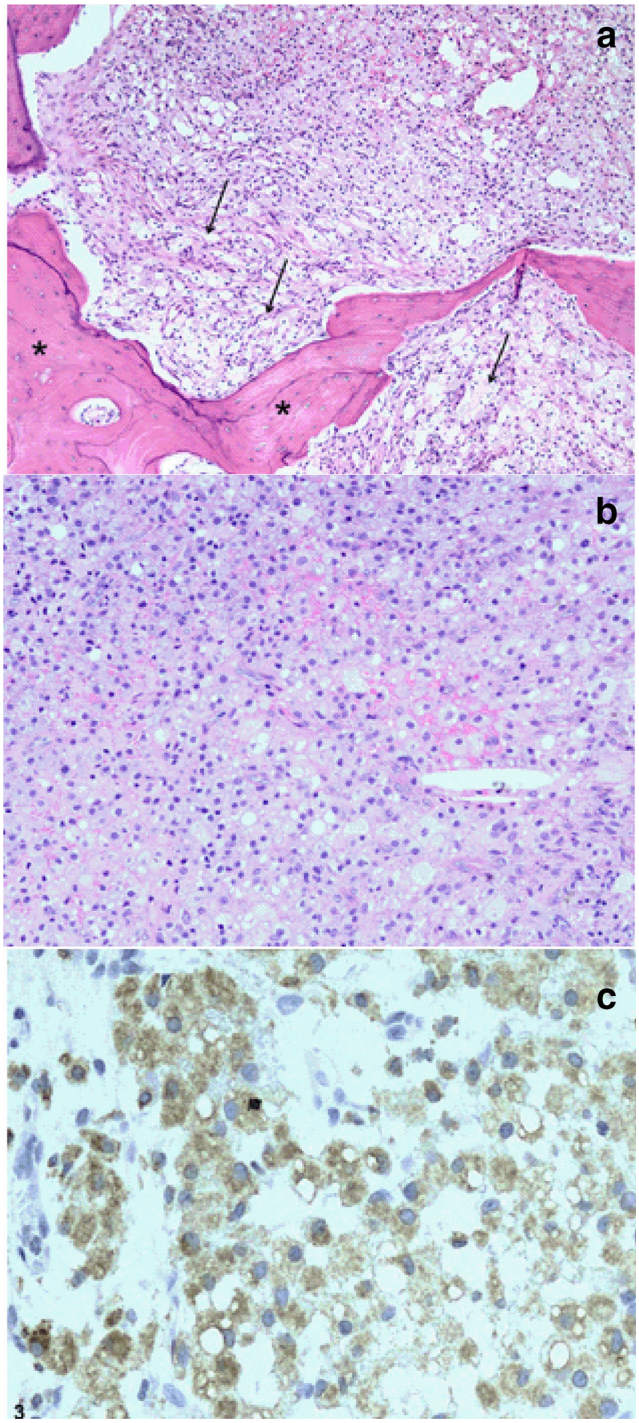

Fig. 2 **a** The bony trabeculae (*) show remodeling changes while the intervening stroma contains numerous histiocytes with clear and granular cytoplasm (arrows) (hematoxylin and eosin stain × 10). **b** Diffuse infiltration of the bone marrow by sheets of histiocytes with foamy, bubbly cytoplasm, but no atypia (hematoxylin and eosin stain × 20). **c** Anti-CD68 antibody stain (brown chromogen, located in the cytoplasm) confirms the cells to be histiocytic in origin (anti-CD68 immunohistochemical stain × 40)

controls. The histiocytes were distributed in sheets between trabeculae of lamellar bone with prominent remodeling. (Fig. 2a, b, c). No malignancy was identified. Rare giant cells were also noted, but no necrosis, granulomata, or viral cytopathic changes were seen, and special stains for acid-fast bacilli (Ziehl-Neilson), fungi (Grocott), bacteria (Gram), and spirochetes (Steiner) were negative, arguing against an infectious etiology. Likewise, no emperipolesis (histiocytes engulfing RBCs or other inflammatory cells as seen in Rosai-Dorfman disease) was seen, and there were no eosinophils or classic Langerhans cells. These latter findings, together with the lack of staining for CD1a and S-100 protein, made diseases such as Langerhans cell histiocytosis or Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) unlikely. A reaction to foreign substances such as polyvinylpyrrolidone (PVP) was also considered, but no polarizable material or intracellular granular deposits were identified (negative PAS, mucicarmine, and Congo Red stains). In addition, there was no history of occupational exposure, injection, or ingestion of such substances. Chester-Erdheim disease was considered, but this systemic histiocytic disease is doubtful given the skeletal distribution and characterization of the lesions (lytic rather than sclerotic), and the lack of significant fibrosis or other endocrinopathies. In addition, *B-RAF* mutation analysis was negative. The overall features are therefore that of a systemic, diffuse histiocytosis of unknown, novel type.

Although asymptomatic, he had a high level of BCTX and prior fracture. Therefore, zoledronic acid treatment was initiated. Three months after the first dose of zoledronic acid, levels of BCTX dropped to 273 ng/L but re-measurement at 15 months post-therapy found high levels of BCTX once more (414 ng/L) and a second infusion of zoledronic acid given. Three years after first presentation to us, the patient remains fracture-free; ongoing periodic measures of BCTX is planned with intermittent zoledronic acid considered if measures are high.

Discussion

We present a novel, fracturing, high turnover metabolic bone disease associated with extensive histiocytosis resulting in skeletal lytic and sclerotic lesions in the axial and proximal appendicular skeleton. The most important differential diagnosis for diffuse skeletal lytic lesions includes metastatic bone disease and multiple myeloma, along with a few rare presentations like Paget's Disease, Langerhan's cell histiocytosis, Erdheim-Chester disease, and diffuse cystic skeletal angiomatosis.

Pelvis radiographs mimicked the sclerotic lesions from metastatic malignancy, but extensive follow-up over 8 years has essentially excluded that possibility. Paget's disease was excluded by absence of its other typical biochemical (high alkaline phosphatase) and radiological findings like cortical thickening and cotton wool spots on skull x rays [1].

Langerhan's cell histiocytosis was excluded based upon lack of systemic symptoms, absence of involvement of visceral organs and the absence of typical punched-out lytic lesions [2]. Moreover, histological findings of diffuse histiocytosis without eosinophils or classic Langerhans cells, and negative S-100 protein and CD1a stains further help eliminate the diagnosis of Langerhans cell histiocytosis [4]. Diffuse cystic skeletal angiomatosis is a rare disease to be considered in patients presenting with diffuse multifocal osteolytic lesions with or without visceral involvement [3]. Geographic osteolytic lesions of diffuse cystic skeletal angiomatosis typically have sclerotic borders which help differentiate it from the lytic lesions in our patient. Most importantly, our patient did not have the typical histopathological findings of diffuse cystic skeletal angiomatosis in the form of cavernous or capillary hemangiomas [3]. Brisk bleeding was not encountered during the open iliac crest bone biopsy. Rare disorders such as Hajdu Cheney syndrome would be expected to manifest additional developmental anomalies and facial dysmorphism and Gorham-Stout syndrome, while associated with severe osteolysis and abnormal lymphangiogenesis, is not associated with histiocytosis and has numerous other features (swelling, pain, high IL-6) that were not seen in our patient.

Our patient had high baseline levels of Beta-C-telo-peptide (BCTX) indicating a high osteoclastic activity which was associated with diffuse osteolytic bone lesions. The etiopathogenesis of novel bone diseases may be classified as osteolytic or osteosclerotic or both, according to the primacy of mechanisms leading to either bone resorption versus bone formation. There is evidence in the literature that enhanced RANKL activity is usually associated with osteoclast-mediated bone destruction in both malignant and non-malignant forms of diffuse histiocytic disorders [4–6]. Therefore, it can be suggested here that there might be an overexpression of RANKL by proliferated histiocytes in the local bone microenvironment which lead to bone resorption and production of diffuse osteolytic lesions.

In conclusion, to our knowledge, this is the first case report of a long-standing, largely asymptomatic and possibly non-progressive disease which can present with a fragility fracture in association with diffuse skeletal histiocytosis and high osteoclastic activity. Its radiological findings in the form of mixed sclerosis and lysis of the axial and proximal appendicular skeleton can mimic many systemic diseases. The diagnosis requires bone biopsy and can be confirmed by excluding the diseases which have similar radiologic and histopathological findings of diffuse histiocytosis. Use of an anti-resorptive drug may be useful to reduce fragility fractures, but careful long term follow-up will be needed to determine if this infiltrative disease is progressive. Similar cases seen at other centers may help define the genesis of this disease in the future.

Compliance with ethical standards

Conflict of interest None.

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