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REVIEW ARTICLE

Musculoskeletal and overgrowth syndromes associated with cutaneous abnormalities

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ABSTRACT

There are cutaneous abnormalities that are characteristic to certain peculiar musculoskeletal conditions. The understanding of associated imaging and clinical skin findings together in this context can play an important role for the dermatologist and radiologist in establishing the correct diagnoses. The scope of dermatological manifestations of many acquired diseases of the soft tissues, muscles or bone is broad. Therefore, the intent of this article is to review those entities that are genetic and/or inherited. The goal of this review is to develop a better understanding of the cases presented. In these cases, collaboration between dermatologists and radiologists may be paramount to generating a diagnosis and monitoring at-risk patients.

INTRODUCTION

The musculoskeletal (MSK) conditions that are associated with cutaneous abnormalities are an unusual and interesting group of disorders. Some, such as neurofibromatosis (NF), are fairly common and well known to most dermatologists and radiologists. Others, such as Maffucci's syndrome, are quite rare. The understanding of associated imaging and clinical findings can play an important role for the dermatologist and radiologist in establishing the correct diagnoses. Although inflammatory, infectious and some malignant conditions have skin, superficial soft tissue and bone involvement, the intent of this article is to review those entities that are genetic and/or inherited and to better understand those cases where collaboration between dermatologists and radiologists can work together to generate a diagnosis and monitor at-risk patients.

Embryogenesis

The ectoderm is the outermost of the three original embryonic germ cell layers. In the vertebrate, the ectoderm is further differentiated into the external ectoderm, neural crest and neural tube. The external ectoderm gives rise to the epidermis and adnexal structures. Melanocytes, craniofacial MSK structures, peripheral neurons, glial cells and limb buds originate from multipotent-migratory cells of the neural crest.

Skin and bones, with or without other tissues differentiated from the embryonic ectoderm germ cells, are the main organs involved in the pathogenesis of diseases reviewed here. An understanding of the radiographic findings associated with cutaneous manifestations of these disorders may allow for earlier diagnosis and prompt therapeutic intervention, with the hope for better care and outcomes.

Neurocutaneous and pigmentary disorders *Neurofibromatosis Type 1*

NF Type 1 (NF1), also called von Recklinghausen's disease, is the most common neurocutaneous disorder with skeletal involvement. The incidence of NF1 is reported to be approximately 1 in 3000 births. It is inherited in an autosomal dominant pattern, although 30–50% of cases arise from new mutations. Mutations in chromosome 17 are responsible for this condition and can be identified before birth by foetal DNA analysis.¹ The gene product is a protein called neurofibromin, which is a regulator of cell division. When mutated, it leads to benign tumour growths in the skin, nervous system, bones and endocrine glands.² Recent data have emerged regarding the P-Stat3/Arid1b/ β -catenin pathway in Schwann cell progenitors that are critical for the initiation of neurofibromas. Genetic deletion of Stat-3, an important neurofibroma oncogene in Schwann cells and Schwann cell progenitors, has been

shown *in vivo* to dramatically slow the formation and growth of neurofibromas.

The cutaneous manifestations of NF1 include café-au-lait macules and patches, neurofibromas and axillary/inguinal freckling (Figure 1). A minimum of six café-au-lait macules measuring >5 mm in pre-pubertal and >15 mm in post-pubertal individuals is required to make the diagnosis. Axillary freckling may also be seen. Neurofibromas can manifest as cutaneous, subcutaneous or plexiform. Although plexiform neurofibroma (PNF) usually presents as a red-brown plaque or sagging skin, it may also manifest as a hyperpigmented patch or plaque with or without hypertrichosis. Cutaneous manifestations of NF1 can be the first presentation of the disease, prompting early diagnosis and care accordingly. Therefore, it is important to palpate when evaluating hyperpigmented patches/plaques to differentiate PNFs from melanocytic congenital nevus or café-au-lait patches. Malignant transformation of PNF to malignant peripheral nerve sheath tumour has been reported in a small number of patients with NF1. Rapid growth, pain or increased firmness should prompt the suspicion of malignant transformation. Pigmented iris hamartomas (Lisch nodules) begin to present around the age of 3 years and can be seen in 90% of adults with NF1. Although very useful for diagnosis, Lisch nodules do not present clinical concerns.

Optic glioma is the most common neurological manifestation in NF1. Its clinical manifestation can vary from asymptomatic to progressive visual compromise. Additionally, most patients with glioma experience precocious puberty. Pheochromocytoma, a rare neurological malignancy affecting <1% of patients with NF1, presents with hypertension. However, the most common cause of hypertension in patients with NF1 is essential hypertension followed by renovascular stenosis. Juvenile myelomonocytic leukaemia and juvenile xanthogranuloma are known to be associated with NF1. More recently, glomus tumours of the fingers and toes have been recognized to occur more frequently in patients with NF1.

Compared with café-au-lait macules, axillary freckling and Lisch nodules that present in the first decade of life, PNF and associated skeletal abnormalities are mostly congenital and warrant palpation of all hyperpigmented lesions in newborns to rule out PNF. If NF is suspected, MSK studies should be conducted to establish proper surveillance and treatment.

Diagnosis and monitoring by superficial and radiographic examination is important in NF-1 due to progression neurological effects and potential for malignant transformation of the neurofibromas, which is believed to be associated with a shorter life expectancy in these patients.^{3,4}

Musculoskeletal imaging

Conventional radiography is an essential diagnostic modality to evaluate skeletal manifestations of NF1. The most common MSK manifestations are spinal deformity (21%), limb-length inequality (7.1%), congenital tibial dysplasia (5%), pectus deformity (4.3%) and hemihypertrophy (1.4%). Additionally, bowing of the long bones, intramedullary longitudinal osteosclerosis and focal gigantism may be seen (Figure 1b). Joint abnormalities include protrusio acetabuli, the absence of the patella, neuropathic arthropathy and dislocation of the knee joints. On conventional chest radiographs, one may see inferior rib notching, and twisted and ribbon-like ribs in the upper thoracic cage.¹

NF1 also affects the calvarial and facial bones. Macrocephaly, the absence or hypoplasia of the greater and lesser wings of the sphenoid, the absence of the orbital floor, enlargement of cranial foramina, sclerosis in the vicinity of the optic foramen (optic nerve sheath meningioma) and paranasal sinus hypoplasia are manifestations best shown on CT images of the skull in patients with NF1. Symmetrical hypoplasia or hyperplasia with split mandibular canal is also best identified on CT images.⁵

The mutation of chromosome 17 seen in NF1 is believed to be associated with development of aneurysmal bone cysts, which can present with sacral scalloping and cramping leg pain. MRI is

Figure 1. Neurofibromatosis. (a) Multiple dermatological images of café-au-lait spots (top-left, bottom-left, top-middle-right, bottom-middle-right) and PA (top-middle-left, bottom-middle left) and lateral (top-right, bottom-right) radiographs of the same patients demonstrating scoliosis in these patients with NF. (b) Lateral radiograph (left) of the tibia demonstrating congenital tibial dysplasia and anteroposterior post-operative radiographs (middle, right) of the tibia demonstrating surgical correction of deformity. (c) Coronal MRI of the chest demonstrating example of a neurofibroma at the right apex. Reproduced from Crawford and Schorry¹ with permission from Wolters Kluwer Health, Inc. Right apical chest paraspinal neurofibroma (arrow).

the modality of choice for evaluating aneurysmal bone cysts. Well-circumscribed multiloculated lesions in the dorsal sacrum with posterior vertebral scalloping and compression of nerve roots is reported in the literature.⁶

Other diagnostic imaging studies recommended in patients with NF

Neurofibromas in patients with NF1 may also be present in internal organs, especially the lungs and liver (Figure 1c). These lesions are best seen on cross-sectional imaging and show characteristic findings. Early detection and localization of internal neurofibromas in patients with NF1 are essential for early planning and treatment as these tumours may enlarge and compress adjacent organs. MRI is the modality of choice to investigate the wide range of benign and malignant tumours of the central nervous system (CNS) in patients with NF. These tumours appear isointense to the brain tissue on T_1 weighted images and hyperintense with smooth margins on T_2 weighted (T2-W) images and enhance intensely following contrast administration. Another characteristic and early finding on T2-W MR images of the brain is unidentified bright objects (UBOs), seen in more than half of the children with NF1. Although the clinical significance of UBOs is not yet understood, their classic location in the cerebellum, brain stem and basal ganglia may contribute to cognitive impairment in these patients. The high sensitivity and specificity of UBOs, as well as their classic locations, have led some authorities to consider UBOs as one of the diagnostic criteria for NF1.

Neurofibromatosis Type II

NF Type II (NF2) is less common than NF1, affecting 1 in 25,000 people. Like NF1, it is due to spontaneous mutation in 50% of affected individuals. The gene defect lies on chromosome 22, where the gene product is a tumour suppressor called merlin or schwannomin. Vestibular schwannomas may be seen along the eighth cranial nerve. In addition to vestibular schwannomas, patients may have gliomas, meningiomas, schwannomas along peripheral nerves and juvenile cataracts. Patients may present with visual impairment, hearing loss, tinnitus and disturbances in balance. A third type of NF, called schwannomatosis, is due to

a mutation in the SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1/integrase interactor 1 (SMARCB1/INI1) gene.⁷ Schwannomas may occur anywhere in the body with the exception of the vestibular nerve, with patients typically presenting with chronic pain due to schwannoma infiltration of peripheral nerves.⁸

Imaging in neurofibromatosis Type 2

Imaging vestibular schwannomas can be accomplished using MRI, as these lesions are similar to meningiomas on imaging, however tend to have an asymmetric relationship to the affected nerve.⁹ Patients with NF2 may also be affected by intracranial and spinal meningiomas, which may appear as hypointense mass lesions on T2-W MRI, with mild hyperintensity on fluid attenuation inversion recovery imaging.⁹

McCune Albright syndrome

McCune Albright syndrome is classically defined as a triad of polyostotic fibrous dysplasia, café-au-lait pigmentation and endocrine hyperfunction, classically presenting as precocious puberty. Postzygotic mutations in the guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1 (GNAS1) gene on chromosome 20 explain the variable spectrum of clinical manifestations in this disease.¹³ Mutations of this gene in melanocytes lead to excess melanin production, resulting in café-au-lait spots. The café-au-lait patches are larger in size, are smaller in number, are asymmetrical and have irregular margins as compared with NF1. In addition, café-au-lait patches often have an irregular border, may follow lines of Blaschko and do not cross the midline. The characteristic MSK finding is polyostotic fibrous dysplasia presenting with bone pain. Autonomous endocrinopathies, such as precocious puberty, thyrotoxicosis and acromegaly are other common clinical findings.

Musculoskeletal imaging

Polyostotic fibrous dysplasias appear as central intramedullary, expansile, ill-defined radiolucent lesions on radiographic images without periosteal reaction but with cortical thinning and occasional endosteal scalloping. Although appendicular and facial bones

Figure 2. McCune-Albright syndrome. (a) Coronal (left), (b) axial (middle) and (c) sagittal (right) CT images of the face demonstrating classic example of polyostotic fibrous dysplasia present in a patient with McCune Albright disease.

are most commonly affected, no bone is spared. Involvement of the skull and facial bones can be striking, with diffuse sclerosis at the base of the skull leading to facial deformity (Figure 2) and progressive visual and auditory impairment.¹⁴ Recurrent pathological fractures are commonly detected on conventional radiography. Shepherd's crook deformity of the proximal femur is characteristic. CT and MRI are the modalities of choice for evaluating the extent of the lesion and adjacent soft tissue.

CT images show expansile lesions with a varying degree of density and a ground-glass appearance that is mixed radiolucent and sclerotic. Hounsfield unit measurements are characteristically between 70 and 130 and can help to confirm the diagnosis.⁶ Axial images of the skull show ground-glass expansion of the skull base with narrowed basal foramina and optic canals. On MRI, fibrous dysplasia is mainly isointense with areas of hypointensity (intermediate to low) on T_1 weighted images. It appears heterogeneously hyperintense (intermediate to high) on T2-W images with heterogeneous enhancement after gadolinium administration.¹⁵

Bone scintigraphy shows non-specific, but often intense, technetium-99m methylene di-phosphonate (^{99m}Tc MDP) radiotracer uptake.¹⁶ A scintigraphic sign of sphenoid wing involvement, the "pirate sign", has been reported.¹⁷

Tuberous sclerosis

Tuberous sclerosis (TS) is a neurocutaneous syndrome inherited in an autosomal dominant pattern. Abnormalities of chromosomes 9 and 16 have been described involving 2 genes, hamartin/tuberous sclerosis 1 (*TSC1*) and tuberin/tuberous sclerosis 2 (*TSC2*), that encode the proteins hamartin and tuberin, respectively. Together, these proteins form a complex that acts as a tumour suppressor by inhibiting the mechanistic target of rapamycin (mTOR) pathway. Prenatal diagnosis can be achieved by foetal DNA analysis. Characteristic central facial angiofibromas, which are fibrous hamartomas of the dermis, are seen in >80% of patients with TS after puberty and can present as early as 2 years of age. Angiofibromas may also appear as a large yellow-pink plaque on the forehead that grows over time. Other well-described skin lesions seen in TS are hypomelanotic macules and café-au-lait macules, which can be present at birth and play a pivotal role in early diagnosis. The hypomelanotic macules can present with various configurations, including polygonal (thumbprint), lanceolate (ash-leaf) or guttate (white freckles or confetti macules), in order of more common/less specific to less common/more specific. When suspicious, a simple Wood's lamp examination can aid in establishing an early diagnosis. Connective tissue nevi (Shagreen patch), fibrous plaques and periungual fibromas are additional skin findings in patients with TS.

Three types of brain lesions seen in TSC include cortical tubers, subependymal nodules and subependymal giant cell astrocytomas. Seizures, developmental delay, mental retardation and autism spectrum disorders may all be associated.

Patients with TS show variable organ expression. Fibromas and hamartomas of various organs, such as renal angiomyolipoma, myocardial rhabdomyoma, pulmonary lymphangiomyomatosis, retinal and subependymal hamartoma, astrocytoma and

gingival fibroma comprise the characteristic internal organ involvement in TS.¹⁰ Angiomyolipomas and renal cysts, while benign, may compromise renal function. Although the clinical triad of seizures, mental retardation and facial angiofibromas classically characterize TS, radiological imaging plays a pivotal diagnostic role. Foetal echocardiographic abnormalities can also be suggestive of the diagnosis. Close imaging, monitoring and characterization of disease severity are important for further referral to related specialists, such as neurologists for the commonly experienced seizure disorders.

Musculoskeletal imaging

MSK involvement is usually asymptomatic and may be seen in up to half of the affected patients. If present, conventional radiography would show periosteal thickening and small lytic lesions of the metatarsals, metacarpals and phalanges. Sclerosis

Figure 3. Tuberous sclerosis. (a) Axial CT image of the pelvis demonstrating osteosclerotic lesion seen in tuberous sclerosis. (b) Axial CT image of the head demonstrating posterior fossa cortical tubers.

of the pelvis, spine and cranium may also be noted. Radiography and CT images of the skull (Figure 3) show the patchy areas of increased bone attenuation, generalized thickening of the cranial vault table and evidence of elevated intracranial pressure including suture diastasis, sellar changes and increased convolutional markings.^{11,12}

Other diagnostic imaging studies recommended in patients with TS

CT scan of the brain in patients with TS shows calcified subependymal nodules along the ventricles as early as infancy. Subependymal astrocytomas in patients with TS can present similar to calcified nodules. However, on follow-up imaging, the former would grow in size compared with calcified nodules that remain relatively stable over time. In infants with TS, echocardiography is recommended to determine the clinical significance of cardiac rhabdomyomas. Follow-up cardiac imaging, echocardiography or MRI is usually performed to ensure involution of cardiac rhabdomyomas.

Hypomelanosis of Ito

Hypomelanosis of Ito (incontinentia pigmenti achromians) is a non-inherited sporadic disease resulting from gene mosaicism, presenting with unilateral or bilateral whorled hypopigmentation following Blaschko's lines. Some patients present with variable extracutaneous findings; these can involve MSK system, CNS and/or eyes.

Musculoskeletal imaging

MSK involvement is characteristic in children and includes limb length discrepancy, scoliosis and hemihypertrophy with or without digital anomalies, such as atrophy, syndactyly, polydactyly, clinodactyly or bifid thumb.

Other diagnostic imaging studies

CT and MR images of the brain can best demonstrate the hemimegalencephaly with delayed fontanel closure in children with clinical CNS manifestation of hypomelanosis of Ito. MRI is the modality of choice to show white matter changes and abnormal neuronal migration.¹⁸

Digitocutaneous dysplasia

Digitocutaneous dysplasia (DCD), also known as terminal osseous dysplasia with pigmentary defect, is a rare X-linked disorder caused by a mutation in the filamin A gene. Patients present with hyperpigmented atrophic-appearing skin plaques and midfacial dysmorphic features including frontal bossing, broad nasal root and telecanthus. The characteristic skeletal manifestation of DCD is multiple digital fibromas that may be associated with bone deformity.¹⁰

Musculoskeletal imaging

Hand and foot radiographic imaging is the first step in evaluating patients with DCD. Radiographs may show fibromas and any bone deformities. MRI should be performed to define the extent of the lesions, if needed. Fibromas often have low signal intensity on both T_1 weighted and T_2 -W sequences, although the signal intensity will vary depending on the cellularity and stage of development of the individual lesion.

Vascular disorders

Gorham-Stout syndrome

Gorham-Stout syndrome (GSS), also known as vanishing bone disease, is a rare syndrome with insidious onset and progressive natural course leading to a relentless osseous destruction. Little is known about its pathogenesis; however, abnormal osteoclast activity is suspected and a hemangiomatous/lymphangiomatous process is strongly implicated. It starts as a monostotic osteolytic process in which bone is replaced with proliferating thin-walled vascular channels, leading to extensive loss of bone matrix and vanishing of the entire affected bone. In the late phase, a mere fibrotic remnant may be present in place of what was once recognized as bone. It can affect any region of the axial or appendicular skeleton, but the shoulder and pelvic girdle are the most commonly involved sites.¹⁹ Its vague clinical presentation, such as weakness, pain, tenderness or pathological fracture, may further delay the diagnosis.

Skin and soft tissue are the main extraosseous foci, which play an important diagnostic role. The cutaneous lesions appear as skin-coloured papules and vesicles. Histopathology shows lymphatic/vascular malformation in these cutaneous lesions, similar to bone histopathology. The importance of the skin manifestations of GSS is underestimated, as they may be the first clinical sign for which the patient seeks medical attention. If GSS is suspected, CT and MRI, after initial radiographs, are the optimal methods of investigation.²⁰

Figure 4. Gorham-Stout syndrome (GSS). (a) Posteroanterior radiograph of the chest in a patient with GSS demonstrating post-surgical changes and osteolytic changes of the ribs over the left upper chest.

Musculoskeletal imaging

Early radiographic changes include massive osteolysis with intra-medullary or subcortical radiolucent foci resembling patchy osteoporosis. Late findings are evident as soft tissue atrophy, fracture, fragmentation and bone dissolution with “pointing” of the remainder of the osseous tissue (Figure 4). A contiguous, regional pattern of bone destruction is highly suspicious for this entity. Of note is the lack of any sclerotic or osteoblastic reaction, which may explain the lack of ^{99m}Tc MDP uptake on delayed images of three-phase bone scintigraphy. However, one may see increased blood flow and soft tissue blood pool during the early phase images.

MRI is the optimal diagnostic tool to assess the extent of the disease. T_1 weighted spin-echo shows low signal intensity in the affected bone with generally increased signal intensity observed on T2-W spin echo images. Tissue enhancement is seen following administration of gadolinium contrast agents.²⁰

The presence of chylothorax and pleural effusion in a child, in concert with neurological impairment and skeletal findings, should prompt a search for involvement of the vertebrae and lungs. Therapy consists of radiation, anti-osteoclastics (bisphosphonates) and interferon, with or without reconstructive surgery.²¹

Klippel trénaunay

Klippel trénaunay, also known as angio-osteohypertrophy, is characterized by low flow capillary–lymphatic–venous malformation of the affected extremity with underlying bone and soft tissue hypertrophy (Figure 5). In the skin and subcutaneous tissue, KT presents as varicose veins, port wine nevus and subcutaneous lymphoedema. Although present at birth, the genetic aetiology has not been fully established. The role of diagnostic imaging is essential in assessment and therapy planning when a surgical option is considered.²²

Musculoskeletal imaging

Conventional radiography allows precise assessment of skeletal asymmetry. Ultrasonography has been traditionally used to characterize vascular abnormalities and the patency of the extremities' deep venous system. CT or MR venography is considered the modality of choice for pre-operative mapping of the venous system of the affected extremity prior to surgical resection. With these techniques, one can establish the low flow nature of the malformation. High flow malformations are seen in other similar conditions including Parkes Weber syndrome.

Multidetector CT (MDCT) and three-dimensional MR venography are new, non-invasive diagnostic imaging modalities that can determine the anatomy, origin, course, relation to adjacent structures, high flow or low flow state and drainage pathways of aberrant vessels of the affected extremity in an efficient manner and with the same image.^{22,23}

Cobb's syndrome

Cobb's syndrome, a non-inherited disorder, involves a cutaneous vascular proliferation in the same dermatome as an underlying spinal angioma or arteriovenous malformation. The vascular malformation within the spinal cord may cause cord compression, weakness, muscle atrophy and eventual loss of sensation

Figure 5. Klippel trénaunay (KT). (a) Anteroposterior radiograph of the bilateral lower extremities demonstrating asymmetric length in patient with KT.

below the level of compression. Occasionally, it may lead to subarachnoid haemorrhage.¹⁰

Musculoskeletal imaging

MRI is considered the screening study of choice to evaluate the extent of spinal cord vascular lesions. Decreased signals on T_1 weighted and T2-W images, described as “flow voids,” outline the nidus within the spinal cord. The T2-W images also demonstrate the draining veins and possibly the feeding arteries to better delineate the extent of the lesion. Notably, haemorrhage, oedema and myelomalacia are better seen on MRI than on any other modality, including CT. MRI is also helpful to evaluate high flow Arteriovenous (AV, haemangioma) vs low flow (venous, lymphatic) vascular anomalies. On gadolinium-enhanced T_1 images, venous (enhanced) and lymphatic (non-enhanced) malformations can be further differentiated.¹⁹

The complete evaluation of a patient suspected of a spinal Arteriovenous malformation (AVM) includes selective spinal angiography. However, MR angiography also is used to demonstrate the architecture of a vascular lesion. Arterial and venous architecture can be visualized on early and delayed phases of MR angiography, respectively.

Proteus syndrome

Proteus syndrome (PS), also known as Wiedemann syndrome, is named after the Greek god Proteus who could change his shape. It is marked by skin overgrowth, bony abnormalities and tumour formation and is due to an activating mutation in AKT1 kinase. The cutaneous lesions of PS include vascular malformations (lymphatic, capillary and venous), cerebriform palmar/plantar hyperplasia and several types of nevi, especially linear epidermal nevi. PS is also characterized by aggressive deep lipomas. Because of the highly variable clinical manifestations, predominance of skeletal abnormalities,² the absence of clinical manifestations at birth and delayed appearance of skin and subcutaneous lesions, radiology plays an important role in the diagnosis, evaluation and management of PS.¹⁰

Musculoskeletal imaging

Limb gigantism and macrodactyly, along with other digital abnormalities, are important skeletal findings occasionally seen in association with scoliosis, macrocephaly, frontal bossing and hyperostosis. Skeletal abnormalities are most problematic for these patients, followed by aggressive lipomas and vascular complications. If orthopaedic intervention is considered, a baseline and follow-up skeletal survey is recommended.

Screening for cranial malformations is important in children with PS. Three-dimensional CT and MRI of the head are important to evaluate for anatomical causes of neurological symptoms, bony overgrowth of the calvarium and facial abnormalities. MRI is the modality of choice to evaluate asymmetrical extremity soft tissue and bone overgrowth, abnormalities in the axial skeleton such as fatty infiltration of the paraspinal muscles, aggressive lipomas with vertebral invasion and the severity of scoliosis. In regard to internal organs, MRI is a vital screening tool to outline the vascular malformations and potentially aggressive lipomas in the absence of clinical symptoms.²⁴

Maffucci's syndrome

Maffucci's syndrome (MS) is a rare syndrome mainly affecting the skin and skeleton. It is thought to be caused by somatic mutations in Isocitrate dehydrogenase 1 (IDH1) and Isocitrate dehydrogenase 2 (IDH2), which lead to activation of the Hypoxia-inducible factor 1-alpha (HIF-1-alpha) pathway that is essential for chondrocytes in the growth plate. It presents with enchondromas, bone deformity and superficial/deep venous malformations (haemangiomas). Venous-lymphatic malformations can occur but are less common. The cutaneous haemangiomas appear as blanching subcutaneous nodules mostly affecting the distal extremities (Figure 6a).

Enchondromas are usually benign and affect the metacarpals and phalanges of the hands and long bones in an asymmetrical fashion. However, up to 30% of patients may have one of their enchondromas transform into a chondrosarcoma. All patients with MS are at high risk for development of malignancy in the bone, brain, pancreas and ovaries and should have periodic surveillance.²⁵ In a related disorder, Ollier's disease, enchondromas may be seen without vascular malformations; however, there is still elevated risk for chondrosarcoma and other malignancies.

Musculoskeletal imaging

Conventional radiographs of the hands (Figure 6b) and feet are often pathognomonic for MS. Enchondromas show as well-demarcated radiolucent lesions with expansile remodelling of the adjacent bone, thinning of the cortex and endosteal scalloping. Of note is the typical “arc-and-ring” appearance indicative of chondroid mineralization in the matrix of the lesions. Thrombosis of venous malformations may cause phleboliths with the typical calcifications in the vessels seen on the radiographs.²⁶

Regular radiographic monitoring is recommended for changes suggesting the development of a chondrosarcoma, which is the most common neoplasm in patients with MS. These findings include deep or extensive endosteal scalloping, cortical destruction, periosteal reaction and new lucency within a previously mineralized bone.²⁷ However, distinction between benign enchondroma and chondrosarcoma on radiographic images is challenging. Even pathologically, one may see overlap between histological characteristics of benign enchondroma and low-grade chondrosarcoma. Advanced imaging techniques can add some valuable information. ^{99m}Tc MDP whole-body bone scintigraphy, with comparison of the activity in the suspected chondrosarcoma to the activity of the anterior iliac spines, is one useful adjunct.

Chondrosarcomas have higher levels of activity than benign lesions.²⁷ A prolonged T_2 relaxation time measured on MR images has been reported, in a single case, as an interesting finding that may be helpful in differentiating benign and malignant cartilaginous tumours.²⁸ Other authors have described dynamic contrast-enhanced MRI as a differentiating method. In addition, fluorine-18 fludeoxyglucose positron emission tomography/CT imaging has been reported to be an objective and quantitative adjunct in the diagnosis, tumour grading and

Figure 6. Maffucci's syndrome (MS). (a) Dermatological findings in a patient with MS showing multiple cutaneous haemangiomas with accompanying radiograph and (b) perioperative image portraying the gross subcutaneous appearance. (c) Anteroposterior radiograph and posteroanterior radiographs of the left hand in a patient with MS showing multiple enchondromas, which have the appearance of expansile lucent lesions with matrix mineralization and haemangiomas, which present as soft-tissue lesions containing phleboliths on radiography. (d) Angiogram of the left hand in a patient with MS demonstrating multiple vascular malformations. Reproduced from Flach et al²⁶ and Li et al⁴⁰ with permission from The Radiological Society of North America (RSNA®) and John Wiley & Sons, Inc., respectively.

prognosis of chondrosarcoma,^{29,30} although initial studies have been carried out only with small numbers of patients.

Connective tissue disorders

Ehlers Danlos syndrome

This is a group of hereditary disorders, which share a characteristic defect in the strength, elasticity and integrity of collagen, mostly affecting the skin and joint capsular structures. The disorder is due to mutations in one of the genes coding for Type V collagen, Collagen, type V, alpha 1 (COL5A1) and Collagen, type V, alpha 2 (COL5A2). The presence of one or more of the following features is based on the specific type (I to IX): skin involvement including hyperextensible elasticity, poor wound healing after minimal trauma, "cigarette paper scars" molluscoid pseudotumours, calcified subcutaneous nodules, varicose veins and ecchymoses.²⁷ Most forms are autosomal dominant with a minority being autosomal recessive. A variety of collagen gene defects, as well as enzymes involved in collagen production and processing, have been described.

Musculoskeletal imaging

The most common skeletal manifestation of Ehlers Danlos syndrome is joint dislocation. In addition, an exaggeration of the concavity of the vertebral bodies may be seen. This is called the posterior vertebral scalloping sign and is seen on lateral radiographic, sagittal CT and sagittal MR images of the spine.³¹

Osteogenesis imperfecta

Osteogenesis imperfecta is composed of heterogeneous genetic disorders of Type 1 collagen synthesis, resulting in thin and easily bruising skin and bones that are easily fractured and deformed. Most cases are caused by defects in the Collagen, type I, alpha 1 (COL1A1) or Collagen, type I, alpha 2 (COL1A2) genes. Several subtypes are identified based on severity, ranging from bowing of the long bones, mild fractures leading to variable degrees of dwarfism, to prenatal fractures and death. Spinal abnormalities are present in almost all subtypes and include platyspondyly and progressive kyphoscoliosis.³⁴ Blue-grey discoloration of the sclera is due to thinning which allows the underlying choroidal veins to show through.

Musculoskeletal imaging

The radiological *sine qua non* of osteogenesis imperfecta is the combination of generalized osteoporosis and the presence of multiple fractures (Figure 7). Radiographic findings in more severe subtypes include thickened and shortened long bones with multiple fractures and occasional hyperplastic callus formation often found around the femur, which appear as an irregular dense mass arising from the cortex and associated with thickened periosteum. This may resemble osteosarcoma, myositis ossificans, chronic osteomyelitis or osteochondroma on radiographic images. Bisphosphonate therapy has resulted in specific imaging findings, such as sclerotic growth-recovery lines in the long bones. The amount of bone growth occurring

Figure 7. Osteogenesis imperfecta (OI). (a) CT scout image demonstrating evidence of multiple prior fractures (left), deformed and shortened bones (right) and scoliosis (both) in patients with OI. (b) Anteroposterior radiograph of paediatric patient with OI depicting generalized osteoporosis.

between doses can be measured using the distance between these growth lines. Chest radiographs may show multiple rib fractures causing broad and deformed ribs. CT and MRI are preferred modalities for evaluation of the vertebrae and skull. Temporal bone CT images may show progressing band such as undermineralized pericochlear areas progressing to promontory and tympanic segments of the facial nerve canal. MR images may demonstrate abnormal enhancement of the otic capsule.³⁵

Marfan's syndrome

Marfan's syndrome is an autosomal dominant disorder affecting multiple organs including the skin, eyes, heart vessels and skeletal system. The disease is autosomal dominant and caused by a defect in the Fibrillin-1 gene, which is important both for structural support in connective tissue and the regulation of transforming growth factor beta. Skin manifestations include decreased subcutaneous fat, striae distensae and elastosis perforans serpiginosa. Of numerous musculoskeletal manifestations, tall stature with significantly reduced upper to lower body segment ratio (or increased lower to upper body ratio) is most commonly seen, followed by disproportionately long limbs ("wing span" greater than height). Other manifestations include kyphoscoliosis, arachnodactyly, pectus abnormalities of the anterior chest wall, osteopenia and a high arched palate.³²

Musculoskeletal imaging

The skull abnormalities, such as dolichocephaly, are asymptomatic and often not radiographed. Spinal abnormalities are clinically significant and affect more than half of the patients. CT or MRI of the lumbosacral spine is the modality of choice in evaluating the dural ectasia (Figure 8). It is believed that the dural sac ratio at L5 and S1 and the sagittal dural sac width at S1 greater than that at L4 are the only statistically significant criteria for dural ectasia in children, adolescents and young adults.³³

Pelvic radiography can be used to assess protrusio acetabulae. Calculation of the metacarpal index is no longer performed due to low sensitivity and specificity.

Dermatofibrosis lenticularis

This is an autosomal dominant disorder, also known as Buschke–Ollendorff syndrome, which occurs due to a loss of function mutation in the LEM Domain Containing 3 (LEMD3)

Figure 8. Marfan's syndrome. (a) Sagittal MRI T_2 sequence of the lumbar spine demonstrating multiple areas of widening/ballooning of the dural sac of the spinal cord consistent with dural ectasia in a patient with Marfan's syndrome.

Figure 9. Dermatofibrosis lenticularis (DL). (a) Anteroposterior radiograph of the pelvis demonstrates multiple small focal sclerotic bony lesions consistent with bone islands in the setting of osteopoikilosis in a patient with DL.

gene leading to increased elastin or collagen. Skin involvement presents with connective tissue nevi and discrete skin coloured to yellow dermal papules that are symmetrically distributed on the trunk, buttocks and arms.³⁶ Osteopoikilosis (skeletal lesions) are osteosclerotic lesions and are often asymptomatic.

Musculoskeletal imaging

On radiographic images, osteopoikiloses are evident as 1–10 mm well-circumscribed round or oval opacities found within the carpal, tarsal and phalangeal bones of the hands or feet; pelvic bones; and epiphyses and metaphyses of the long bones (Figure 9). Osteopoikiloses may change in size and number or even disappear on follow-up radiography. Although osteopoikiloses are believed to be sclerotic bone-forming lesions, they do not show radiotracer uptake on bone scintigraphy.³⁷ MR images show multiple low-signal lesions on all pulse sequences, which are characteristically uniform in size and symmetrically distributed.

Focal dermal hypoplasia

This is a rare X-linked disorder also known as Goltz syndrome or Goltz-Gorlin syndrome. It is due to a defect in the Human porcupine homolog (PORCN) gene that is required for function of the Wntless type (Wnt) proteins, which play a role in embryonic tissue development. The skin, bones, teeth and other organs may be involved. Patients may have distinct facial features including cleft lip and palate, small ears, pointed chin and facial asymmetry. Eye abnormalities are common. Cutaneous involvement includes atrophic dyspigmented telangiectatic streaks and the absence of skin (cutis aplasia) or red-yellow nodules (fat herniation) in Blaschko's lines. Papillomas may be seen on the lips, and in the axilla, perineum or periumbilical areas.³⁸ Patients may have missing, fused or webbed digits.

Musculoskeletal imaging

The skeletal deformities seen in focal dermal hypoplasia consist of syndactyly, oligo/poly syndactyly with “lobster claw” deformity. The majority of patients present with scoliosis and short

stature. On radiographic images (Figure 10), one may see osteopathia striata, vertical striations in the metaphyses of long bones caused by altered density, in addition to the spinal curvature.³⁹

Pansclerotic morphea

Pansclerotic morphea is a sclerotic process that extends beyond the skin into the underlying musculoskeletal structures. The cause is unknown, but it is thought to have genetic and environmental aetiologies. The onset is usually during childhood.

Figure 10. Focal dermal hypoplasia (FDH). (a) Anteroposterior radiograph of the right knee depicting vertical striations in the metaphysis of the femur and tibia caused by altered osseous density consistent with osteopathia striata in a patient with FDH.

Although it lacks the systemic involvement seen in generalized scleroderma, virtually any part of the body can be affected. When the skin overlying joints is affected, progression of the disease can lead to severe to complete immobility of those joints. Head involvement can result in neurological and ocular impairment. Involvement of the thoracic region can compromise respiratory function. This can progress to significant associated morbidity and even mortality.

Musculoskeletal imaging

MRI is the diagnostic modality of choice in assessment of pansclerotic morphea. In the early inflammatory stage, MRI can best show the thickening of the dermis and inflammatory infiltration involving the underlying subcutaneous fat and connective tissue, which is seen as increased signal intensity on short tau inversion recovery sequence and contrast-enhanced T_1 weighted images and hypointense signals on unenhanced T_1 images. With time, the inflammatory process extends to the bone presenting as a band-like high intensity signal along the subcortical bone. In the inflammatory phase of the disease, MRI is the modality of choice to assess the depth of involvement compared with other imaging modalities or clinical assessment. In some cases, MRI can detect early musculoskeletal involvement when not clinically suspected. Moreover, it is reported that the signal intensity on MR images correlates with disease activity. Therefore, in assessment of patients with

Figure 11. Pansclerotic morphea. (a) Axial CT scan of the bilateral lower extremities demonstrating asymmetric size of the thigh due to sclerotic changes in the setting of pansclerotic morphea.

morphea, a baseline MRI seems prudent to investigate the depth of inflammatory infiltration and underlying musculoskeletal involvement. Muscular and osseous changes can in part be reversible, seen on follow-up imaging studies, in those patients who respond to therapy, such as haematopoietic stem-cell transplantation. Once sclerosis has replaced inflammation, conventional radiographic imaging or CT scan can best demonstrate the sclerotic musculoskeletal changes (Figure 11).

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