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On the Cover

What is the diagnosis?
A 45-year-old woman with kidney failure due to obstructive nephropathy was referred to our nephrology clinic with worsening pain in the lower back, hip, and knee. She had been on hemodialysis for 9 years without receiving calcitriol, vitamin D analogues, or calcimimetics. Physical examination revealed no swelling or tenderness. Serum alkaline phosphatase level was 2418 U/L and intact parathyroid hormone level was 2300 pg/mL. Ultrasound imaging showed four enlarged parathyroid glands. An iliac crest bone biopsy was performed after doxycycline double labeling. Doxycycline was given orally at a dosage of 100 mg twice daily for 3 days for the first label, and was given again at the same dosage 2 weeks later for the second label. The patient became able to stand up and walk after parathyroidectomy with autotransplantation, physical therapy, and starting oral calcitriol.

Image Description:
Villanueva bone staining was performed on the bone biopsy specimen.
Left image: Light microscopy demonstrated large groups of osteoblasts adjacent to an increased volume of osteoid occupying 20% of the bone volume, and clusters of osteoclasts with a marked amount of fibrous tissue occupying 33% of the tissue area.
Center image: Fluorescent microscopy showed a double-labeled segment indicating recent mineralization, but revealed a large amount of unmineralized osteoid.
Right image: Polarized light microscopy demonstrated both mechanically strong lamellar bone and weak woven bone.
Increased bone turnover and insufficient mineralization confirmed the diagnosis of mixed uremic osteodystrophy due to secondary hyperparathyroidism.

Teaching Points:
Mixed uremic osteodystrophy is characterized by the concurrence of excessive bone resorption and delayed mineralization in the context of extensive osteoclastic and osteoblastic activity. Despite the progress in biochemical markers of bone turnover, bone biopsy remains the gold standard for the assessment of bone metabolism. Although bone biopsy is not frequently performed due to its invasiveness, these images remind us of the complexity of bone metabolism, which should be kept in mind when treating patients with CKD.

(Images and text provided by Yasuhiro Oda and Tatsuya Suwabe, Nephrology Center, Toranomon Hospital Kajigaya, Kanagawa, Japan; Junichi Hoshino, Nephrology Center, Toranomon Hospital Kajigaya, Kanagawa, Japan and Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan; Naoki Sawa, Nephrology Center, Toranomon Hospital Kajigaya, Kanagawa, Japan; Keichi Kinowaki, Department of Pathology, Toranomon Hospital, Tokyo, Japan; Kenichi Ohashi, Department of Pathology, Toranomon Hospital, Tokyo, Japan and Department of Pathology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; Takeshi Fujii, Department of Pathology, Toranomon Hospital, Tokyo, Japan; and Yoshifumi Ubara, Nephrology Center, Toranomon Hospital Kajigaya, Kanagawa, Japan and Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan; with acknowledgment to Akemi Ito, Ito Bone Histomorphometry Institute, Niigata, Japan, for performing the histomorphometric analysis of the bone biopsy specimen.)