DIAGNOSIS OF ENDOCRINE DISEASE

Mosaic disorders of FGF23 excess: Fibrous dysplasia/McCune–Albright syndrome and cutaneous skeletal hypophosphatemia syndrome

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Abstract

Fibrous dysplasia/McCune–Albright Syndrome (FD/MAS), arising from gain-of-function mutations in $G\alpha_s$, and cutaneous skeletal hypophosphatemia syndrome (CSHS), arising from gain-of-function mutations in the Ras/MAPK pathway, are strikingly complex, mosaic diseases with overlapping phenotypes. Both disorders are defined by mosaic skin and bone involvement, and both are complicated by increased FGF23 production. These similarities have frequently led to mis-diagnoses, primarily in patients with CSHS who are often assumed to have FD/MAS. The intriguing similarities in skeletal involvement in these genetically distinct disorders have led to novel insights into FGF23 physiology, making an understanding of FD/MAS and CSHS relevant to both clinicians and researchers interested in bone and endocrine disorders. This review will give an overview of FD/MAS and CSHS, focusing on the roles of mosaicism and FGF23 in the pathogenesis and clinical presentation of these disorders.

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Introduction

Mosaicism is defined as the presence of two or more cell populations with distinct genotypes within an organism, typically arising from post-zygotic mutational events.

Mosaicism is increasingly recognized as an important contributor to human health and disease, in part, due to genomic technologies that have enabled detection and characterization of an ever-growing number of disorders.

Invited Author's profile

Alison Boyce, MD, is a pediatric endocrinologist in the Skeletal Disorders and Mineral Homeostasis Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland, USA. Dr Boyce's work focuses on bone and mineral metabolism, using rare and pediatric skeletal disorders as models through which human physiology can be understood. She leads investigations in fibrous dysplasia/McCune–Albright syndrome, a rare disease affecting the skeletal and endocrine systems, and has characterized many aspects of this disorder and its treatment. Additional studies focus on fibroblast growth factor-23 and mosaic skeletal disorders.

Because mosaic diseases often involve genetic changes that would be lethal in their germline states, they provide unique opportunities to investigate physiologic processes and gain biological insights. However, these disorders also present unique challenges to diagnosis and management. The variable involvement of multiple tissue types can lead to dramatic phenotypic variations. Diagnoses in mosaic disorders are most often made clinically; however, because they are rare and non-inheritable, clinicians have limited opportunities to gain direct clinical experience.

The purpose of this review is to provide an overview of two mosaic disorders that have striking phenotypic overlap. Fibrous dysplasia/McCune–Albright syndrome (FD/MAS) and the more recently described cutaneous skeletal hypophosphatemia syndrome (CSHS) are both defined by mosaic skin and bone involvement, complicated by increased FGF23 production. These similarities have frequently led to mis-diagnoses, primarily in patients with CSHS who are often assumed to have FD/MAS. The intriguing similarities in skeletal involvement in these genetically distinct disorders have led to novel insights into FGF23 physiology, making an understanding of FD/MAS and CSHS relevant to both clinicians and researchers interested in bone and endocrine disorders.

Genetic etiology

FD/MAS and CSHS arise from *de novo* mutations in non-germline cells during embryogenesis. The etiologies of somatic mutations are complex and may be related to errors in DNA replication, environmental insults, and other factors (1). The developmental timing and location of these mutational events determine the location and extension of affected tissues. When the mutation occurs at earlier stages of development, extensive affected postnatal tissue can be expected; when it occurs later in embryogenesis or during fetal development, fewer and smaller areas are affected. If the mutation occurs prior to gastrulation, more than one germ layer can be affected, leading to the involvement of tissues and organs of different embryonic origins.

FD/MAS results from gain-of-function mutations in *GNAS*, which encodes the α -subunit of the G_s G protein-coupled receptor (GPCR). In most cases, mutations affect codon R201, replacing an arginine residue with histidine or cysteine (2). Mutations in *GNAS* codon G227 have also been reported, representing less than 5% of cases (3). *GNAS* mutations inactivate the regulatory GTPase motif of $G\alpha_s$ and its isoforms, leading to constitutive

receptor signaling and dysregulated production of cyclic AMP (cAMP), protein kinase A (PKA) activation, and downstream signaling.

CSHS arises from gain-of-function mutations in a *RAS* gene. Only *NRAS* Q61R and *HRAS* G13R mutations have been associated with CSHS to date (4, 5), however *NRAS* G12, G13, P34; *HRAS* G12, Q61; and *KRAS* G12 mutations have been found in other cutaneous mosaic RASopathies (6, 7), and future studies may associate these mutations with CSHS. Like *GNAS* mutations in FD/MAS, *RAS* mutations in CSHS lie within a regulatory GTP-binding region, locking the protein into a permanently active state. This results in activation of the protein kinase activity of RAF kinase, leading to phosphorylation of MEK and constitutive activation of the MAPK signaling pathway.

The diverse clinical manifestations of FD/MAS and CSHS underscore the ubiquitous nature of GPCR/ $G\alpha_s$ /PKA and tyrosine kinase/Ras/MAPK pathways. The study and characterization of these diseases therefore has the potential to expand our understanding of the roles of these pathways in human physiology.

Prevalence

FD/MAS and CSHS are both rare, non-hereditary conditions and there are no high-quality epidemiologic data to accurately determine prevalence. FD has been estimated to account for approximately 7% of benign bone tumors; however, MAS (involving extraskeletal features) is much rarer, with an estimated prevalence of 1:1 000 000 to 1:100 000 (8). CSHS has only recently been characterized, and one metanalysis identified 56 cases with a phenotype consistent with CSHS in the published literature (4). It is therefore likely that CSHS is comparatively much rarer than FD/MAS.

Taxonomy

Historically, most mosaic conditions have been grouped phenotypically into clinically defined syndromes. Only recently have improvements in genetic testing techniques enabled the association of many of these syndromes with specific somatic mutations. This new body of evidence has enabled a more systematic approach to classifying mosaic diseases. However, disease taxonomy should not rely solely on genotype, because multiple additional factors, such as the pattern and time of expression and

gene-environment interactions, strongly influence the phenotypes, comorbidities, and medical needs of individuals with somatic mutations. An illustrative example is an otherwise healthy patient with an acquired *GNAS*- or *RAS*-related neoplasm. This is essentially a form of mosaicism; however, this patient would bear little in common clinically with patients affected by FD/MAS or CSHS. Therefore, genotype, phenotype, and environment must all be taken into account when defining disease entities (9).

FD/MAS: Polyostotic FD as a skeletal disorder was initially described in 1938 by pathologist Louis Lichtenstein, who aptly speculated that FD results from ‘perverted activity of the specific bone-forming mesenchyme’ (10). The association of FD with precocious puberty and skin hyperpigmentation was separately reported in 1936 by Donovan McCune and Fuller Albright, leading to the conception of MAS as a syndromic ‘triad’ of these features (11). It was later recognized that other hyperfunctioning endocrinopathies and extraskeletal features (with or without FD) may occur in varying combination in patients with *GNAS* mutations, leading to decades of taxonomic confusion regarding the diagnostic criteria for FD/MAS. Recently, an international consortium of clinicians, researchers, and advocates have attempted to clarify FD/MAS taxonomy through published consensus guidelines (12). According to this proposed system, the term ‘FD’ in isolation refers exclusively to skeletal disease. Extraskeletal features associated with MAS are (1.) café-au-lait macules with characteristic features, (2.) gonadotropin-independent sex steroid production, (3.) characteristic thyroid lesions with or without non-autoimmune hyperthyroidism, (4.) GH excess, and (5.) neonatal hypercortisolism. MAS is defined as the combination of FD and one or more extraskeletal features or the presence of two or more extraskeletal features. For inclusivity, the disease entity is commonly referred to as ‘FD/MAS’ in order to encompass individuals with and without extraskeletal disease.

CSHS was defined in 2014 as a multisystemic disorder involving focal bone lesions, pigmented skin lesions, and elevated circulating levels of FGF23, arising from gain-of-function mutations in the Ras/MAPK pathway (4, 13). Historically, epidermal and congenital melanocytic nevi have been rarely reported in association with extracutaneous findings, including skeletal malformations, precocious puberty, neurologic abnormalities, and hypophosphatemia (14, 15). Depending on the pattern of involvement, a wide range of taxonomic terms have been applied, including epidermal nevus syndrome,

Becker’s nevus syndrome, Schimmelpenning–Feuerstein–Mims syndrome, and others (16, 17, 18). The genetic etiologies of many of these syndromes are unknown; however, mutations in *RAS* gene family members have been identified in isolated and syndromic keratinocytic, sebaceous, and melanocytic nevi, typically in patients with widespread involvement of skin and other organ systems (15, 19, 20). A cohort study identified *RAS* mutations in five patients with phenotypes involving focal bone lesions, pigmented skin lesions, and FGF23-mediated hypophosphatemia, establishing a shared genetic etiology for this constellation of features (21). Therefore, the divergence of this phenotype and its associated clinical complications, as well as the identification of Ras activation as the common causative etiology, prompted the definition of CSHS as a distinct entity.

FD/MAS and CSHS thus illustrate two approaches to disease taxonomy. FD/MAS aims to more broadly group the various phenotypic features resulting from $G\alpha_s$ activation into a single taxonomic entity. In contrast, CSHS groups rare clinical variants of several previously defined dermatologic syndromes of Ras/MAPK pathway activation into a unique taxonomic entity, based on common phenotypic features that dictate clinical presentation and management.

Pathogenesis and histopathology

FD is characterized by replacement of the hematopoietic and adipose bone marrow with fibrous stroma. This tissue is a mixture of mutant and WT bone marrow stromal cells (BMSCs) that acquire an abnormal fibroblastic phenotype under the influence of $G\alpha_s$ activation. Proliferation of these abnormal BMSCs leads to the formation and expansion of FD lesions.

The fibrous stroma in FD is low to moderately cellular, highly proliferative and variably dense, and collagenized (Fig. 1). FD BMSCs may give rise to abnormal osteoblasts, which produce woven bone matrix forming unconnected, curvilinear trabeculae. Trabeculae are sometimes absent in FD and vary in quantity and pattern among and within lesions. FD bone is poorly mineralized and often hypercellular, which may present with expanded osteocytic lacunae. FD osteoblasts are characterized by a flat-stellate rather than a cuboidal morphology. This morphological change arises due to cAMP dysregulation, which leads to cytoskeleton reorganization and retraction of the cell body (22). FD osteoblasts deposit collagen fibers perpendicularly to the bone matrix, forming structures

Figure 1

Histopathologic images. Within each section, left and right panels are bright field (Goldner trichrome staining) and polarized light microscopy, respectively, shown at low and high power. FD tissue is overly fibrotic with woven undermineralized bone deposition. Note the absence of adipocytes and hematopoietic marrow. CSHS skeletal lesions demonstrate normal marrow cellularity and lamellar bone matrix, with focal patches of fibrous stroma and woven bone. Severe osteomalacia with prominent visible osteoid is apparent in both tissue types. Of note, the patient with FD had chronic longstanding hypophosphatemia and was on treatment at the time the specimen was obtained. The patient with CSHS did not have clinically significant hypophosphatemia. Ad, adipocyte; FS, fibrous stroma; Hp, hematopoiesis; LB, lamellar bone; Od, osteoid; Oc, osteoclasts; Os, osteoblasts; ShF, Sharpey fibers; V, vascularization; WB, woven bone.

termed Sharpey fibers. Osteoclastogenesis is highly prevalent, featuring osteoclasts located either on the bone surface or at ectopic locations. As lesions age, red and yellow marrow can reappear in FD marrow spaces, and lesions trend to form fluid-filled cysts (23).

CSHS: Due to the limited number of cases, the histopathological features of CSHS are poorly defined and still subject to further characterization. In this section, we collect observations from three published references (4, 13, 24) and bone samples from two patients seen at the NIH.

In contrast to FD, CSHS bone lesions do not seem to have altered hematopoiesis and adipogenesis (Fig. 1). In fact, many marrow areas appear normal except for focal regions of fibrous stroma. Stromal dysplastic cells do not appear to replace or alter bone marrow cells. Like FD, skeletal CSHS lesions demonstrate marked osteomalacia, with up to 80% of the bone surfaces lined with osteoid and deep unmineralized regions. However, most of the bone matrix has a lamellar structure, with focal areas in which the parallel structure is interrupted by small patches of woven bone. These areas are irregularly mineralized, hypercellular, and associated with dysplastic stroma. CSHS trabeculae and cortical bone have an altered

architecture, with unconnected trabeculae and porotic cortical bone. Although osteoclasts are prevalent in CSHS skeletal lesions, this appears to occur to a lesser degree than in FD and, unlike FD, is never present in ectopic sites. CSHS skeletal lesions also feature numerous bone formation rims, in which osteoblasts have a normal cuboidal appearance.

Lesional osteomalacia is a prominent feature of FD and CSHS; however, in both disorders it has been observed even in the absence of frank hypophosphatemia (e.g. the CSHS patient in Fig. 1 was normophosphatemic). It is therefore likely that osteoblast dysfunction is a key contributor, potentially due to deposition of abnormal matrix with impaired ability to support calcium phosphate precipitation. Further investigation is needed to determine the etiologies and mechanisms of osteomalacia in these disorders.

GNAS and RAS in FGF23 regulation

The degree and severity of hypophosphatemia is variable in both FD/MAS and CSHS. While elevated FGF23 levels

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Table 1 Representative clinical features.

Features	Fibrous dysplasia/McCune-Albright syndrome	Cutaneous Skeletal Hypophosphatemia Syndrome
Dermatologic	Café-au-lait macules	Café-au-lait macules Hyperpigmented melanocytic nevi Phakomatosis pigmentokeratotic Giant congenital melanocytic nevi Keratinocytic epidermal nevi Nevus sebaceous
Skeletal	Focal dysplastic lesions	Focal dysplastic lesions Hypoplastic cranial bones
Endocrine	FGF23-mediated hypophosphatemia Precocious puberty Hyperthyroidism Growth hormone excess Neonatal hypercortisolism	FGF23-mediated hypophosphatemia Precocious puberty
Neurologic	Neurodevelopmental abnormalities	Neurodevelopmental abnormalities Ventriculomegaly Macro- and micro-cephaly Neurocutaneous melanosis
Malignancies	Thyroid cancer Skeletal sarcomas Pancreatic cysts Breast cancer Others	Thyroid cancer Malignant melanoma Pheochromocytoma Brain tumors Others
Others	Hematologic abnormalities Tachycardia, hypertension	Hematologic abnormalities Ophthalmologic abnormalities

have been well-documented in patients with both disorders (4, 25, 26), the prevalence of clinically significant hypophosphatemia has not been well-established in either disease. However, based on current evidence it appears to be higher in CSHS: one large metanalysis reported 50% of published CSHS cases were hypophosphatemic (4), while a large FD/MAS cohort study has observed a 16% prevalence (personal observation, AMB). The particularities of cAMP vs MAPK signaling pathways in FGF23 transcription, translation, and posttranslational processing likely account, in part, for this variability.

FD/MAS: Murine and *in vitro* studies have shown that upregulation of cAMP signaling in osteogenic cells leads to increased FGF23 transcription (27, 28). Moreover, transfection of mutant $G\alpha_s$ into HEK293 cells leads to increased FGF23 production (26). However, mice and human studies show conflicting data regarding the effects of PTH infusion (which activates $G\alpha_s$) on serum FGF23 levels (29, 30, 31). This may be, in part, due to overlapping regulatory effects of PTH and FGF23 on both phosphate and vitamin D metabolism. Interestingly, cAMP signaling in bone cells not only stimulates FGF23 transcription but also its inactivation through cleavage (26, 27), and this mechanism appears to play an important role in determining the net amount of intact FGF23 secreted in the bloodstream. This has been further evidenced in patients with FD/MAS, who have an increased ratio of C-terminal

(fragmented and inactive) to intact (and biologically active) FGF23 in their serum (26, 27). This suggests that increased FGF23 degradation due to altered processing might partially mitigate the hypophosphatemic effects of FGF23 overproduction in patients with FD/MAS.

CSHS: In contrast to $G\alpha_s$, Ras/MAPK pathway signaling appears to have more 'clean' and direct effects on FGF23 production. Several observations support that fibroblast growth factor receptor 1 (FGFR1) activation leads to FGF23 production through Ras/MAPK signaling. For example, pathogenic gain-of-function *FGFR1* mutations have been detected in patients with osteoglophonic dysplasia – a rare form of achondroplasia associated with FGF23-mediated hypophosphatemia (32). Mouse models have consistently demonstrated that stimulation and inhibition of *Fgfr1* in bone cells lead to increased and decreased biologically active FGF23 in the blood, respectively (33, 34, 35). The identification of a fibronectin and *FGFR1* fusion protein as the molecular driver of ectopic FGF23 production in a subset of phosphaturic mesenchymal tumors further highlights the strong influence of MAPK signaling on FGF23 production (36). These data suggest that the *Fgfr1*/Ras/MAPK pathway is a stronger and more direct regulator of FGF23 production in comparison to GPCR/ $G\alpha_s$ /PKA pathway and may explain the relatively higher prevalence of clinically significant hypophosphatemia in CSHS in comparison to FD/MAS.

Figure 2

Clinical images in fibrous dysplasia/McCune–Albright syndrome. (A) Café-au-lait macules reflect along the spine of an adolescent girl (arrows), demonstrating typical jagged borders and distribution along the midline of the body. Note the obliquity in this patient's hips and shoulders, reflective of underlying scoliosis. (B) Lentigines involving the oral mucosa (arrows) and outer lips (arrowhead) in an adult patient. (C) Radiograph from the patient in panel A shows severe scoliosis involving the thoracic and lumbar spine (arrows). Expansile FD lesions are apparent in the right 11th and 12th ribs (asterisks). The patient has a surgical implant visible in the proximal right femur related to a previous fracture repair. (D) 3D computed tomography scan demonstrates multiple expansile FD lesions involving the calvarium, maxilla, and mandible (arrows). (E) Pelvic ultrasound in a 3-year-old girl with pubertal symptoms and elevated estrogen levels reveals a large ovarian cyst (arrow). (F) ^{18}F -NaF PET/CT scan shows multiple areas of tracer uptake in the skull, ribs, spine, and long bones, consistent with polyostotic FD (arrows). Note the expected physiologic, symmetric uptake in the metaphyses throughout in this growing child.

Clinical description

Mosaicism is inherent in the clinical features of both FD/MAS and CSHS. Skin lesions occur in a distinctive distribution following developmental lines of Blaschko, reflecting patterns of embryonic cell migration. Bone lesions likewise occur in a patchy, irregular distribution and may range from trivial disease, affecting only a few areas, to severe disease, involving most of the skeleton. Endocrine and other extraskeletal features are variably involved, contributing to the broad clinical spectrum that varies greatly between individuals. Specific disease features are included in Table 1 and discussed in further detail.

Dermatologic features

FD/MAS: Café-au-lait macules are a classically described feature of MAS (11), affecting approximately 2/3 patients (37). Hyperpigmentation occurs due to constitutive signaling through the melanocyte stimulating hormone receptor in *GNAS* mutation-bearing melanocytic cells. Typical of mosaic lesions, these macules have jagged borders and are located along the midline of the body (Fig. 2A). There does not appear to be a geographic

relationship between the location of skin lesions and dysplastic bone lesions (38).

Pigmentation involving the lips and oral mucosa has been recently described as an additional cutaneous feature of FD/MAS (39) (Fig. 2B). In contrast to café-au-lait macules, which are present at or shortly after birth, these lesions develop in adulthood and may progress with age. Interestingly, these resemble the oral lentigines that occur in patients with Carney Complex, a disorder arising from *PRKARIA* mutations resulting in activation of the cAMP-dependent PKA, suggesting a degree of clinical and biochemical overlap between these disorders.

CSHS: Dermatologic features of CSHS share some commonalities with MAS but are more striking in their diversity (4, 40) (Fig. 3A, C and E). This likely reflects the involvement of Ras mutation-bearing cells from multiple embryonic lineages (21). Epidermal nevi affect approximately 60% of patients and derive from cells of ectodermal origin. Keratinocytic epidermal nevi commonly occur on the trunk and extremities, appearing as either linear or whorled plaques that may vary from skin-colored to hyperpigmented. Nevus sebaceous, another subset of epidermal nevi typically found on the

Figure 3

Clinical images in cutaneous skeletal hypophosphatemia syndrome (CSHS). (A) Phakomatosis pigmentokeratotica is a subtype of melanocytic nevi characterized by the combination of epidermal nevi and speckled lentiginous nevi (black arrowheads). Nevus sebaceous is a subtype of epidermal nevus presenting as smooth, waxy plaques and may be associated with alopecic patches (white asterisks). Café-au-lait macules are frequently superimposed (black arrows). (B) The patient in Panel A has a hypoplastic, lytic-appearing calvarial lesion adjacent to the area of phakomatosis pigmentokeratotica on her scalp visible on a 3D computed tomography scan (black arrow). (C) A child with severe rickets leading to 'windswept' deformities of the lower extremities. Note the presence of epidermal nevi on the chest and abdomen (black arrows). (D) Radiographs of the lower extremities from the child in Panel C again show 'windswept' deformities and evidence of rachitic metaphyseal changes (white arrows). Note the heterogeneity and cortical irregularity in the dysplastic left femur (black arrow). (E) Photograph of a child's hand shows widening at the wrist consistent with rickets (arrow) and expansile deformities of the third and fourth digits (asterisks). Cutaneous melanocytic nevi are apparent throughout. (F) Hand radiograph from the child in Panel E shows diffuse demineralization due to longstanding severe hypophosphatemia. Areas of dysplastic bone are apparent in the metacarpals and expanded third and fourth digits (asterisks). (G) Magnetic resonance imaging of the brain shows melanin deposition (arrow) consistent with neurocutaneous melanosis.

head and neck, present as smooth, waxy plaques and may be associated with alopecic patches and eczematous reactions. Mutations in neural crest-derived cells give rise to hyperpigmented melanocytic nevi, affecting approximately 40% of patients. Café-au-lait macules have a similar appearance and distribution to those found in MAS. Phakomatosis pigmentokeratotica refers to the association of nevus sebaceous and speckled lentiginous nevi and likewise occurs in a patchy, segmental distribution. Giant congenital melanocytic nevi are a dramatic feature of CSHS that may involve large portions of the body. Hair follicles may be infiltrated and enlarged by mutation-bearing melanocytes, producing a hairy appearance. Patients often present with multiple superimposed cutaneous features, leading to strikingly complex skin findings.

Skeletal features

FD/MAS: The clinical presentation in Fibrous Dysplasia (FD) depends on the location and extent of skeletal involvement. In the craniofacial region, complications arise due to FD lesion expansion, leading to facial asymmetry and rarely functional impairment such as vision and hearing loss (41, 42) (Fig. 2D). In the appendicular skeleton, affected areas tend to fracture and deform under weight-bearing forces, such as the classic 'shepherd's crook' coxa vara deformity of the proximal femur (43) (Fig. 4B). Spinal FD frequently leads to scoliosis (Fig. 2A), which in rare cases may be progressive and potentially lethal (44). Metabolic abnormalities such as MAS endocrinopathies and FGF23-mediated hypophosphatemia can contribute

to skeletal complications; screening and treatment of extraskeletal features is therefore a critical component of management. Bone pain is also a common feature. Its etiology is poorly understood; however, pain appears to increase with age and is not associated with overall skeletal disease burden (45, 46).

FD has distinctive radiographic features apparent on multiple imaging modalities (47). Nuclear medicine scans such as technetium-99 scintigraphy or ^{18}F -NaF PET/CT scans show increased tracer uptake in affected areas with high sensitivity (48, 49) (Fig. 2F). Craniofacial lesions are best evaluated with CT, where they demonstrate a homogeneous 'ground glass' appearance that may develop heterogeneous areas of radiolucency with age (41) (Fig. 4A). Appendicular lesions also show a distinctive 'ground

glass' character on X-rays, along with cortical thinning that may produce an appearance of endosteal scalloping (Fig. 4B, C and D, right panels).

The mainstay of management in FD is surgical. Orthopedic procedures are focused on repairing fractures and correcting and preventing deformities. Techniques commonly used in other skeletal disorders, such as bone grafting, are frequently ineffective in FD and many surgeons prefer the use of intramedullary rods (50, 51). Outcomes from craniofacial procedures are often suboptimal, due to post-operative FD regrowth in approximately 50–85% of patients (52), and should generally be limited to correction of functional deficits and severe deformities. Somewhat surprisingly, scoliosis appears to respond well to traditional spinal fusion techniques (44).

Figure 4

Radiographic skeletal features in fibrous dysplasia/McCune-Albright syndrome (FD/MAS) and cutaneous skeletal hypophosphatemia syndrome (CSHS). (A) Computed tomography images of the skull. The left panel depicts an expansile lesion in the infra-orbital region with 'ground glass' homogeneity, typical of FD (arrow). The right panel shows a hypoplastic, lytic-appearing lesion in the same region in a patient with CSHS (arrow). (B) Radiographs of the proximal femora. The left panel shows diffuse involvement with a homogeneous 'ground glass' FD lesion (white arrows). Note the characteristically thin cortices. There is an expansile deformity of the proximal medial portion of the femur (black arrowhead). There is a mild coxa vara deformity of the femoral shaft. The right panel shows a femur from a patient with CSHS demonstrating a similar degree of involvement (white arrows). In comparison to the FD lesion in the left panel, this radiograph shows a more heterogeneous, 'streaky' appearance with mixed sclerotic and lytic elements. The lesion appears to involve the cortices but, in contrast to FD, their thickness is relatively preserved. (C) Radiograph of the humeri. The left panel shows diffuse involvement with FD, again demonstrating homogeneous radiolucency and cortical thinning (arrows). The right panel shows a lesion in a patient with CSHS, demonstrating a heterogeneous 'streaky' appearance involving the cortices (arrows). (D) Hand radiographs. The left panel shows expansile, homogeneous FD lesions affecting multiple metacarpals and proximal phalanges (asterisks). A patient with CSHS (right panel) demonstrates heterogeneous areas of involvement (asterisks). Note the diffuse demineralization and metaphyseal irregularity consistent with longstanding hypophosphatemia (white arrow).

Antiresorptive therapies have been advocated as a potential treatment strategy due to the high levels of osteoclastogenesis in FD tissue. Retrospective studies have failed to detect any effect of bisphosphonates on FD histopathology (53), lesion size, or rate of new lesion formation (54), but have suggested potential pain relief with i.v. bisphosphonates (45, 55). A randomized, placebo-controlled trial of the oral bisphosphonate alendronate detected increased FD lesion density in children (but not adults) with FD and did not improve pain, fracture, or other clinically relevant outcome measures (56). Concerningly, osteonecrosis of the jaw was reported in 5% of bisphosphonate-treated patients in one large retrospective series, suggesting that FD may potentially carry an increased risk for this complication (57). The current evidence therefore supports that bisphosphonate use in FD should be limited to treatment of bone pain, using the lowest effective dose and interval.

Recent evidence suggests that inhibition of receptor activator of nuclear kappa-B ligand (RANKL), a protein that promotes osteoclast differentiation, may be a potentially effective treatment. FD BMSCs express high levels of RANKL, and RANKL levels are increased in FD patient serum (58). In a mouse model of FD, treatment with an anti-RANKL antibody led to increased bone density and decreased marrow fibrosis (59, 60, 61, 62). In patients with FD/MAS, treatment with the monoclonal anti-RANKL antibody denosumab has been associated with decreased pain and lesion expansion; however, denosumab discontinuation has led to rebound increased bone turnover and life-threatening hypercalcemia (59, 63). At present, denosumab treatment in patients with FD should be limited to clinical trials and on a compassionate basis with extreme caution for patients with severe morbidity.

CSHS: In comparison to FD, the skeletal dysplasia associated with CSHS has been described in considerably less detail. All skeletal compartments have been reported to be affected, supporting a wide range of potential involvement. Like in FD, patients frequently present with fractures and deformities of weight-bearing bones (Fig. 3C and E). Hemibody asymmetry is reported in up to 20% of patients with CSHS (4), which may be due to skeletal deformities and/or growth plate abnormalities in limbs affected by dysplastic bone (40) (Fig. 2E and F). Scoliosis appears to be a common feature, reported in up to 40% of patients (4). In contrast to craniofacial FD which typically causes morbidity due to lesion expansion, craniofacial involvement in CSHS often leads to hypoplastic bone (Fig. 3B). Reports range from mild asymmetric calvarial

thinning and maxillary hypoplasia to severe osteolysis with large calvarial defects (4, 24, 64, 65, 66). Of note, in reported cases, epidermal nevi often overlay the affected regions of craniofacial bone, leading to speculation that post-zygotic paracrine effects from skin lesions may contribute to the development of skull disease (40, 67). Further studies are needed to investigate this potential association. In the extracranial skeleton, there does not appear to be a geographic relationship between affected skin and the location of dysplastic bone lesions, indicating that lesions in these areas likely arise from primary dysplastic processes (4). The radiographic appearance of bone lesions has not been fully characterized, and lesions are often confused with FD on X-rays, contributing to frequent mis-diagnosis. In comparison to FD, CSHS skeletal lesions are more heterogeneous, with poorly defined cortical-medullary junctions and mixed lytic/sclerotic elements (Fig. 4B, C and D, right panels). The bony cortex is frequently involved and may display some degree of endosteal scalloping, but is typically less thin in comparison to FD.

Clinical management in CSHS is comparatively less well-defined than FD, but similarly consists primarily of surgical repair and prevention of fractures and deformities. There are no medical therapies known to alter the disease course and no reports of use of anti-resorptive medications. Unlike FD, osteoclastogenesis is not highly prominent in dysplastic tissue in CSHS, therefore anti-resorptives are a less intuitive potential treatment strategy.

FGF23-mediated hypophosphatemia

Overproduction of FGF23 is a distinctive feature of both FD/MAS and CSHS and an important contributor to skeletal morbidity. In both disorders, rickets results in impaired growth, metaphyseal abnormalities, and pseudofractures in both dysplastic and unaffected areas of the skeleton. However, dysplastic bone may be particularly vulnerable to the effects of hypophosphatemia. In patients with FD, hypophosphatemia is a demonstrated risk factor for long bone fractures (68), progressive scoliosis (44), and cranial base deformities (69). The association between hypophosphatemia and skeletal complications in CSHS has not been evaluated systematically; however, there are case reports of improved ambulation and decreased pain after starting treatment with phosphorus and vitamin D analogs (4).

Clinical investigation has confirmed in FD and strongly suggests in CSHS that dysplastic bone is the source of FGF23 overproduction (21, 25). This is unsurprising,

given that bone is the tissue source of FGF23 under normal physiologic conditions (70). This has important therapeutic implications in CSHS, because patients have frequently undergone painful and disfiguring skin resections under the mistaken assumption that dysplastic skin lesions produce FGF23 (4). Because dysplastic bone lesions appear to produce FGF23, the severity of phosphate wasting parallels the degree of skeletal involvement, leading to more frequent and severe hypophosphatemia in patients with higher skeletal disease burdens. Interestingly, data suggest that FGF23 production may decrease over time in both disorders. An age-related decrease in serum FGF23 and bone turnover markers has been well-established in FD/MAS (54); improved hypophosphatemia in adults has also been reported in CSHS, although some patients persist (4). This may reflect age-related apoptosis or senescence of mutation-bearing skeletal cells (71).

Treatment of hypophosphatemia in both FD/MAS and CSHS consists of oral phosphorus and vitamin D analogs (72). The recent approval of the anti-FGF23 antibody burosumab for treatment of X-linked hypophosphatemia raises the possibility that this medication may also be helpful for other forms of FGF23 excess, including FD/MAS and CSHS. Burosumab offers several advantages over conventional therapy, including greater ease of administration, greater gastrointestinal tolerability, and decreased hypercalciuria (73, 74). Unmineralized osteoid is a prominent feature of dysplastic lesions in both FD and CSHS, even in patients who are normophosphatemic on conventional therapy (Fig. 1), and it is unknown whether burosumab treatment can alter this tissue-level osteomalacia. Another important unanswered question is whether systemic burosumab has potential effects on mineralization and cell proliferation in dysplastic lesions. Investigation into these tissue-specific effects is needed before burosumab can be used routinely in patients with FD/MAS and CSHS.

Other endocrinopathies

FD/MAS: Hyperfunctioning endocrinopathies are a key feature of FD/MAS. G_s -mediated G-protein coupled receptors play a central role in multiple hormone signaling cascades, making this a frequent manifestation of $G\alpha_s$ activation.

The most common endocrinopathy is gonadotropin-independent sex steroid production, which affects ~85% of girls and women with FD/MAS (37). Recurrent estrogen-producing ovarian cysts lead to a relapsing-remitting course, presenting with acute onset breast development

and linear growth acceleration (Fig. 2E). Cyst resolution leads to withdrawal bleeding, which is often the event that prompts patients to seek care. Management is aimed at preventing premature skeletal maturation, preserving adult height, and preventing psychosocial distress from early development. The aromatase inhibitor letrozole is considered first-line treatment (75). Patients with significant bone age advancement may develop secondary central puberty as a complication of peripheral puberty and may benefit from adjuvant GnRH agonist therapy (8, 75). Recurrent ovarian cysts persist into adulthood and are frequently associated with dysfunctional uterine bleeding (76). While pregnancy is typically possible and safe in women with FD/MAS, fertility may be impaired (76).

Testicular lesions, comprised of Leydig and Sertoli cell hyperplasia, are found in ~85% of boys and men with FD/MAS (77). Lesions may present with diffuse macro-orchidism and on ultrasonography appear as discrete hypo- and hyperechoic lesions with or without microlithiasis. Precocious puberty develops in only 10–15% of affected boys and can typically be managed with a combination of testosterone receptor blockers and aromatase inhibitors (77).

Thyroid disease occurs in ~2/3 of patients, manifesting with thyromegaly and ultrasonographic findings such as discrete nodules and diffuse heterogeneity (37, 78). About half of affected patients have frank hyperthyroidism, which typically responds well to anti-thyroidal medications. Surgery is often preferred for long-term management. Clinicians may also consider radioablation; however, due to mosaic involvement within the gland, there is a hypothetical risk of exposing non-affected tissue to a sub-therapeutic dose of radioiodine (12).

Growth hormone excess affects approximately 15% of patients with FD/MAS (37) and has been identified as a risk factor for craniofacial morbidity, including vision loss (79), hearing loss (42), and craniofacial FD expansion (52). Patients typically respond well to somatostatin analogs and growth hormone receptor blockers, used alone or in combination (80).

Neonatal hypercortisolism is a rare and potentially serious complication of FD/MAS, affecting <5% of patients (37, 81). Disease presents exclusively in the first year of life and can lead to severe illness and death if not recognized early. Most patients are treated with adrenalectomy; however, spontaneous resolution of hypercortisolism has been reported in up to 1/3 patients, therefore it may be appropriate to observe patients who are stable on medical therapy (81).

CSHS: Unlike $G\alpha_s$, Ras does not play a central role in multiple hormone signaling pathways. Other than the notable exception of FGF23 excess, endocrinopathies do not appear to be a common feature of CSHS. Central precocious puberty has been reported in several patients (82, 83); however, most of them had neurologic abnormalities, calling into question whether puberty was a primary manifestation of CSHS or a consequence of underlying brain anomalies. Pheochromocytoma has been reported in one adult patient (84), and there are case reports of benign thyroid nodules and medullary thyroid carcinoma in pediatric patients (4, 65).

Neuropsychiatric features

FD/MAS: $G\alpha_s$ and cAMP have long been recognized as potential contributors to synaptic plasticity and neuropsychiatric disease (85, 86). Neuropsychiatric abnormalities, including psychotic, speech, and language disorders, have been reported in patients with FD/MAS, but have not yet been systematically described (81, 87). Interestingly, transgenic mice expressing the activating Q227L mutation (reported in <5% of patients with FD/MAS) demonstrate neurobehavioral abnormalities (88). Defining the neuropsychiatric phenotype in FD/MAS is therefore a high priority for research and may inform understanding of more common disorders, including major depression and schizophrenia. However, like other features of FD/MAS, neuropsychiatric involvement is likely to be highly variable depending on the relative amount and distribution of mutation-bearing tissue in the CNS. At present, children with FD/MAS should be monitored for developmental abnormalities, with a low threshold for further evaluation and intervention if issues arise.

CSHS: The Ras pathway plays numerous roles in neurodevelopment and neuronal signaling (89); it is therefore not surprising that neurological abnormalities are frequently encountered in patients with CSHS and other RASopathies (90, 91). A large metanalysis reported neurologic disorders in 45% of patients with CSHS, the most frequent being neurodevelopmental delays and intellectual disability, followed by ventriculomegaly and seizures (4). Other manifestations included macro- and microcephaly, spastic hemiplegia, hyperreflexia, and neurocutaneous melanosis (4). Subjects with giant congenital melanocytic nevus, particularly those with posterior and satellite nevi, are prone to develop neurocutaneous melanosis, characterized by melanocytic proliferation in the brain (92) (Fig. 3G). The most likely

etiology of these neurologic abnormalities is the presence of mutation-bearing cells in the brain. Others have speculated that post-zygotic paracrine effects from skin lesions may also contribute, noting that nevi on the face and scalp appears to increase the likelihood of CNS involvement in patients with epidermal nevus syndromes (93). However, further research is needed to investigate this potential association.

All patients with CSHS should be considered at risk for neurologic sequelae and young children should be referred for early interventional services and neurodevelopmental evaluation. Brain imaging to evaluate for structural abnormalities should be strongly considered, especially in patients with giant melanocytic nevi.

Malignancies

FD/MAS: G-protein dysregulation commonly contributes to tumorigenesis, and studies have reported that up to 4.2% of all tumors in the general population harbor gain-of-function *GNAS* mutations (94). The $G\alpha_s$ R201 mutations associated with FD/MAS are commonly found in sporadic, hyperfunctioning pituitary tumors (28%), thyroid adenomas (5%), and pancreatic intraductal pancreatic mucinous neoplasms (IPMNs) (95, 96, 97). Pancreatic IPMNs are found in up to 50% in patients with FD/MAS; however, malignant transformation to pancreatic adenocarcinoma appears to be a rare development, with only one reported case (98).

Women with FD/MAS were reported to have a 3.5–4-fold increased risk of breast cancer compared to the general population in one large series (99). Disease presented at a relatively young age (36–46 years); however, outcomes were highly favorable, with 100% survival and no recurrence or metastases. Women with FD/MAS are therefore recommended to initiate breast cancer screening at an earlier age compared to the general population, that is, 50 years of age based on current guidelines (99).

The potential for transformation of FD into bone cancers has been well-established, including osteosarcoma, chondrosarcoma, and others (100, 101, 102, 103). Patients typically present with acute expansion and/or focal pain, and imaging may demonstrate extension of the lesion through the bony cortex. Due to the absence of rigorous epidemiologic studies, the prevalence of malignant transformation in FD has not been established. In the NIH cohort of approximately 200 patients, two cases of osteosarcoma have been identified, suggesting a prevalence of around 1% (personal observation, AMB). Risk factors for

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malignant transformation include therapeutic external beam radiation – a harmful practice in FD which has been largely abandoned (101, 104, 105, 106). Additional rarely reported tumors include thyroid cancer (107, 108), testicular cancer (77), ovarian tumors (109, 110), and hepatoblastoma (111).

CSHS: Activating *RAS* mutations, particularly those altering *RAS*'s GTPase domain, are well known tumor drivers (112). A variety of benign extracutaneous neoplasms have been reported in patients with CSHS, including thymoma, giant cell granuloma, bladder leiomyoma, ocular dermoids, benign vascular tumors, and others (4). Malignant transformation appears to be relatively uncommon; however, cases of congenital rhabdomyosarcoma (83), medullary thyroid cancer (65), and a malignant brainstem tumor (113) have been reported. Although the vast majority of tumors identified in patients with CSHS have not been sequenced, given their early onset and known association with sporadic *RAS* mutations (<http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>), they are likely directly disease related.

The various skin lesions in patients with CSHS also harbor potential for malignant transformation. Giant cutaneous melanocytic nevi likely have the highest risk for transformation to malignant melanoma, reported in <1–5% of cases (114). Nevus sebaceous commonly transform into secondary benign tumors such as trichoblastoma or syringocystadenoma papilliferum; however, the risk for malignant transformation (most frequently into basal cell carcinoma) is very low (<1%) (115). The risk of malignant transformation of keratinocytic epidermal nevi is extremely rare (116). It is not currently recommended to remove epidermal nevi for cancer prevention. However, skin lesions in patients with CSHS should be monitored regularly by a dermatologist and patients should be educated about concerning signs and symptoms.

Interestingly, there are no reports of osteosarcoma or other skeletal malignancies in CSHS. This observation is consistent with the low prevalence of *RAS* mutations in sporadic bone tumors (<http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>). However, the rarity of CSHS and lack of rigorous epidemiologic studies make the skeletal malignancy risk difficult to ascertain, and this should be considered in the differential if patients present with concerning features such as rapid lesion expansion.

Other features

A wide range of tissue may harbor *GNAS* and *RAS* mutations; however, numerous factors affect the likelihood of

manifesting clinical disease. Depending on the physiologic role of the $G\alpha_s$ or *Ras* pathways, some tissues may display subtle or no detectable phenotype. In contrast, mutations may have strong deleterious effects in other cell types, selecting against cell survival and prohibiting disease in certain tissues. More detailed phenotyping studies are likely to uncover the presence (or absence) of additional manifestations of FD/MAS and CSHS, which will inform understanding of $G\alpha_s$ and *Ras* physiology.

FD/MAS: Although disruption of bone marrow architecture and hematopoiesis are key histologic features of FD (Fig. 1A), somewhat surprisingly, patients do not typically develop clinically apparent hematologic disease. However, rare reports of bone marrow failure and extramedullary hematopoiesis associated with extensive skeletal disease have emerged, suggesting that FD may impact overall marrow function to some extent (117, 118). Platelet dysfunction has also been reported in patients with FD/MAS, although its clinical significance is unclear (119). Tachycardia and hypertension have been reported in patients with extensive bone disease, and it is unknown whether this represents a primary effect of $G\alpha_s$ activation in cardiovascular tissue or a secondary physiologic response to increased cardiac demand (37, 120).

CSHS: Ophthalmologic disorders have been reported in approximately 1/4 patients with CSHS, most commonly colobomas, limbal dermoids, strabismus, and corneal opacities (4). Interestingly, like the brain and skin, the eyes are ectodermal in origin, suggesting that tissues derived from this germ layer feature prominently in the clinical presentation of CSHS.

Marrow function in CSHS has not been systematically evaluated. Hematopoiesis appears to be preserved in dysplastic skeletal tissue (Fig. 1); however, there are two known cases of chronic anemia and thrombocytopenia (121) (personal observation, D O and A M B), suggesting potential deleterious effects.

Future directions

Critical knowledge gaps in both FD/MAS and CSHS have limited the development of novel diagnostics and treatments. Given the rarity of these diseases, collaboration among international investigators and patient advocacy organizations is a high priority to improve health outcomes. The FD/MAS International Consortium has made important contributions in promoting such collaborations, supporting patient registries and developing consensus guidelines for evaluation and management (12, 122). The development of similar collaborative organizations for CSHS is needed.

Conclusion

FD/MAS and CSHS represent two strikingly complex disorders with distinct and overlapping phenotypes. The unique presentation with skeletal mosaicism and FGF23 overproduction in these genetically divergent diseases has led to increased understanding into the complexity of FGF23 physiology. Further investigation in these disorders is likely to lead to additional novel biological insights and ultimately to improved diagnostics and treatments for patients.

Declaration of interest

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