

Persistent knee pain in a patient with systemic lupus erythematosus

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In the present issue of this Journal, Vieira MB et al. reported a case of a female patient with systemic erythematosus lupus with end-stage renal disease. She had been on hemodialysis and transitioned to peritoneal dialysis. In spite of treatment with active vitamin D and cinacalcet, she developed severe hyperparathyroidism due to poor adherence to medication. She presented right knee pain, with osteolytic lesions on radiology exams and a bone biopsy compatible with brown tumors. Medical treatment was optimized, with clinical improvement. However, due to poor treatment compliance sustained control of hyperparathyroidism was not achieved, parathyroidectomy was considered and a tetracycline-labeled bone biopsy revealed histological findings suggesting high turnover bone disease (HTBD) evolving to adynamic bone disease (ABD). Four years later, imagiological reevaluation revealed enlarged bone lesions and she was submitted to parathyroidectomy.

As it is nicely described in the manuscript, this is a complex and challenging case in the field of chronic kidney disease – mineral and bone disorder (CKD-MBD). Renal osteodystrophy (ROD) is an alteration in bone morphology due to CKD¹. It is the skeletal component of the systemic disorder of CKD-MBD that is best evaluated by histomorphometry of bone biopsy. Bone biopsy has several clinical indications such as^{1,2,3} before parathyroidectomy if the results of biochemical determinations are not consistent with advanced secondary or tertiary hyperparathyroidism; inconsistencies among biochemical parameters precluding a definitive interpretation, or unexplained skeletal fracture or bone pain. The revised KDIGO guidelines keep it simple – perform a bone biopsy if knowledge of the type of ROD will impact treatment decisions⁴.

Parathyroid hormone (PTH) is still the most useful biomarker for bone turnover in CKD⁵. In general, extreme PTH levels predict bone turnover in dialysis patients. Prediction of underlying histology is less discriminatory when PTH levels are within the middle range. With cut-offs between 161 and 450 pg/mL, reported PTH positive predictive values for the diagnosis of HTBD are between 62 and 100%². Brown tumors are bone lesions that represent a serious complication of advanced hyperparathyroidism⁶. The clinical management of brown tumors is to reduce elevated PTH by pharmacological treatment, with surgical parathyroidectomy reserved for nonresponders or patients with painful symptomatology. In the reported case, when the patient had PTH above 1000 pg/mL associated with brown tumors, the underlying histology would certainly be HTBD and, at this stage, parathyroidectomy was also an option. Medical treatment was tried with transient success. When bone biopsy was performed to evaluate ROD, patient had oscillating PTH values between < 200 and > 1000 pg/mL. The bone biopsy was important because it revealed HTBD but with findings suggesting an evolution to ABD. Accordingly, the clinical team decided not to perform the parathyroidectomy. At that moment, with suspected evolution to ABD, if the surgery had been performed we can speculate that not only would it not have been useful to resolve bone pain, but it could have been harmful to the bone quality – risking precipitating overt ABD.

According to KDIGO¹, bone turnover is evaluated using bone formation rate (BFR), a dynamic parameter calculated based on tetracycline labels. In this case, it would have been important to have the quantitative bone histomorphometric information described in the

paper, including BFR (or at least information about tetracycline labels on fluorescence microscopy). Osteoblast and osteoclast surfaces are also (static) parameters used to infer bone turnover⁷.

In the published case, the bone biopsy surprisingly revealed evolution to ABD, in a patient with PTH levels frequently above 1000 pg/mL. I must state that this evolution to ABD would not be my first bet. However, it is not so surprising considering the abrupt suppression of the parathyroid gland (PTH levels dropped from above 1000 pg/mL to less than 200 pg/mL two months after therapeutic adjustment) some time before bone biopsy and steroid treatment. Glucocorticoids have known adverse effects on bone metabolism⁸. Corticosteroids stimulate osteoclast-mediated bone resorption and reduces osteoblast-mediated bone formation. In fact, corticoids induces apoptosis in osteoblasts, thereby decreasing bone formation. This patient had history of multiple cycles of high dose corticosteroids and was taking prednisolone. So steroid therapy may have contributed to low bone turnover. Peritoneal dialysis (PD) has been considered as a risk factor for ABD⁹. However, studies evaluating ROD in PD with bone biopsies are old, with inconsistent results and included mostly patients treated with a dialysate Ca²⁺ 1.75 mmol/L. Preliminary results from our group (data not published) suggest that the spectrum of ROD in PD patients may be changing – in patients treated with dialysate Ca²⁺ 1.25 mmol/L, HTBD is the most frequent form of ROD.

Bone biopsy is a safe procedure with total incidence of complications reported as < 1%¹⁰. However, it is an underused complementary tool to guide sometimes complex therapeutic decisions in CKD-MBD. Perceived traditional constraints to bone biopsy are invasiveness of procedure, fear of pain, lack of technical training, costs, lack of specialized centers with expertise to process bone samples and interpret the results as well as a limited understanding of the nature of information provided. In the experience of our laboratory, bone biopsy is a safe, well-tolerated procedure, with no pain and so far with no major complication.

It is important to highlight that this complex case reminds all clinical nephrologists of the value of reevaluating patients, especially when data is not concordant. It was the follow-up showing expansion of lesions previously attributed to brown tumors that led to the decision to perform parathyroidectomy, with subsequent stabilization in bone lesion size. In the field of CKD-MBD (and many others), it is important not to take decisions based on isolated laboratory values, but to integrate information from different sources. It is also important to check the tendency of parameters of CKD-MBD, how they evolve over time, in order to avoid rushed clinical decisions.

Finally, if this patient develops a fragility bone fracture in the future, that will raise a new challenge. With the clinical background previously discussed and the current low PTH values (10 pg/mL), ABD will be the most likely diagnosis. In that clinical scenario, nephrologists will have to consider using different therapeutic tools in our field, such as anabolic bone agents.

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