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by short bulbous roots, pulp calcification, and radicular dentin depos ited in swirls. The disorder is caused by gene mutations in GALNT3, FGF23, or α-Klotho, leading to FGF23 deficiency or resistance. The reduced activity of FGF23 leads to increased renal tubular reabsorption of phosphate, elevated serum phosphate, and spontaneous soft tissue calcification from elevated calcium-phosphate concentration product. The disease usually presents in childhood and continues throughout the patient’s life. The calcific masses are typically painless and grow at variable rates, sometimes becoming large and bulky. The masses are often located near major joints but remain extracapsular. Joint range of motion is not usually restricted unless the tumors are very large. Com plications include compression of neural structures and ulceration of the overlying skin with drainage of chalky fluid and risk of secondary infection. Small deposits not detected by standard radiographs may be detected by 99mTc bone scanning. The most common laboratory findings are hyperphosphatemia and elevated serum 1,25-dihydroxyvitamin D levels. Serum calcium, parathyroid hormone, and ALP levels are usually nor mal. Renal function is also usually normal. Urine calcium and phosphate excretions are low, and calcium and phosphate balances are positive. An acquired form of the disease may occur with other causes of hyperphosphatemia, such as secondary hyperparathyroidism associ ated with hemodialysis, hypoparathyroidism, pseudohypoparathyroid ism, and massive cell lysis following chemotherapy for leukemia. Tissue trauma from joint movement may contribute to the periarticular cal cifications. Metastatic calcifications are also seen in conditions associ ated with hypercalcemia, such as in sarcoidosis, vitamin D intoxication, milk-alkali syndrome, and primary hyperparathyroidism. In these con ditions, however, mineral deposits are more likely to occur in protontransporting organs such as kidney, lungs, and gastric mucosa in which an alkaline milieu is generated by the proton pumps. TREATMENT Tumoral Calcinosis Therapeutic successes have been achieved with surgical removal of subcutaneous calcified masses, which tend not to recur if all calci fication is removed from the site. Reduction of serum phosphate by chronic phosphorus restriction may be accomplished using low dietary phosphorus intake alone or in combination with oral phos phate binders. The addition of the phosphaturic agent acetazol amide may be useful. Limited experience using the phosphaturic action of calcitonin deserves further testing. ■ ■DYSTROPHIC CALCIFICATION Posttraumatic calcification may occur with normal serum calcium and phosphate levels and normal ion-solubility

product. The depos ited mineral is either in the form of amorphous calcium phosphate or hydroxyapatite crystals. Soft tissue calcification complicating con nective tissue disorders such as scleroderma, dermatomyositis, and systemic lupus erythematosus may involve localized areas of the skin or deeper subcutaneous tissue and is referred to as calcinosis circum scripta. Mineral deposition at sites of deeper tissue injury including periarticular sites is called calcinosis universalis. ■ ■ECTOPIC OSSIFICATION True extraskeletal bone formation that begins in areas of fasciitis following surgery, trauma, burns, or neurologic injury is referred to as myositis ossificans. The bone formed is organized as lamellar or trabecular, with normal osteoblasts and osteoclasts conducting active remodeling. Well-developed haversian systems and marrow elements may be present. A second cause of ectopic bone formation occurs in an inherited disorder, fibrodysplasia ossificans progressiva. ■ ■FIBRODYSPLASIA OSSIFICANS PROGRESSIVA This is also called myositis ossificans progressiva; it is a rare autosomal dominant disorder characterized by congenital deformities of the hands and feet and episodic soft tissue swellings that ossify. The disor der is caused by an activating mutation in activin receptor A type 1. Ectopic bone formation occurs in fascia, tendons, ligaments, and connective

tissue within voluntary muscles. Tender, rubbery induration, some times precipitated by trauma, develops in the soft tissue and gradually calcifies. Eventually, heterotopic bone forms at these sites of soft tissue trauma. Morbidity results from heterotopic bone interfering with nor mal movement and function of muscle and other soft tissues. Mortality is usually related to restrictive lung disease caused by an inability of the chest to expand. Laboratory tests are unremarkable.

Until recently, there was no effective approved medical therapy. Bisphosphonates, glucocorticoids, and a low-calcium diet have largely been ineffective in halting progression of the ossification. Palovaro tene has been shown to reduce new heterotopic ossification by 60% versus historical controls but increased premature epiphyseal closure in children. In 2023, the therapy was approved in the United States for females over age 8 and males over age 10. Another potential therapeu tic option, REGN2477 (also known as garetosmab), an anti–activin A antibody, is in clinical trials. Surgical removal of ectopic bone is not recommended because the trauma of surgery may precipitate forma tion of new areas of heterotopic bone. Dental complications, including frozen jaw, may occur following injection of local anesthetics. Heritable Disorders of Connective Tissue CHAPTER 425 Acknowledgment The authors acknowledge the contribution of Dr. Murray J. Favus to this chapter in previous editions of Harrison’s. ■ ■FURTHER READING Boyce AM, Collins MT: Fibrous dysplasia/McCune-Albright syn drome: A rare, mosaic disease of Gαs activation. Endocr Rev 41:345, 2020. De Castro LF et al: Safety and efficacy of denosumab for fibrous dys plasia of bone. N Eng J Med 388:8, 2023. Pognolo RJ et al: Reduction of new heterotopic ossification (HO) in the open-label, phase 3 MOVE trial of palovarotene for fibrodysplasia ossificans progressive (FOP). J Bone Miner Res 38:3, 2022. Ralston SH et al: Diagnosis and management of Paget’s disease of bone in adults: A clinical guideline. J Bone Miner Res 34:579, 2019. Shapiro JR, Lewiecki EM: Hypophosphatasia in adults: Clinical assessment and treatment considerations. J Bone Miner Res 32:1977, 2017. Singer FR et al: Paget’s disease of bone: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 99:4408, 2014. Tan A et al: Long-term randomized trial of intensive versus symptom atic management in Paget’s disease of the bone: The PRISM-EZ Study. J Bone Miner Res 32:1165, 2017. Wu CC et al: Diagnosis and management of osteopetrosis: Consensus guidelines from the osteopetrosis working group. J Clin Endocrinol Metab 102:3111, 2017. Section 5 Disorders of Intermediary Metabolism Joan C. Marini, Fransiska Malfait

Heritable Disorders of Connective Tissue CLASSIFICATION OF CONNECTIVE

TISSUE DISORDERS Some of the most common conditions that are transmitted genetically in families are disorders that produce clinically obvious changes in the bone, cartilage, skin, or relatively acellular tissues such as tendons

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