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Review

Unraveling melorheostosis: insights into clinical features, diagnosis, and treatment

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Abstract

Melorheostosis is a rare bone disease characterized by abundant bone formation with a characteristic radiographic appearance that resembles "dripping candle wax." Recent data have shown that the majority of cases are due to somatic activating mutations in bone. Melorheostosis has several clinical and radiographic presentations, which are now known to be caused by different somatic mutations such as *MAP2K1*, *SMAD3*, *KRAS*, and *LEMD3*. This review provides a comprehensive look at the clinical features, diagnostic approaches, and current treatment options for melorheostosis, alongside future research directions aimed at improving patient outcomes.

Keywords: rare bone disease, osteoblasts, *MAP2k1*, *SMAD3*, genetics

Lay Summary

Melorheostosis is a rare bone disease where excess bone growth creates a unique "dripping candle wax" pattern on X-rays. Recent research has found that most cases are caused by genetic mutations that occur in the bones. This review covers the key types of melorheostosis, the clinical findings, and discusses future research efforts to improve care for patients.

Introduction

The foundational principle of human physiology is strict homeostasis. Consequently, despite our extensive knowledge of physiological pathways and pharmacology, our ability to modulate human diseases remains limited.

However, focused study of certain diseases where nature has already delivered the desired outcomes can lead to significant therapeutic advancements. For example, research into the *PCSK9* gene, in which some patients exhibit abnormally low LDL cholesterol levels, paved the way for the development of the cholesterol drug evolocumab.[1] In the bone field, sclerosteosis is a noteworthy example. A mutation in the SOST gene leads to increased bone density. Remarkably, a mere decade after identifying this mutation, the FDA approved the drug romosozumab[2] for the treatment of osteoporosis.

Melorheostosis (OMIM #155950) is another disease where otherwise healthy individuals develop marked bone formation. Despite its discovery in 1922 by Léri and Joanny, the condition remains poorly understood and largely enigmatic.[3] This review will provide an overview of the disease and discuss recent insights into its pathogenesis.

Clinical description

Melorheostosis is a radiographic diagnosis. While the presentation varies, the diagnosis is made when areas of hyperostotic bone are identified, usually 1 arm or leg. The condition may range from small areas of dense bone to extreme presentations with excessive bone formation throughout the limb and heterotopic ossification. The pathognomonic finding is "dripping candle-wax" in which it appears that hot wax has been applied to the side of the bone (Figure 1). Melorheostosis can be clearly diagnosed when (1) there is excessive bone formation in 2 or more adjacent bones and (2) the lesions exhibit elevated uptake (hot) on bone scan.

The disease usually presents in late adolescence or early-adulthood with swelling, pain, deformity, or limb length discrepancy. A common presentation is minor trauma that leads to a radiograph being obtained and melorheostosis then identified. In more severe cases, patients may develop deformity, ankylosis, and severe pain from the bony overgrowth. There is wide variation between patients in melorheostosis phenotype, from just a few bones affected to an entire limb (Figure 2). This disease is generally sporadic (non-inherited) and the prevalence is estimated to be 1/1 000 000.[4] The primary complaint in melorheostosis is pain of a deep constant throbbing nature. Patients with melorheostosis have quality of life scores one standard deviation below population norms.[5] Currently, there is no known treatment for melorheostosis.

Genetic types

In a remarkably prescient study, Freyschmidt[6] identified radiographic subtypes of melorheostosis, which we now recognize as distinct diseases with different genetic origins. The types are classical, endosteal, and melorheostosis

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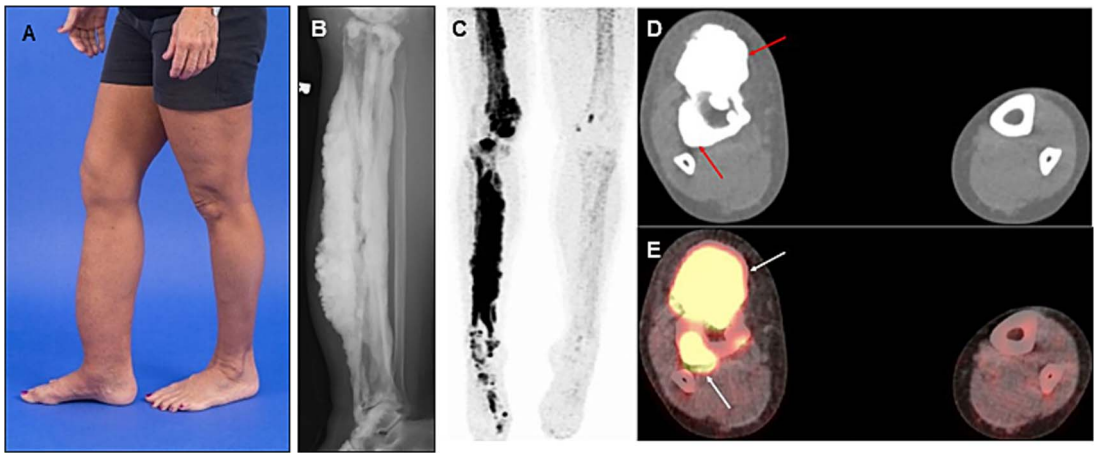

Figure 1. Clinical and radiographic appearance of classical melorheostosis. (A) Clinical photograph showing limb enlargement. (B) Lateral radiograph of the tibia shows flowing hyperostosis. (C) and (D) Increased uptake is seen in 18F-sodium fluoride PET scan. From Kang et al.,[7] used by permission.

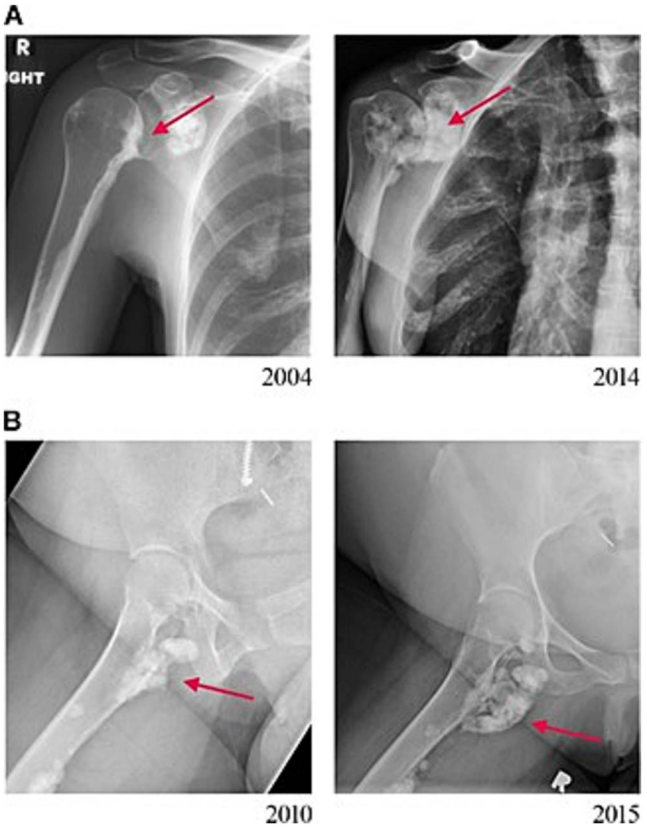

Figure 2. Slow progression of melorheostosis. (A) Anterior-posterior radiograph of the shoulder shows increase in melorheostosis after 10 yr. (B) Lateral radiograph of hip shows increased in size and density of exostosis. From Jha et al.,[23] used by permission.

with osteopoikoikolosis. Since these conditions are now understood as essentially separate diseases, it is most effective to interpret the clinical and scientific findings within the context of each specific subtype.

Classical melorheostosis (*MAP2K1*)

The key characteristics of classical melorheostosis are (1) flowing periosteal hyperostosis and (2) extraosseous mineralization. The excessive bone formation tends to affect multiple bones in the extremity, goes across joints, and can result in bone formation in adjacent ligaments and soft tissue. The majority (87%) of patients with classical melorheostosis have a somatic mosaic mutation in *MAP2K1*, which encodes the protein *MEK1*.[7]

Bone lesions tend to be expansive with irregular cortices. Lesions in the soft tissues or heterotopic areas of ossification are common and are best evaluated with CT. The bone is extremely tough. Surgical reports often note that the bone is difficult to cut and tends to damage drill bits and surgical instruments.

Patients with classical melorheostosis often exhibit skin manifestations. The skin may appear thickened, resembling scleroderma, with macular erythematous regions. These skin lesions tend to be patchy, irregular, and commonly occur over areas with underlying bone abnormalities.[5,8]

While Fryns[9] was the first to propose that melorheostosis was due to somatic mutation in 1995, this was not proven until 2018 by Kang et al.[7] After informed consent, 15 patients with melorheostosis underwent paired surgical biopsies of affected and unaffected bone. DNA was extracted from bone and sent for whole exome sequencing. Genetic analysis revealed somatic activating mutations in the negative regulatory domain of *MAP2K1*. Interestingly, while phenotypic manifestations of melorheostosis are so varied, the mutations mapped to same region just 1 residue apart (K57N, K57E, and Q56P). The mutation was present in just 6%-60% of the bone cells. De Ridder et al.[10] have independently confirmed somatic *MAP2K1* mutations in melorheostosis.

Histological analysis of affected bone revealed dense cortical bone with abundant haversian canals (Figure 3).[11] In classical melorheostosis, abundant osteoid (unmineralized bone matrix) is present. Fratzl-Zelman et al.[12] showed that the bone is actually less mineralized and more porous due to frequent haversian channels. The periosteal surface is flat compact lamellar bone. The deeper regions are more woven and irregular.

The erythematous skin overlying affected bone is often *MAP2K1* mutation positive. Affected melorheostosis skin contained abundant dermal arterioles with thickened tunica media. The cells in the area of the blood vessels are enriched for the *MAP2K1* mutation.[8]

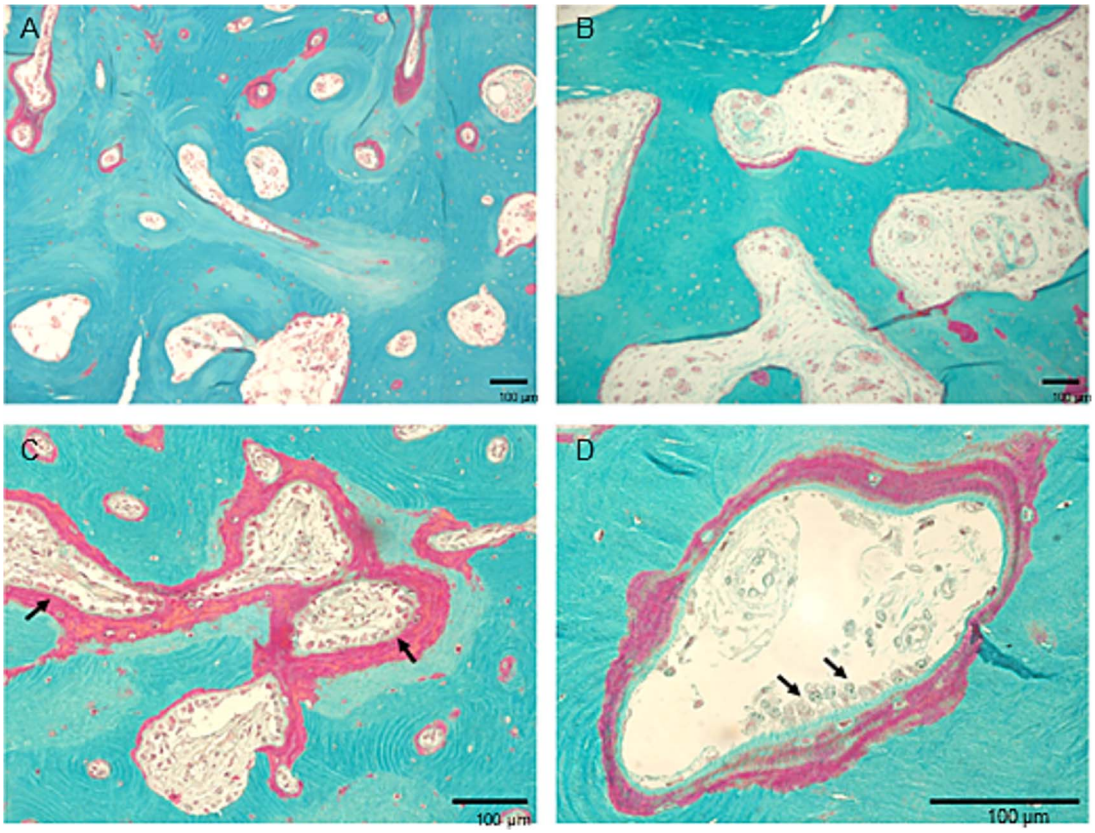

Figure 3. Histology of melorheostosis. (A) Woven bone and abundant osteoid seen in affected bone of melorheostosis. (B) Haversian canals have multiple arterioles. (C) Higher magnification view shows abundance unmineralized bone matrix. (D) Large number of osteoblasts (arrows) seen on endosteal surface. From Fick et al.,[11] used by permission.

Cellular studies offer some insights into the pathophysiology of melorheostosis. The ERK pathway is hyperactive in mutation positive cells, which can be blocked by the MEK inhibitor trametinib. Affected osteoblasts tend to proliferate more, produce more collagen I, and have high RANKL/OPG ratios.[7]

MAP2K1+ fibroblasts from patients also proliferate more and secrete large amounts of VEGF. The VEGF secretion decreases in the presence of trametinib. Conditioned media from affected fibroblasts can cause normal endothelial cells to form more tubules in a co-culture model, confirming a pro-angiogenic phenotype from the mutation.[13]

When affected fibroblasts were reprogrammed to induced pluripotent stem cells (iPSCs), the increased VEGF secretion continued. Mutation-bearing iPSCs showed significantly elevated VEGF secretion, proliferation, and collagen I secretion. When differentiated into osteoblasts, the cells showed increased mineralization and increased VEGF secretion. Administration of VEGF to unaffected iMSCs during osteogenic differentiation was sufficient to increase mineralization. Blockade of VEGF by bevacizumab reduced mineralization in iPSC-derived affected osteoblasts and in affected primary patient-derived osteoblasts. These data indicate that the increased bone formation is driven, in part, by abundant VEGF secretion.[14]

In summary, the basic science findings explain many (but not all) of the clinical manifestations of classic melorheostosis.

- The wide variation between patients and peculiar anatomic distribution is likely due to the somatic mutations occurring randomly during embryogenesis and then seeding the growing limb bud.[15] Patients with milder melorheostosis likely experienced a mutation later during embryogenesis, while earlier mutations lead to more limb involvement.
- Melorheostosis bone is extremely hard. This is not due to excess mineralization, but due to its structure. The outer surface of melorheostotic bone is thick, compact lamellar bone running in alternate directions like plywood. The lower levels are also thickened, contain woven bone, and have abundant osteoid and osteoblasts.[12]
- The marked increased bone turnover seen in histomorphometry and bone scan is likely due to an elevated RANKL/OPG ratio produced by mutation positive osteoblasts that recruit osteoclasts to the site.[7]
- The macular erythematous skin lesions are due to increased size and density of dermal blood vessels.[8]
- The exact reason why the *MAP2K1* mutations in osteoblasts lead to such excessive bone formation remains unknown. But several findings point to angiogenesis as a part of the mechanism: The haversian canals have increased arterioles, as does the skin. The mutation frequency is enriched around the blood vessels. Affected fibroblasts and iPSC-derived osteoblasts secrete VEGF, which is known to drive osteoblastogenesis.[14]

Endosteal melorheostosis (*SMAD3*)

Endosteal melorheostosis is a distinct radiographic, clinical, and genetic entity from classical melorheostosis. Radiographs and CT scans show flowing hyperostosis confined to the inner

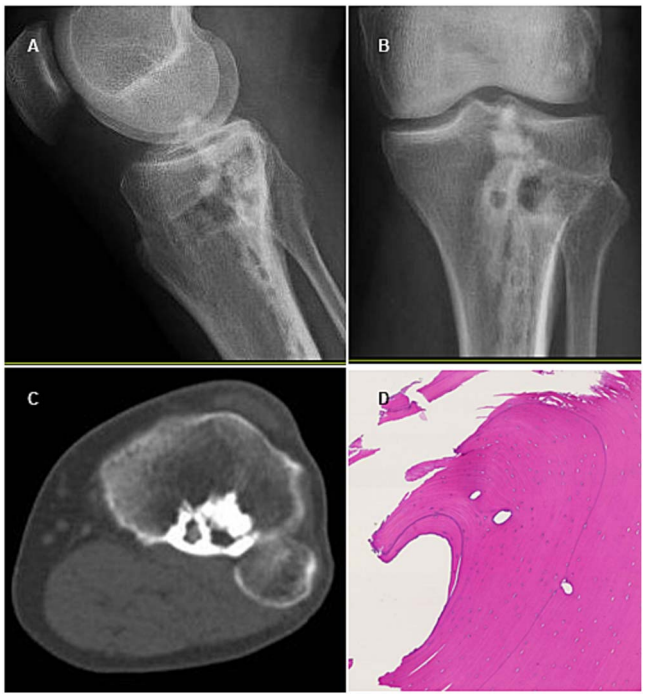

Figure 4. Example of endosteal melorheostosis. (A) Anterior-posterior and (B) lateral radiograph of the tibia show bone formation on the endosteal surface. (C) CT scan further reveals the disorganized pattern. (D) Histological appearance is notable for thick cortical bone with no osteoid.

surface of the bone (Figure 4). The lesions exhibit increased uptake on bone scan. This extra bone is unevenly shaped, asymmetric, and can affect multiple adjacent bones. Endosteal melorheostosis is sometimes called "osteoma-like," but osteomas do not affect multiple bones.

Four patients with *SMAD3* lesions were identified by whole-exome sequencing and amplicon sequencing to have mutations at the same locus (S264Y or S264F) in bone and, to a lesser extent, overlying skin. The *SMAD3* mutations were found to enhance TGF-β pathway signaling in osteoblasts, promoting osteoblast differentiation and mineralization. In vitro investigations revealed a constitutive increase in TGF-β signaling due to the *SMAD3* mutations, inhibiting cell proliferation while promoting osteogenic differentiation and extracellular matrix mineralization. In the presence of BMP2, mineralization was reduced.[16]

Endosteal melorheostosis is somewhat less common than classical melorheostosis. Only 26% (4/15) of people in the first study of endosteal melorheostosis had a biopsy that showed the disease. The histology of endosteal bone showed dense cortical bone with long parallel lamellae bone but did not exhibit the osteoid or increased haversian canals. BMD analysis revealed higher mineral content.[16]

In summary, endosteal melorheostosis has a distinct radiographic appearance, no skin findings, absence of osteoid on histology, and increased mineralization in vitro due to activation of the TGF-β pathway.

Melorheostosis with osteopoikolosis (*LEMD3* and *KRAS*)

Osteopoikolosis (OMIM #166700) a benign condition resulted in "spotted bones" or islands of radiodensity within an otherwise normal skeleton. Osteopoikolosis is

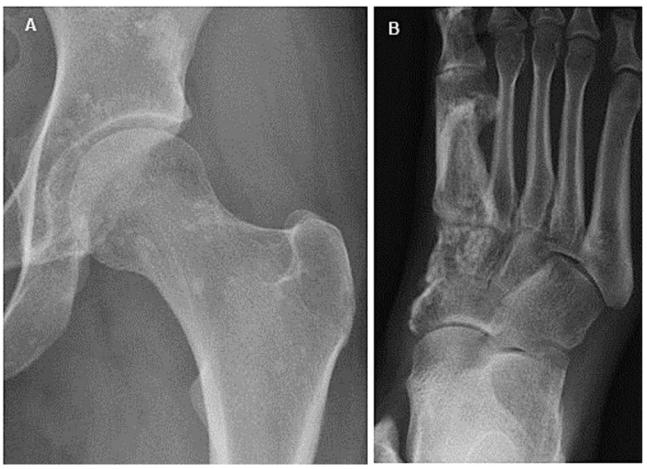

Figure 5. Radiographs of the (A) hip and (B) foot in a patient with osteopoikolosis and melorheostosis. *LEMD3* germline mutation was confirmed on genetic testing.

an autosomal dominant condition caused by heterozygous loss-of-function germline mutations in the *LEMD3* gene.[17] Buschke-Ollendorff syndrome consists of osteopoikolosis plus skin findings such as disseminated dermatofibrosis.[17] Osteopoikolosis is cold on bone scan. Some patients with osteopoikolosis will present with melorheostosis (Figure 5).

Hellemans et al.[18] examined 3 kindreds of patients with osteopoikolosis, some of which had Buschke-Ollendorff or melorheostosis. Heterozygous germline *LEMD3* mutations were identified but additional somatic mutations in *LEMD3* that might explain Buschke-Ollendorff or osteopoikolosis with melorheostosis were not identified. Further study of patients with sporadic melorheostosis without osteopoikolosis failed to identify germline or somatic mutations in *LEMD3*.[17] Thus *LEMD3* germline mutations are associated with familial melorheostosis, but not the more common sporadic melorheostosis. *LEMD3* encodes the nuclear membrane protein MAN1, which antagonizes TGF beta signaling through SMAD2/3.

Whyte et al.[19] studied a child with significant femur melorheostosis, osteopoikolosis, and a large epidermal nevus. A germline loss of function mutation in *LEMD3* was identified as well as a somatic mutation in *KRAS* in the skin of the nevus and the skin overlying the melorheostosis lesions. This represented the first firm evidence that somatic mutations play a role in melorheostosis. Kang et al.[7] also noted 1 coexisting somatic *KRAS* mutation in a patient with *MAP2K1*+ melorheostosis. Whyte et al.'s data connect melorheostosis with the family of disorders known as RASopathies, where mutations in the RAS/MAPK pathway result in skin, muscle, bone, and developmental abnormalities, and can be treated with MEK inhibitors.[20]

Clinical evaluation and management

Regardless of the subtype of melorheostosis, the clinical management remains the same. Unfortunately, treatment options are limited.

Recommended evaluation

After a routine history and physical exam, plain radiographs are usually sufficient to diagnose melorheostosis. CT scan is

helpful to define the lesion and identify extraosseous lesions. MRI is less helpful but can show soft tissue abnormalities.[21] Bone scan is the best modality to confirm the diagnosis. A traditional technetium whole body bone scan will suffice, but the 18F-sodium fluoride PET scan provides more detail and can identify small lesions.[22] Melorheostosis will show increased uptake on the bone scan, and other areas of melorheostosis may be identified.

While laboratory evaluations can be performed, they are rarely helpful. Jha et al.[23] found no elevation in bone turnover markers in classical or endosteal melorheostosis. Similarly, serum chemistries were largely normal.

It is reasonable to look for areas of nerve entrapment caused by melorheostosis. Physical exam and ultrasound may be helpful. There are case reports of carpal tunnel release and peroneal nerve decompression being used to ameliorate symptoms in specific cases.[3]

A dermatology consultation with full skin exam may be helpful to identify macular erythematous or scleroderma-like skin lesions. Evidence of nevi or dermatofibrosis may lead to the diagnosis of Buschke-Ollendorff syndrome.

Treatment

While there is no known treatment for melorheostosis, some helpful strategies exist. First, it is important that patients do not ignore their general health. A common problem in the management of rare diseases is that all symptoms are ascribed to the rare disease and few practitioners are willing to treat rare conditions. We have observed patients with melorheostosis presenting with uncontrolled hypertension, hyperglycemic diabetes, and marked vitamin D depletion.

Counseling is of value. Patients with endosteal melorheostosis can be reassured that they can expect a lower burden of disease and higher function, though pain remains a problem. Patients find it helpful to understand that the condition is a somatic mutation, and thus will not be passed to progeny and is not inherited. While the condition is generally progressive, the process is slow and takes decades to worsen (Figure 2). Most patients with melorheostosis live full lives, are employed, and have healthy children. Quality of life scores are lower than aged-matched controls but primarily due to pain.[5,24]

Treatment is largely symptomatic. Nonsteroidal anti-inflammatory drugs are helpful and should be the first line of treatment. Physical therapy is beneficial for patients with melorheostosis by promoting muscle strength, functional activities, and endurance.[25]

Bisphosphonates have been used to treat melorheostosis, but their current role is unclear. In both endosteal and classic melorheostosis, the source of the disease is a mutation in the osteoblasts. Bisphosphonates reduce osteoclast activity, thereby allowing bone growth by tipping the balance in favor of osteoblasts. But there are case reports documenting symptomatic improvement after administration of zoledronate or pamidronate.[26] Another strong inhibitor of osteoclasts, denosumab has been used as well.[27]

In rare cases, surgery to decompress melorheostostic lesions can be helpful. In the Mayo case series of 23 patients, 11 underwent surgery for removal of hyperostotic bone or decompression of impacted nerves.[24] Surgery appears to be most beneficial for contractures or treatment of ankylosed joints.

Future directions

Two major questions remain. (1) Why do mutations in *SMAD3* or *MAP2K1* lead to such dramatic bone overgrowth? And (2) Is there any option for treatment that can alleviate the pain and progression of melorheostosis?

With melorheostosis mutations affecting 10% or less of the cells in lesion, it seems likely that the cells are influencing the normal cells around them to create more bone. A key step to truly understand the pathogenesis of melorheostosis will be creation of an animal model that recapitulates the somatic mosaic condition of melorheostosis. Germline mutations in *MAP2K1* are lethal. Germline mutations in *SMAD3* produce a different disease, Loeys–Dietz syndrome, without hyperostosis. The mutation must be activated either prenatally or postnatally and primarily in the bone. Then, the role of VEGF blockers, bisphosphonates, or other inhibitors of mineralization can be carefully dissected.

Melorheostosis, with its distinct genetic mutations and lack of effective treatments, presents a promising opportunity for pharmaceutical companies to develop targeted therapies. Because melorheostosis affects multiple sites, the treatment would have to be oral or intravenous that can treat the affected bone while sparing the normal skeleton. The treatment will have to be well tolerated, given the high functional status of the majority of patients. The treatment need not lead to full regression but simply reduce the elevated osteoblastic activity. NaF bone scan may play a role as a disease marker to provide an objective measure of early reduction in bone activity.

Leveraging insights for other skeletal diseases

Melorheostosis exemplifies the significant and positive impact of autonomous patient organizations. The Melorheostosis Association (melorheostosis.org) stands as a prime platform facilitating connections among patients, caregivers, and fostering research advancements. Establishing an online community coupled with regular interactions is a pivotal stride for patients afflicted with similar rare diseases, propelling progress.

We highlight the incredible value provided by the willingness of patients to join a research study and undergo a paired tissue biopsy. This approach may serve as a research blueprint for tackling other diseases of unknown etiology. The patients' selfless participation led promptly to the identification of pathogenic gene mutations. With the elucidation of *MAP2K1*, *SMAD3*, and *KRAS* as causative mutations in melorheostosis, the enticing potential of pinpointing a treatment or leveraging the pathway to address other disorders now lies within tangible reach.

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Author contributions

Timothy Bhattacharyya (Conceptualization, Funding acquisition, Investigation, Writing—original draft).

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Conflicts of interest

None declared.

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