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KEY CLINICAL MESSAGE

EC are a common complication, and STS has been used for treatment. We presented a young female on PD with BT, finding ABD, and the therapeutic including STS. Lesions disappearing. ABD is increasing, and, is necessary to redefine PTH values, and close monitoring of parameters that guide variations in turnover.

Key words: low bone turnover, brown tumour, sodium thiosulphate, adynamic bone disease.

INTRODUCTION

Mineral and bone disorders (CKD-MBD) are common chronic kidney disease (CKD) complications associated with cardiovascular outcomes and mortality in dialysis patients [1–5]. The spectrum of bone disease in peritoneal dialysis (PD) patients is yet to be clarified; it has recently been shown that up to 54% of patients with parathormone (PTH) within the goal recommended by KDIGO [6] had histomorphometry compatible with low bone turnover (LBT), according to *Pereira et al* [7]. In this case, many abnormalities of calcium and phosphate metabolism are described, mainly the presence of a positive calcium balance, which may result in an over-suppression of PTH [8,9]. Moreover, without efficient phosphate binding therapy, all PD patients have a positive phosphorus balance, witnessing continuous intrinsic inflammation activity accompanied by calcium and phosphorus imbalance, leading to extraosseous calcifications (EC), especially vascular calcifications (VC), regardless of bone turnover [10]. As a result, a reduction in serum calcium, phosphate and parathyroid levels control are important to prevent EC, while a solution of sodium thiosulphate (STS) has been used to treat a variety of metastatic calcifications related to CKD-MBD, acting as a potent calcium chelator, antioxidant, and vasodilator agent. Herein, we report a case of a young female CKD patient on PD with adynamic bone disease (ABD) and brown tumour (BT), who was successfully treated by intravenous STS, which was the cornerstone treatment.

METHODS

We decided to carry out immediate therapeutic interventions, including stopping calcitriol and cinacalcet prescriptions, changing the phosphorus chelator from calcium acetate to sevelamer carbonate and finally switching from CAPD to conventional high-flow haemodialysis (HD), three weekly five-hour sessions. Likewise, treatment with STS 25g intravenously after the haemodialysis session was initiated, performing a bone biopsy to obtain a left anterior superior iliac crest sample, according to the technique described by *Barreto et al* . [11], after tetracycline labelling procedure [12], demonstrating an ABD according to histomorphometry analysis.

DISCUSSION

It is well known that EC, like the BT described in our case, start primarily with the super saturation of plasmatic calcium and phosphorus. DP could precipitate this abnormality, because without an efficient phosphate-binding therapy, all patients undergoing PD have the trend of remarkable positive phosphorus balance unless they have severely malnourished status [13]. Phosphate transfer across the peritoneal membrane is almost exclusively diffusive and can be improved by increasing the number of CAPD cycles and dialysis solution dwelling time [14]. Additionally, there is an additional risk factor associated with calcium phosphate binders' therapy, contributing to developing LBT because they can provoke positive calcium balance that could result in over-suppression of PTH [13,15].

In our case, it was clear that CKD-BMD began within PTH values expected based on KDIGO goals, using the prescribed calcimimetics. However, the PTH over-suppression did not recover despite more than six months after suppressing the hormone curbing, turning to a different biochemical pattern suggestive of LBT. The whole therapeutic arsenal available to control secondary hyperparathyroidism includes oral calcium and vitamin D analogues, high calcium concentrations in the dialysate, calcimimetics, and hypoparathyroidism induced by parathyroidectomy, all of which have largely contributed to increasing prevalence of ABD. [13,16].

Even though there are complex mechanisms for explaining ABD appearance, there are two important aspects that must be borne in mind. Firstly, over-treatment of secondary hyperparathyroidism without appropriate follow-up could be a key reason that justifies the increase in ABD diagnoses, and secondly, there is probably a real need to redefine the PTH target values. In this sense, LBT should be considered when PTH is below150 pg/ml in patients with advanced CKD, with a sensitivity and specificity of the PTH cut-off point for diagnosis of 68.6% and 61.2% respectively at said hormone levels [16, 17]. However, the target range of PTH levels proposed for CKD patients in dialysis [6] is not a guarantee of normal bone turnover, as we saw in our case.*Pereira et al.* analysed 49 patients with CKD on PD with bone biopsy, finding ABD as a frequent pattern (42.9%) in patients with PTH within the recommended plasmatic range [6]; ABD was found in 59% of cases, and the median PTH in patients with adynamic bone was 312 (60–631) pg/mL [7].

Identifying the possible reasons for LBT is a decisive step in guiding therapeutic strategies, because of the fact that ABD management is usually multitargeted, including a change of dialysis therapy, hypercalcemia and hyperphosphatemia avoidance, using calcium-free phosphate binders, all of which are fully recommended even for normal calcemic and hypercalcaemic patients.

In the best-case scenario, calcium balance should be maintained neutral, with no net flux of calcium from the bones to the extracellular fluid, thus, in theory, with a dialysate calcium concentration of 2.5 mEq/L, no net flow of calcium should occur [18]. The 2007 CKD-MBD guidelines suggest the use of a calcium concentration in the dialysate between 2.5 mEq/L and 3.0 mEq/L. Nevertheless, a recent kinetic modelling study in HD patients [19] depicted that a dialysate calcium concentration less than 2.5 mEq/L would be necessary to prevent long-term calcium accumulation in a significant proportion of patients, and that calcium can also be removed during ultrafiltration. Normal subjects and CKD patients using 800 mg calcium diet had slightly negative to neutral calcium balance results, whereas taking 1500 mg of calcium in addition to regular diet intake from calcium carbonate daily sources would result in a positive calcium balance in subjects with stage 3 and 4 CKD who are already consuming a calcium-adequate diet [20].

Spasovski et al . demonstrated that there were changes in parameters for reflecting higher bone turnover in patients treated with dialysate calcium of 2.5 mEq/l, probably by prevention of a positive calcium balance and enabling sustained stimulation of PTH secretion, allowing LBT prevention [21], meanwhile *Sethi et al* developed measures to show an increased bone turnover in patients receiving 2.5 mEq/l of dialysate calcium, most likely resulting from inhibition to a positive calcium balance and continuously stimulating PTH secretion [22].

Moreover, the use of sevelamer has been studied and it is fully capable of achieving better control of phosphemia without concomitant use of elemental calcium. In addition, in experimental studies in murines, using sevelamer within diet besides normalising the serum phosphorus, surprisingly a reversion of the CKD-

induced trabecular osteopenia was found, increasing osteoblast surfaces in the metaphyseal trabeculae of the tibia and femur, and also had reinforced osteoid surfaces and more importantly, the bone formation rates [23]. Subsequently,*Ferreira et al.* evaluated patients with bone biopsies at the beginning and end of a one-year-period with sevelamer hydrochloride or calcium carbonate, the group in sevelamer treatment resulted in no statistically significant changes in bone turnover or mineralisation compared with calcium carbonate, yet bone formation rate was higher and trabecular architecture improved only with sevelamer [24,25].

The former measures were implemented in our patient, including adjustments in dialysis time, achieving better control of the calcium-phosphorus balance, according to our requirement, as shown in table 1.

EC type BT is a well-known complication of CKD that appears on average at approximately 3.5 years after dialysis onset; its incidence increases with a longer renal-replacement period. Nevertheless, in our patient the tumour appeared after a short time in PD, which draws attention to the fact that the disappearance of EC was achieved after just three months of using the STS, which was significantly faster than expected.

In addition, going deeper with STS, it is a well-known drug, having until now weak but growing evidence built in the last decade, mainly in the management of calciphylaxis over many years [26]. Despite this, a number of mechanisms have been proposed, primarily involving complexation with calcium ions or dissolution of calcium deposits, both of which were recently rebutted by *O'Neill* and *Hardcastle* [27], proposing a more relevant antioxidant action that targets inflammation and intimal hyperplasia based on the fact that thiosulfate can be oxidised to sulphate, yet, there being no robust evidence, so it remains in use due to its availability, tolerance, and safety.

Moreover, only a few case reports and some small-case-series have demonstrated real efficacy in the treatment of BT [28-31], with the aggregate that usually results being partial, perhaps due to the use of low doses of STS at the beginning of the therapy. In our case, we started with a full dose, maintaining the same continuously, without interruptions, because it was well-tolerated, and the x-ray images promptly demonstrated a substantial size reduction of the tumour. Herein we believe that this therapeutic behaviour guaranteed more rapid regression of the lesions, needing as little as a three-month-period of treatment to almost disappear. Indeed, the patient was without lesions after more than one year of follow-up after treatment completion.

Finally, it is important to remark that CKD-MBD patterns changed over time, and the diagnosis of ABD is increasing, which makes it necessary to redefine PTH cut-off points, mainly in PD. Likewise, close monitoring of biochemical parameters that guide variations in turnover is necessary, with prevention of possible risk factors related to LBT.

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Contributions:

Dra Hernandez: Organised the bone-renal policlinic in CAVRR, controlled and followed up the clinical case, collected patients' informed consent, obtained the clinical data, presented the patient to surgery and subsequently follow-up.

Dr Enos: Helped in the analysis of the case and data, literature review, follow-up and paper translation.

Statement of ethics: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Data availability statement: All data that support the findings of this study are included in this case report. Details are available on request from the corresponding author

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