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Novel use of burosumab in refractory iron-induced FGF23-mediated hypophosphataemic osteomalacia

Rheumatology key message

- Burosumab ought to be considered in the management of iron-induced FGF23-mediated hypophosphataemic osteomalacia.

Dear Editor, Refractory iron-induced fibroblast growth factor 23 (FGF23) mediated hypophosphataemic osteomalacia is an uncommon complication of parenteral iron therapy. Treatment thus far in case reports has consisted of iron cessation and phosphate substitution [1–4]. To our knowledge, we describe the first reported use of burosumab therapy for this condition.

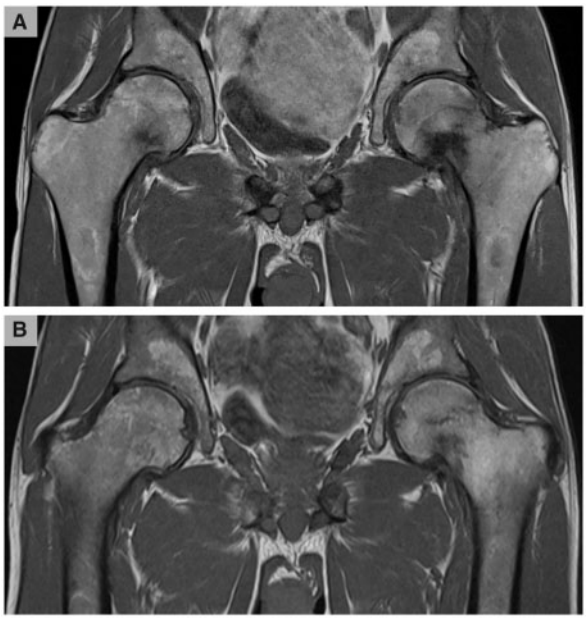
We present a 32-year-old man with severe Crohn's disease and iron-deficiency anaemia. Computed tomography angiography revealed focal ileocolic venous portal hypertension with recurrent lower intestinal blood loss. A transjugular intrahepatic portosystemic shunt was not considered feasible and regular infusions of 250 mg ferric carboxymaltose fortnightly were instituted over oral therapy, given the extensive gastrointestinal disease.

After one year, the patient developed severe foot and leg pain and was diagnosed with multiple insufficiency metatarsal and tarsal fractures. Laboratory workup revealed profound hypophosphataemia (0.38 mmol/l), elevated FGF23 (320 RU/ml) and no pathogenic variants in PHEX, ENPP1, SLC34A3, DMP1 or KLOTHO. He was started on Sandoz phosphate, alfacalcidol and was switched from ferric carboxymaltose to iron isomaltoside. There was no appreciable clinical benefit and tolerability to oral phosphate supplementation was poor, owing to an increase in diarrhoea.

One year later, he developed progressive severe left hip pain after minor trauma. MRI demonstrated a femoral pseudofracture. He was switched to central intravenous phosphate replacement for ten hours a day, five days a week with partial weight bearing. Follow-up MRI three months later demonstrated a complete left femoral fracture, new right femoral pseudofracture and multiple pelvic fractures (Fig. 1A).

Given the progression of his bone disease and likely need for bilateral hip arthroplasty, the patient was started on burosumab (0.3 mg/kg) subcutaneously every four weeks. After the first dose, he reported a significant resolution of symptoms mirrored with improvements in laboratory measures. Serum phosphate levels improved from 0.38 mmol/l to 1 mmol/l and alkaline phosphatase levels reduced from 218 IU/l to 175 IU/l. Furthermore, subsequent MRI showed complete resolution of the right femoral head fracture and near complete healing of the left femoral and pelvic fractures (Fig. 1B).

Fig. 1 T1-weighted MRI of the patient's pelvis prior to and after three doses of burosumab (0.3 mg/kg)



(**A**) demonstrates a complete left femoral intramedullary subcapital fracture, right femoral pseudofracture and multiple pelvic fractures. (**B**) shows complete resolution of the right femoral neck pseudofracture and near complete healing of the left femoral fracture and pelvic fractures.

The mechanism of iron-induced FGF23 synthesis is incompletely understood, with increases in FGF23 from both iron treatment and iron deficiency [5]. High levels of FGF23 cause diminished bone mineralisation by reducing renal 1α-hydroxylase activity and renal tubular phosphate reabsorption. Additionally, ferric carboxymaltose-induced FGF23 elevation has been suggested to cause secondary hyperparathyroidism and calcitriol deficiency, which subsequently further adds to the hypophosphataemia [6]. Burosumab is a human recombinant monoclonal antibody that binds FGF23 and is licensed for paediatric X-linked hypophosphataemia [7].

We report the first documented use of burosumab in refractory iron-induced FGF23-mediated osteomalacia with successful outcomes including avoidance of costly orthopaedic surgery. This case further highlights the wider clinical advantages of burosumab in other FGF23-mediated diseases.

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Sacroiliitis in a patient with Rosai-Dorfman disease: new bone location or overlap with axial spondylarthritis?

Rheumatology key message

- We report the first association between Rosai-Dorfman disease and sacroiliitis.

SIR, Rosai-Dorfman disease (RDD) is a rare non-Langerhans-cell histiocytosis characterized by histology (enlarged CD68+, CD1a− and S100 histiocytes with lesions of emperipolesis). RDD can be an isolated entity or be associated with rheumatologic conditions (lupus, JIA). To date, no association between RDD and SpA has been reported. A 39-year-old patient suffered from unexplained fever for 1 month. He had medical history of appendicitis. He had no smoking or drinking habits and worked as a disc jockey in a nightclub. He travelled in Italy and Spain. The patient was referred to hospital for fever of 39°C without night-sweat or weight loss. Physical examination showed bilateral, painful, red eyes without vision loss. An ophthalmologist concluded bilateral anterior uveitis. The patient complained of dry cough with normal cardiopulmonary examination. He also described peripheral arthralgia. Skin examination showed erythematous, pigmented punctiform lesions of the legs going up to buttocks, and on cheeks and back. He also had three nodular lesions on his legs and arms (Fig. 1). Biological examinations showed white cell counts at 10.11×10^9/l, haemoglobin at 10.9 g/dl, platelet counts at 513×10^9/l and CRP was at 194 mg/l. Liver function tests showed cholestasis (gamma-Gt: 6 ×upper to the normal limit and alkaline phosphatase: 3 N). Cardiac echography showed no evidence for endocarditis and body CT was unremarkable; specifically it showed no lymphadenopathy. (^{18}F)-fluorodeoxyglucose-PET showed isolated mild radiotracer uptake on aorta (maximum standardized uptake value 3.8) (Fig. 1) without thickening or enhancement of aortic wall on MRI. It also showed radiotracer uptake of the left sacroiliac joint (maximum standardized uptake value 2.6) (Fig. 1). MRI showed a left sacroiliitis with bone marrow oedema suggestive of SPA regarding the Assessment of SpondyloArthritis International Society (ASAS) criteria for the definition of sacroiliitis (Fig. 1). Bone scintigraphy showed an isolated lesion of the right clavicle (Fig. 1) and both sacroiliac joints. Due to arthralgia, aortitis and sacroiliitis, screening was carried out for infections (including *Mycobacterium tuberculosis*, *Yersinia*, *Chlamydia tracomatis*, *Rickettsia coroni*, *Coxiella burnetii*, *Bartonella henselae* and *Tropheryma whipplei*) and for autoimmune diseases (lupus, ANCA-associated vasculitis, RA, cryoglobulinaemia), and was negative. *HLA B27* gene was negative.

Skin biopsy showed infiltration of tissues by enlarged histiocytes expressing CD68+ and S100+ but not CD1a on immuno-staining, and demonstrated abundant lesions of emperipolesis and strong expression of phospho-Erk. characteristic of RDD (Fig. 1). c.361T>A mutation of the *MAP2K1* gene was present on biopsy sample. Patient had a spontaneous improvement of fever, arthritis and cholestasis, and a decrease of CRP level at 1 month. At 6 months' follow-up, the patient no longer had fever, arthritis or increased CRP level. He only had one episode of spontaneous reversible hearing loss compatible with RDD manifestation. To date, the patient has received no specific treatment for either RDD or SpA.

We report the first association of RDD with sacroiliitis. Concurrence of RDD with immunologic conditions had been reported for lupus, haemolytic anaemia and JIA in a few patients [1–3], mostly with extranodal presentation. RDD is a rare histiocytosis characterized by infiltration of tissues by CD68+, CD1a−, S100+ histiocytes, with large nuclei and lesions of emperipolesis [1, 4]. Initial RDD presentation is cervical lymphadenopathy, but almost half of the patients present extranodal manifestations (skin, eyes, CNS, ENT, bone). Bone involvement is rare (<10% of patients with extranodal presentation). Bone lesions are usually solitary or multiple, involving metaphyseal and/or diaphyseal region of bones (especially skull, radius, humerus, tibia, clavicle) [5], but to date no sacroiliac involvement has been reported. Imaging shows lytic or sclerotic lesions raising the differential diagnosis (or the association) with bone neoplasm, or 'L-group' histiocytosis. (^{18}F)-fluorodeoxyglucose-PET (including long bones) is recommended for initial staging evaluation, and to distinguish isolated RDD or overlap with other pathological conditions (neoplasia, 'L-group' histiocytosis) [1, 6]. Sacroiliitis is a radiologic condition mainly described in axial SpA (axSpA). Diagnosis of axSpA is based on clinical manifestations, imaging and frequent association with the *HLA B-27* gene. MRI in axSpA shows inflammation (bone marrow oedema) and/or joint structural changes (erosions, sclerosis, fat lesions or ankylosis, new bone formation, sclerosis or fat infiltration) of sacroiliac joints [7]. Regarding bone imaging, MRI is suggestive (but not typical) of SpA, as only small solitary unilateral bone marrow oedema might be in the dorsocaudal region of the left joint, together with no evidence of axSpA-typical structural changes, such as erosions, sclerosis of fat lesions visible on T1 and Volumetric interpolated breath-hold examination sequences. Radiotracer uptake in the