Letter Regarding "Granulomatous Inflammation and Hypercalcemia in Patients With Severe Systemic Oxalosis"

To the Editor: Perrin *et al.*[1] have reported a case series of 5 patients suffering from primary hyperoxaluria and systemic oxalosis who presented with inflammatory lesions on fluorodeoxyglucose-positron emission tomography/computed tomography and mild hypercalcemia. Biopsy results of the bone lesions revealed calcium oxalate deposits and granuloma with macrophages expressing RANKL. On the basis of these results, denosumab was administered to lower calcemia, with only mild effect.

We recently reported a similar presentation of primary hyperoxaluria with severe hypercalcemia and high $1,25(OH)_2$ vitamin D level.[2] In our case, the hypercalcemia was probably triggered by excess of vitamin C administration, leading to increased oxalate deposits and activation of a tissular granulomatous response. As in the series by Perrin *et al.*,[1] a bone biopsy result revealed calcium oxalate deposits with numerous inflammatory granulomas. On the basis of previous publications reporting treatment of sarcoidosis-induced hypercalcemia with ketoconazole, we tried it unsuccessfully (Figure 1). Nevertheless, low-dose corticoid treatment (prednisone 15 mg/d) rapidly normalized serum calcium and $1\text{-}25(OH)_2$ vitamin D level. A maintenance therapy with 7.5 mg prednisone per day was enough to prevent recurrence of hypercalcemia.

As denosumab is known to cause severe hypocalcemia in patients with chronic kidney disease and as discontinuation of treatment is associated with high risk of vertebral fractures, we propose that low-dose corticoid therapy should be considered first for hypercalcemia-associated oxalosis in patients with primary hyperoxaluria.[3,4] Finally, vitamin C supplementation needs to be provided with caution and only under close monitoring in patients with primary hyperoxaluria with low estimated glomerular filtration rate.

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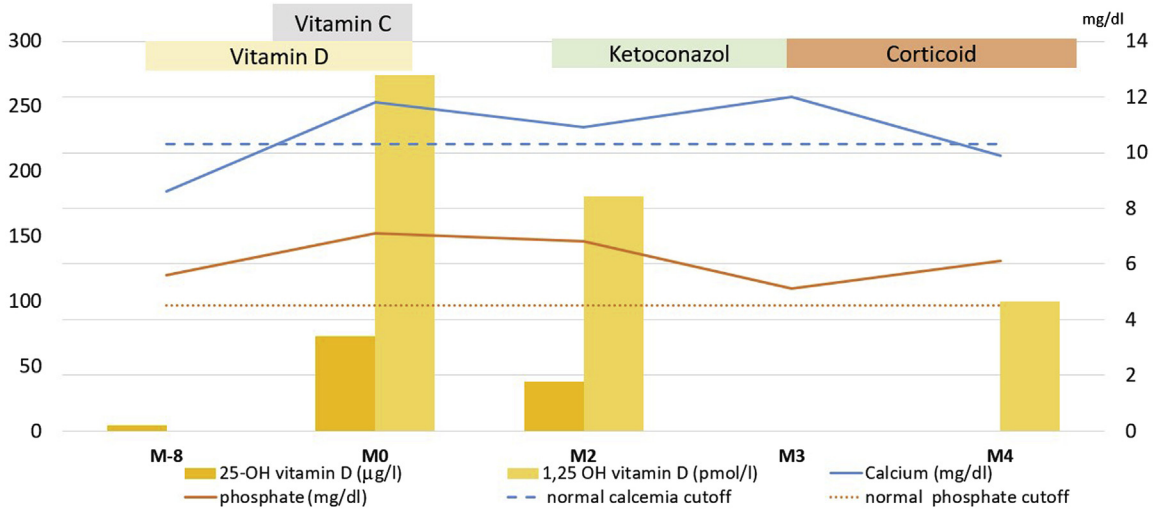

Figure 1. Evolution of phosphocalcic parameters. M, month.

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In Reply to "Letter Regarding 'Granulomatous Inflammation and Hypercalcemia in Patients With Severe Systemic Oxalosis'"

The Authors Reply: We recently reported a case series of 5 patients with primary hyperoxaluria and emphasized the importance of granulomatous inflammation in severe systemic oxalosis.[1] All cases presented diffuse hypermetabolic lesions on fluorodeoxyglucose-positron emission tomography/computed tomography and hypercalcemia. Hypermetabolic foci corresponded to areas of granulomatous inflammation elicited by calcium oxalate crystals. We thank Halfon *et al.* for their interest in our study. In line with the results from us and other groups,[2] they describe a patient with primary hyperoxaluria, hypercalcemia, and high 1,25 $(OH)_2$ vitamin D levels who was successfully treated with corticosteroids.[1] In our study, there was no report of vitamin C treatment. Some aspects of the clinical management of this condition require further discussion. During follow-up, we occasionally detected severe hypercalcemia in 3 of the 5 study patients (cases numbers 1, 2, and 3); notably, hypercalcemia in case number 3 resulted in life-threatening coma. High doses of steroids given for induction immunosuppression or acute graft rejection were only temporarily successful in controlling hypercalcemia (cases numbers 1, 2, and 3). Unfortunately, hypercalcemia recurred when corticosteroids were tapered under 15 mg/kg/d. Furthermore, a maintenance therapy with 7.5 mg/d of steroids in cases number 1 and 2 did not prevent recurrence.

Considering the elevation of bone resorption markers, the presence of lytic bone lesions, and the high incidence of fractures observed in our study, bone antiresorptive agents (e.g., bisphosphonates or denosumab that is not renally cleared) may be a part of the therapeutic armamentarium to control hypercalcemia and to prevent fractures in patients with systemic oxalosis.

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