Learning objectives

Neurofibromatosis type 1 (NF1) affects multiple organ systems, and musculoskeletal abnormalities are seen in up to 50% of patients. The distinctive feature of NF1 is neurofibromas; we will discuss in detail the different types of neurofibromas and also their imaging features. The skin, soft tissue and skeletal manifestations of this condition would also be described in this review.
Background

NF1 is a common neurocutaneous condition with an autosomal dominant pattern of inheritance. It is caused by either a mutation or deletion of the NF1 gene on chromosome 17. Neurofibromin, the gene product, functions as a tumour suppressor and is important in skeletal development and growth. The loss of neurofibromin leads to an increased risk of benign and malignant tumours formation in affected individuals.
Findings and procedure details

Neurofibromas
Neurofibromas are benign peripheral nerve sheath tumours. Three types of neurofibroma are classically described: localised, diffuse, and plexiform, and all three types can be associated with NF1.

1. Localised Neurofibroma
   • Localised neurofibromas are the most common type of neurofibroma. Localised neurofibromas in NF1 patients more frequently involve large deep nerves (such as the sciatic nerve and brachial plexus), are larger in size and usually multiple in number.
   • Neurofibromas are well-defined, soft-tissue masses on CT, are low attenuating and hypodense relative to muscle, and show little or no contrast enhancement.
   • They are fusiform-shaped masses with tapered ends on MRI, of low to intermediate signal intensity on T1-weighted images, and high signal intensity on T2-weighted images. A characteristic target sign may be seen, which consists of high signal intensity in the periphery and low signal intensity in the central region of the lesion. Enhancement of neurofibromas are heterogenous.
   • The split-fat sign, best appreciated on T1-weighted images, represents a rim of fat that surrounds the tumour. This sign is not specific for neurofibromas but is suggestive that the tumour originates in the intermuscular space, in which neurogenic tumours are the most frequent cause.

2. Diffuse Neurofibroma
   • Diffuse neurofibromas are poorly defined lesions that spread along connective tissue septa. They surround rather than destroy adjacent normal structures. Children and young adults are more commonly affected, typically involving the skin and subcutaneous tissues of the head and neck. Most diffuse neurofibromas are isointense or mildly hyperintense in relation to muscle on T1-weighted images, and hyperintense to muscle on T2-weighted images. Diffuse neurofibromas often enhance intensely after IV gadolinium administration.

3. Plexiform Neurofibroma (Fig. 1)
   • Plexiform neurofibromas are essentially pathognomonic of NF1, affecting approximately 30% of patients.
   • CT of plexiform neurofibromas reveals large multilobulated low-attenuation masses, usually within a major nerve distribution. MRI shows large
conglomerate masses consisting of numerous neurofibromas. The involved nerve is diffusely thickened, and there is often extension into the nerve branches. Plexiform neurofibromas have a characteristic ringlike or separated pattern; this pattern is best observed on T2 weighted images and contrast-enhanced T1 weighted images.

4. Malignant Peripheral Nerve Sheath Tumour (Fig. 2)

- The lifetime risk of developing malignant peripheral nerve sheath tumour (MPNST) in NF1 is around 8 to 13%, and they usually arise in preexisting plexiform neurofibromas. Sudden increase in size in a previously stable neurofibroma, new onset of pain, neurological symptoms of motor weakness and sensory deficits should raise the suspicion of malignant transformation.
- MPNSTs most commonly involve major nerve trunks including sciatic nerve, brachial plexus and sacral plexus. MRI features that can help distinguish peripheral nerve sheath tumours from neurofibromas include: increased largest dimension of the mass, peripheral enhancement pattern, perilesional edema, intratumoral cystic lesion, and heterogeneity on the T1-weighted images.

Skin and Soft Tissue Manifestations of NF1

- Dermal neurofibromas appear as circumscribed masses on plain radiographs and on cross-sectional imaging (Fig. 3). Ultrasound is useful in differentiating dermal neurofibromas into localised, diffuse and plexiform subtypes (Fig. 4, 5 and 6). When examined by sonography, dermal neurofibromas are classically described as hyperechoic lesions with an embedded component of interconnecting tubular and/or nodular hypoechoic structures of variable extent. The abnormalities can involve the superficial epidermis, dermis and the subcutaneous tissues, occasionally affecting the surface of underlying muscle as well. Majority of these lesions show increase vascularity by colour Doppler ultrasound with colour flow detected within the ductal hypoechoic components.
- Plexiform neurofibromas may be associated with massive and disfiguring enlargement of an extremity and the condition is called elephantiasis neuromatosa (Fig. 7 and 8). It can be accompanied by osseous hypertrophy related to chronic hyperaemia.

Axial Skeleton Manifestations of NF1

1. Orbit

- Sphenoid wing dysplasia (Fig. 9) is a characteristic (but not pathognomonic) feature of NF1. Classic radiological descriptions are hypoplasia of the greater and lesser wings of sphenoid, and anteroposterior enlargement of
the middle cranial fossa. Possible complication of a defect in the sphenoid wing is the herniation of temporal lobe into the posterior aspect of the orbit.

2. Chest Wall

-Thoracic skeletal abnormalities include ribbon-ribs deformity/thinned ribs and rib notching (Fig. 3).

3. Spine

- Spinal manifestations, such as scoliosis and kyphosis, are common in NF1. Scoliosis (Fig. 10) most commonly involves the lower cervical and upper thoracic spine, and can be divided into non-dystrophic or dystrophic types.
- The clinical and radiological features in the non-dystrophic type are similar to that of idiopathic scoliosis.
- Dystrophic scoliosis is characteristic of NF1, and evidence of skeletal dysplasia could be seen on plain radiographs. It is associated with additional kyphosis, and onset is earlier than in non-dystrophic cases. Four to six segments of vertebrae are typically involved, with other dystrophic features that include: vertebral scalloping, thinning of ribs or spindling of the transverse processes, wedging of one or more vertebral bodies, foraminal enlargement and defective pedicles.
- Another finding characteristic of NF1 in the spine is dural ectasia (Fig. 11), which is an expansion of the thecal sac. Dural ectasia may result in posterior vertebral scalloping and lateral thoracic meningocele formation (Fig. 12).
- The neurofibromas in the spine generally affect the dorsal nerve roots and are intradural extramedullary tumours, which can extend extradurally through the neural foramina, then appearing as "dumb-bell" or "hourglass" tumour.

**Appendicular Skeleton Manifestations of NF1**

- Approximately 2% of individuals with NF1 develop bowing of the long bones, particularly the tibia, and the bowing is typically anterolateral. Bowing may also be seen in the fibula or upper extremity but is less common.
- Pseudoarthrosis, a false joint, occurs due to non-union and abnormal osseous remodelling after a bowing fracture. Anterolateral bowing of the lower leg with subsequent pseudarthrosis (Fig. 13) is quite specific for NF1.
- Other findings in the appendicular skeleton in cases of NF1 include: atrophic, thinned or absent fibulas, radius and ulna; subperiosteal haemorrhage with abnormal easy detachment of the periosteum from the bone; intramedullary longitudinal streaks of increased density; multiple non-ossifying fibromas; focal gigantism in the form of a digit or an entire limb. Bone erosion from an adjacent neurofibroma can also be observed.
Fig. 1: Plexiform Neurofibroma. Coronal T2-weighted MRI of the cervicothoracic (left) and lumbar (right) spine shows multiple lobulated T2 hyperintense lesions along paravertebral sympathetic chains and nerve roots, in keeping with multiple neurogenic tumours. There is also plexiform neurofibroma which appears as a multi-lobulated T2 hyperintense mass at left cervical region (blue arrow).

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Fig. 2: Malignant Peripheral Nerve Sheath Tumour. Lateral radiograph (left) shows resorption of the middle part of fibula. Apparent soft tissue swelling with increase density is also noted at calf region. Post-gadolinium T1-weighted MRI image (right) shows a heterogeneously enhancing lesion at posterior compartment of left upper leg. A hypointense peripheral rim is also detected. Findings are in keeping with a malignant peripheral nerve sheath tumour.

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Fig. 3: Dermal Neurofibromas & Rib Notching. Chest radiograph shows inferior rib notching at right 3rd rib (blue arrow). Thoracolumbar scoliosis is also present. Note the multiple round and circumscribed soft tissue masses representing cutaneous neurofibromas.

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Fig. 4: Localised Neurofibroma. Selected sonographic images show well-defined hypoechoic lesions at the dermal (above) and superficial subcutaneous (below) layers, consistent with localised dermal neurofibromas.

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**Fig. 5:** Diffuse Neurofibroma. Ultrasound image shows an ill-defined hypoechoic lesion affecting the dermal layer with superficial extension to epidermal layer, in keeping with an early diffuse superficial neurofibroma. Doppler images (not shown) showed internal vascularity.

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Fig. 6: Plexiform Neurofibroma. Anterior thigh lesion with hypoechoic tubular and nodular structures at dermal and subcutaneous tissue layers, likely a plexiform neurofibroma.

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Fig. 7: Elephantiasis Neuromatosa. Radiographs of right elbow and forearm show gross diffuse increase in soft tissue. There are also features of a neuropathic elbow joint with joint dislocation, resorption of distal humerus, proximal ulna and radius, and presence of osseous debris. Wrist joint is also radially deviated and subluxed.

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Fig. 8: Elephantiasis Neuromatosa. Coronal CT angiogram of right upper limb in same patient as Fig. 7. It shows extensive amorphous soft tissue masses involving the whole right upper limb, compatible with plexiform neurofibromatosis. Multiple internal dysplastic vessels are present.

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Fig. 9: Sphenoid Wing Dysplasia. Coronal CT of the orbit in a 12 year old male patient shows dysplastic right greater wing of sphenoid, causing mild elevation of the medial aspect of the floor of right middle cranial fossa. A defect is seen at lateral aspect of right posterior orbital floor, through which orbital fat herniation is noted inferiorly.

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**Fig. 10:** Scoliosis. Presence of thoracolumbar scoliosis in the frontal and lateral radiographs of thoracic and lumbar spine. Dysplastic features are also noted at lower thoracic levels. They include wedging of the vertebrae and ill-definition of the pedicles, which could be due to defective formation.

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Fig. 11: Dural Ectasia. T2-weighted sagittal MRI image of thoracic spine shows dural ectasia, manifesting as enlargement of the thecal sac, posterior vertebral scalloping and enlargement of neural foramina.

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Fig. 12: Lateral Meningocele. T1-weighted coronal (above) and T2-weighted axial (below) MRI images at thoracolumbar junction show a homogenous, lobulated lesion following CSF signal intensity on all sequences at left paraspinal region, extending into the spinal canal and causing enlargement of left neural foramen, in keeping with a thoracic lateral meningocele. The spinal cord is displaced to the right.

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**Fig. 13:** Pseudoarthrosis. Frontal (above) and lateral (below) radiographs of the right leg show anterolateral bowing of the tibia. Old fracture at the thinned right fibula with pseudoarthrosis formation due to non-union.

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Conclusion

Neurofibromatosis type 1 is the most common phakomatosis and has a multi-faceted presentation, affecting multiple organ systems. Nearly all parts of the skeleton and surrounding soft tissues can be involved. Radiologists should be familiar with the different imaging manifestations of NF 1.
References
