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## PICTORIAL ESSAY

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# Musculoskeletal Manifestations of Neurofibromatosis Type 1: a Pictorial Review

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### ABSTRACT

*Neurofibromatosis type 1 (NF1) is a common neurocutaneous condition with an autosomal dominant pattern of inheritance. It affects multiple organ systems, and musculoskeletal abnormalities are seen in up to 50% of affected patients. Neurofibromas are the hallmark of NF1. Of the three types of neurofibromas (localised, diffuse, and plexiform), plexiform neurofibromas are pathognomonic of NF1. There is a lifetime risk (around 8% to 13%) for NF1 patients of developing malignant peripheral nerve sheath tumours from pre-existing neurofibromas. Plexiform neurofibromas may be associated with massive and disfiguring enlargement of an extremity, a condition referred to as elephantiasis neuromatosa. Dermal neurofibromas usually appear as circumscribed masses on plain radiographs and cross-sectional imaging. In the axial skeleton, NF1 can affect the orbit (sphenoid wing dysplasia), chest wall (ribbon ribs deformity/thinned ribs), or spine (non-dystrophic and dystrophic scoliosis, dural ectasia). One of the most common manifestations in the appendicular skeleton is anterolateral bowing of the tibia with formation of pseudarthrosis after bowing fracture. NF1 is the most common phakomatosis and affects 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 NF1.*

*Key Words: Neurocutaneous syndromes; Neurofibroma; Neurofibromatosis 1; Pseudarthrosis; Scoliosis*

## 中文摘要

### 1型神經纖維瘤病的肌肉骨骼表現：圖像綜述

葉筱筠、李芷茵、袁銘強

1型神經纖維瘤病（NF1）是一種常見神經皮膚病，具有常染色體顯性遺傳模式。它影響多器官系統，高達50%患者出現肌肉骨骼異常。神經纖維瘤是NF1的顯著特點。在三種類型的神經纖維瘤中（局限型、瀰漫型和叢狀型），叢狀神經纖維瘤是NF1的特殊病癥。NF1患者已存在神經纖維瘤發展為惡性外周神經鞘瘤的終生風險約8%至13%。叢狀神經纖維瘤可導致肢體的重度畸形性肥大，後者稱為神經瘤性象皮病。皮膚神經纖維瘤通常在平片和橫斷面成像上顯示圓形包裹的腫塊。在軸向骨骼中，NF1可影響眼眶（蝶骨翼變形）、胸壁（帶狀肋骨畸形 / 肋骨變薄）或脊柱（非發育性或發育性脊柱側凸、硬膜擴張）。附肢骨骼中最常表現之一是脛骨的前外側彎曲，並在弓形骨折後形

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成假關節。NF1是最常見的皮膚病且影響多個器官系統，幾乎牽涉所有骨骼部分和周圍軟組織。放射科醫生應熟悉NF1的不同影像學表現。

## INTRODUCTION

Neurofibromatosis type 1 (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.<sup>1</sup> 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 tumour formation in affected individuals.<sup>2</sup> The National Institutes of Health Consensus Development Conference has formulated the diagnostic criteria for NF1 (Table).<sup>3</sup>

NF1 affects multiple organ systems, and musculoskeletal abnormalities are seen in up to 50% of affected patients.<sup>1</sup> The distinctive feature of NF1 is neurofibromas. We discuss the different types of neurofibromas and their imaging features. The skin, soft tissue, and skeletal manifestations of this condition will also be described in this pictorial review.

## NEUROFIBROMAS – HALLMARKS OF NF1

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.

### Localised Neurofibroma

Localised neurofibromas are the most common type of neurofibroma, representing approximately 90% of

cases. The majority are solitary and not associated with NF1. Localised neurofibromas in NF1 patients more frequently involve large deep nerves (such as the sciatic nerve and brachial plexus) and are larger in size and usually multiple in number.<sup>4</sup>

Neurofibromas are well-defined soft-tissue masses on computed tomography (CT), and are low in attenuation and hypodense relative to muscle; the low attenuation is because of the high lipid content of myelin from Schwann cells. They show little or no contrast enhancement.<sup>5</sup>

On magnetic resonance imaging (MRI), neurogenic tumours are fusiform-shaped masses with tapered ends. They are of low-to-intermediate signal intensity on T1-weighted images and of high signal intensity on T2-weighted images. A characteristic target sign may be seen and consists of high signal intensity in the periphery and low signal intensity in the central region of the lesion.<sup>5</sup> This feature corresponds with pathological findings of peripheral myxoid material and central fibrous tissue (with high collagen content). Enhancement of neurofibromas are heterogeneous.

The split-fat sign, best appreciated on T1-weighted images, represents a rim of fat that surrounds the tumour. This sign is not specific to neurofibromas but is suggestive that the tumour originates in the intermuscular space, in which neurogenic tumours are the most frequent cause.<sup>5</sup>

### Diffuse Neurofibroma

Like localised neurofibromas, most diffuse neurofibromas occur in an isolated pattern; the incidence of neurofibromatosis among patients with diffuse neurofibroma has been reported to be approximately 10%. Children and young adults are more commonly affected, typically involving the skin and subcutaneous tissues of the head and neck. Diffuse neurofibromas are poorly defined lesions that spread along connective tissue septa. They surround rather than destroy adjacent normal structures.<sup>6</sup> Two different types of growth pattern have been described: plaque-like or infiltrative.

Most diffuse neurofibromas are isointense or mildly hyperintense in relation to muscle on T1-weighted

**Table.** Diagnostic criteria for neurofibromatosis type 1<sup>3</sup>

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Two or more of the following must be present:

1. Six or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
2. Two or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
3. Axillary or groin freckling
4. Optic pathway glioma
5. Two or more Lisch nodules (iris hamartomas seen on slit lamp examination)
6. Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis)
7. First-degree relative with neurofibromatosis type 1

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images, and hyperintense to muscle on T2-weighted images. Prominent internal vascularity of the lesion is a common finding, and diffuse neurofibromas often enhance intensely after intravenous gadolinium administration.<sup>6</sup>

### Plexiform Neurofibroma

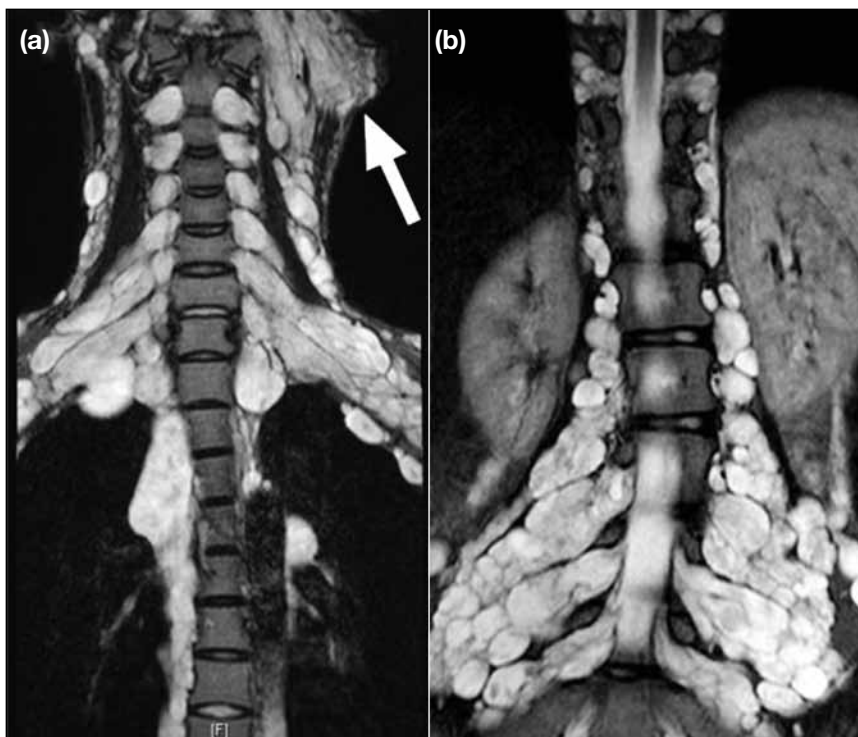
Plexiform neurofibromas (Figure 1) are essentially pathognomonic of NF1, affecting approximately 30% of patients, and development of these lesions usually precedes cutaneous neurofibromas. They usually involve a long segment of a major nerve trunk and extend into the nerve branches. Because of their large size, plexiform neurofibromas commonly extend beyond the epineurium into the surrounding tissue.<sup>4</sup>

CT of plexiform neurofibromas reveals large multilobulated low-attenuation masses, usually within a major nerve distribution. MRI shows large conglomerate masses comprised of numerous neurofibromas. The involved nerve is diffusely thickened and there is often extension into the nerve branches. Plexiform neurofibromas have a characteristic ring-like or separated pattern that represents their complex fascicular arrangement. This pattern is best observed on T2-weighted images and contrast-enhanced T1-weighted images.<sup>7</sup>

### Malignant Peripheral Nerve Sheath Tumour

The lifetime risk of developing malignant peripheral nerve sheath tumours (MPNSTs; Figure 2) in NF1 is around 8% to 13% and occurs predominantly in individuals aged 20 to 35 years.<sup>2</sup> MPNSTs usually arise in pre-existing plexiform neurofibromas. Sudden increase in size of a previously stable neurofibroma, new onset of pain, or neurological symptoms of motor weakness and sensory deficits should raise the suspicion of malignant transformation.<sup>4</sup>

MPNSTs most commonly involve major nerve trunks including the sciatic nerve, brachial plexus, and sacral plexus.<sup>4</sup> Several MRI features have been identified that can help distinguish MPNSTs from neurofibromas. They include increased largest dimension of the mass, peripheral enhancement pattern, perilesional oedema, intratumoural cystic lesion, and heterogeneity on T1-weighted images.<sup>8</sup> On positron emission tomography, MPNSTs are fluorodeoxyglucose-avid masses. Although benign nerve sheath tumours can also have mildly increased fluorodeoxyglucose uptake, uptake in MPNSTs is usually higher than in benign neurogenic tumours (mean maximum standardised uptake value 8.5 in MPNSTs, vs 1.5 in benign nerve sheath tumours).<sup>9</sup>



**Figure 1.** Plexiform neurofibroma. Coronal T2-weighted magnetic resonance imaging of (a) the cervicothoracic and (b) the lumbar spine showing multiple lobulated T2 hyperintense lesions along paravertebral sympathetic chains and nerve roots, in keeping with multiple neurogenic tumours. There is also plexiform neurofibroma that appears as a multilobulated T2 hyperintense mass at the left cervical region (arrow) in image a.



**Figure 2.** Malignant peripheral nerve sheath tumour. Patient with known neurofibromatosis type 1 presenting with a left calf mass that has increased in size and associated with pain. (a) Lateral radiograph showing resorption of the middle part of the fibula. Apparent soft tissue swelling with increased density is also noted at calf region. (b) Post-gadolinium T1-weighted magnetic resonance image showing a heterogeneously enhancing lesion at the posterior compartment of the left upper leg, with predominantly peripheral enhancement. (c) On T2-weighted image, ill-defined oedema is seen extending into adjacent muscles at the posterior compartment of the left leg. Findings are consistent with a malignant peripheral nerve sheath tumour.

Imaging is not entirely reliable in differentiating a benign lesion from MPNST; the most common imaging finding for a MPNST is a non-specific soft tissue mass. If the lesion does not have distinctive imaging findings, but clinical features are suspicious of malignancy, a carefully planned biopsy should be obtained.<sup>5</sup>

### SKIN AND SOFT TISSUE MANIFESTATIONS OF NF1

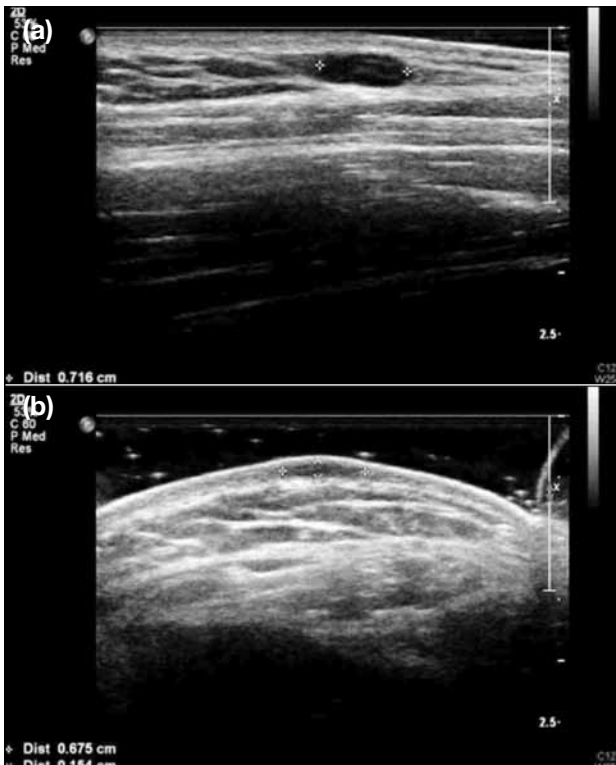
Dermal neurofibromas begin to appear around early childhood and puberty subsequent to the detection of cafe au lait spots. They appear as circumscribed masses on plain radiographs and on cross-sectional imaging (Figure 3).<sup>1</sup> Ultrasound is useful in differentiating dermal neurofibromas into localised, diffuse, or plexiform subtypes (Figures 4 to 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 subcutaneous tissues, occasionally also affecting the surface of underlying muscle. Most of these lesions show increased vascularity on 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

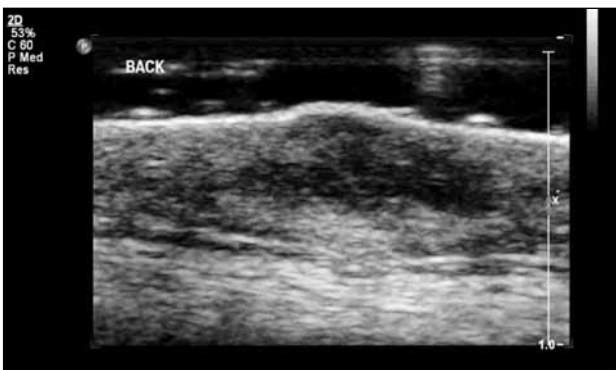


**Figure 3.** Dermal neurofibromas and rib notching. Chest radiograph showing inferior rib notching at right third rib (arrow). Thoracolumbar scoliosis is also present. Note the multiple round and circumscribed soft tissue masses representing cutaneous neurofibromas.

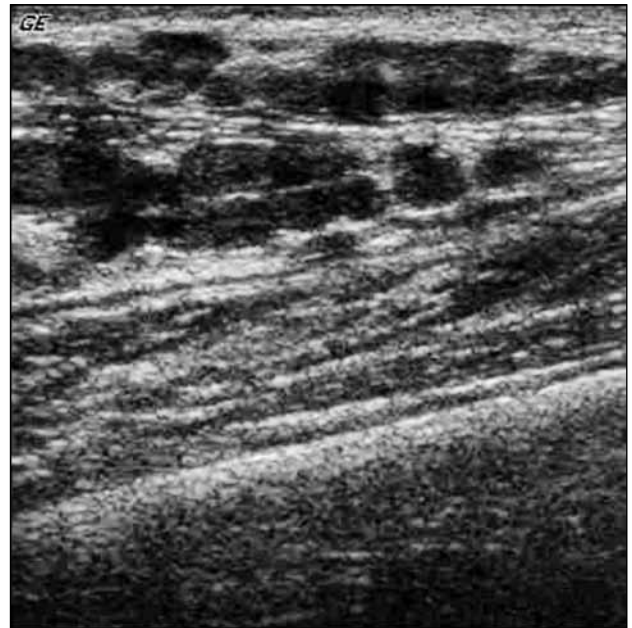
and the condition is called elephantiasis neuromatosa (Figures 7 and 8). It can be accompanied by osseous hypertrophy related to chronic hyperaemia.<sup>4</sup>



**Figure 4.** Localised neurofibroma. Selected sonographic images showing well-defined hypoechoic lesions at the (a) superficial subcutaneous and (b) dermal layers, consistent with localised dermal neurofibromas.



**Figure 5.** Diffuse neurofibroma. Ultrasound image showing 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.



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



**Figure 7.** Elephantiasis neuromatosa. Radiographs of right elbow and forearm showing 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.

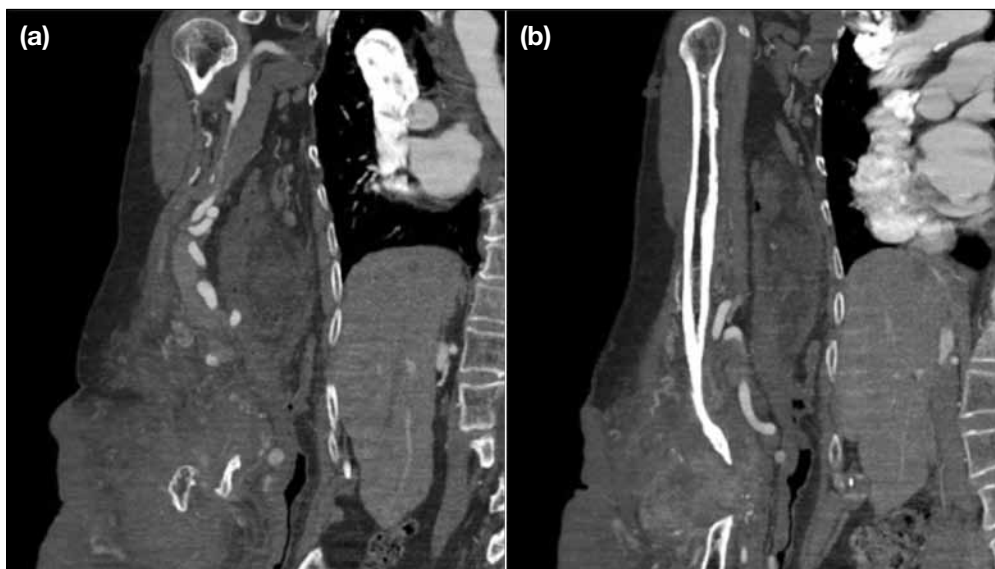
## SKELETAL MANIFESTATIONS OF NF1

### Axial Skeleton

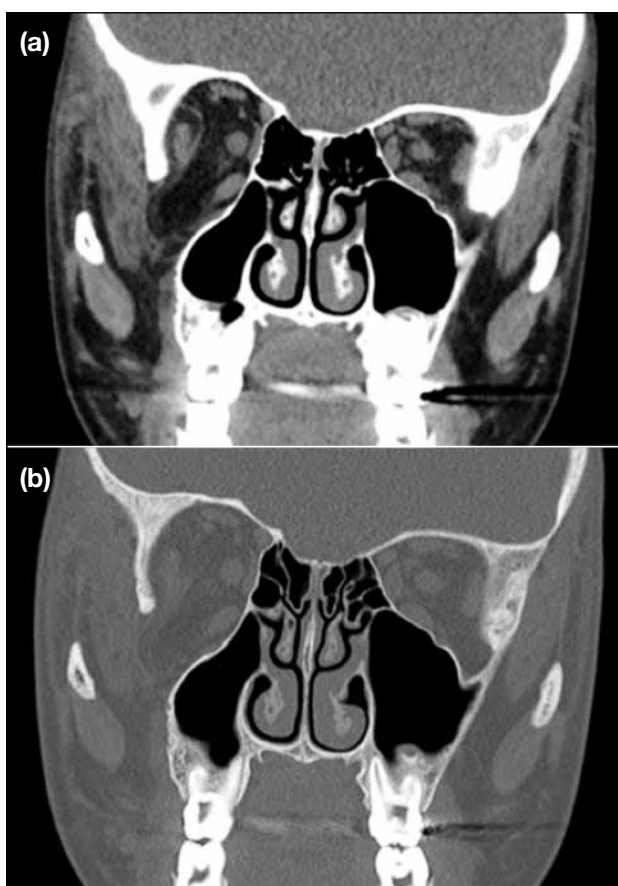
#### Orbit

Sphenoid wing dysplasia (Figure 9) is a characteristic (but not pathognomonic) of NF1. The bony changes have been attributed to mesodermal dysplasia although

the deformities also occur frequently with an optic nerve glioma or orbital plexiform neurofibroma.<sup>1,10</sup> 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 herniation of the temporal lobe into the posterior aspect of the orbit.



**Figure 8.** Elephantiasis neuromatosa. Coronal computed tomography angiogram of right upper limb in the same patient as Figure 7, showing extensive amorphous soft tissue masses involving the whole right upper limb, compatible with plexiform neurofibromatosis. Multiple internal dysplastic vessels are present.



**Figure 9.** Sphenoid wing dysplasia. Coronal computed tomography of the orbit in (a) soft tissue and (b) bone windows in a 12-year-old male patient showing 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 the lateral aspect of the right posterior orbital floor, through which orbital fat herniation is noted inferiorly.

### *Chest Wall*

Thoracic skeletal abnormalities include ribbon ribs deformity/thinned ribs and rib notching (Figure 3). They can be caused by extrinsic compression by neurofibromas of the intercostal nerves that produces cortical erosion of the lower borders of the ribs, or occur as a consequence of primary dysplastic defects in bone formation.<sup>11</sup>

### *Spine*

Spinal manifestations, such as scoliosis and kyphosis, are common in NF1. The true prevalence of spinal deformity is unknown, with figures in the literature ranging from 2% to 69%.<sup>12</sup> Scoliosis most commonly involves the lower cervical and upper thoracic spine (Figure 10) and can be non-dystrophic or dystrophic.<sup>2</sup>

The clinical and radiological features in the non-dystrophic type are similar to those of idiopathic scoliosis. Dystrophic scoliosis is characteristic of NF1, and evidence of skeletal dysplasia can be seen on plain radiographs. It is associated with additional kyphosis, and onset is earlier than in non-dystrophic cases.<sup>2</sup> 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.<sup>12,13</sup> Dystrophic scoliosis is rapidly progressive and may require early spinal fusion.<sup>2</sup>

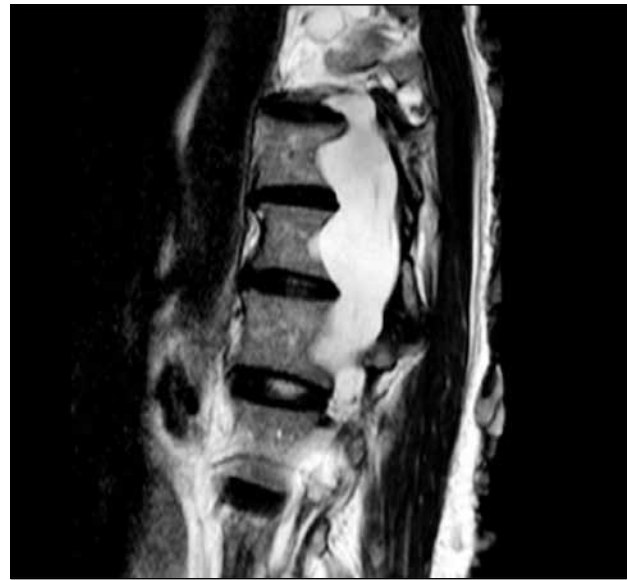
Another characteristic finding of NF1 in the spine is dural



**Figure 10.** Scoliosis. Presence of thoracolumbar scoliosis in the (a) frontal and (b) 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 that may be due to defective formation.

ectasia (Figure 11). It is an expansion of the thecal sac, and its formation may be a consequence of primary bone dysplasia. Dural ectasia may result in posterior vertebral scalloping and lateral thoracic meningocele formation (Figure 12) that can lead to destabilisation of the vertebrae with spontaneous subluxation or dislocation.<sup>12</sup> Posterior vertebral scalloping is diagnosed when the depth of scalloping exceeds 3 mm in the thoracic spine, or more than 4 mm in the lumbar spine.<sup>1</sup>

Neurofibromas in the spine generally affect the dorsal nerve roots and are intradural extramedullary tumours that can extend extradurally through the neural foramina, then appearing as 'dumb-bell' or 'hourglass' tumours.<sup>13</sup>



**Figure 11.** Dural ectasia. T2-weighted sagittal magnetic resonance image of thoracic spine showing dural ectasia, manifesting as enlargement of the thecal sac, posterior vertebral scalloping and enlargement of neural foramina.

### Appendicular Skeleton

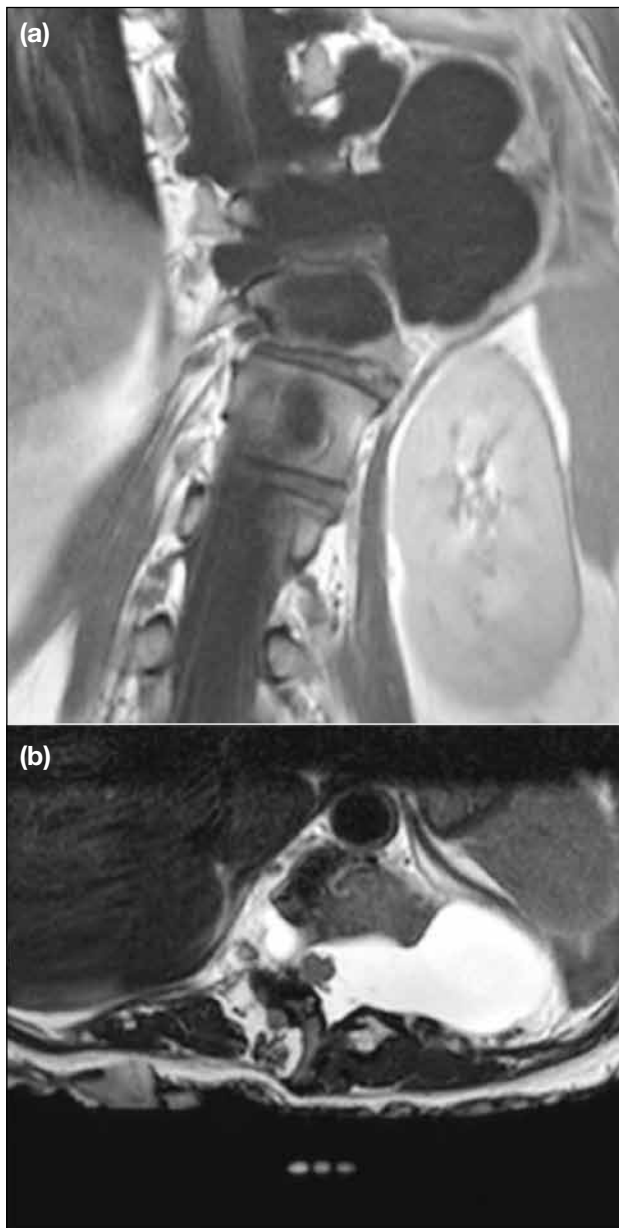
Approximately 2% of individuals with NF1 develop bowing of the long bones, particularly the tibia.<sup>2</sup> It is caused by an intrinsic defect in bone formation and is usually apparent in the first year of life. The bowing of the tibia is typically anterolateral. Bowing may also be seen in the fibula or upper extremity but is less common.

Pseudarthrosis, 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 is quite specific for NF1 (Figure 13), and in and of itself should alert the physician to the potential diagnosis.<sup>14</sup> Such skeletal findings may precede the emergence of neurofibromas.

Other findings in the appendicular skeleton 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; and focal gigantism in the form of a digit or an entire limb.<sup>15</sup> Bone erosion from an adjacent neurofibroma can also be observed.

### CONCLUSION

NF1 is the most common phakomatosis and has a multifaceted presentation, affecting multiple organ



**Figure 12.** Lateral meningocele. (a) T1-weighted coronal and (b) T2-weighted axial magnetic resonance images at thoracolumbar junction showing a homogenous, lobulated lesion following cerebrospinal fluid 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.

systems. It is a mesodermal dysplasia, and nearly all parts of the skeleton and surrounding soft tissues can be involved. Radiologists should be familiar with the different imaging manifestations of NF1.



**Figure 13.** Pseudarthrosis. (a) Frontal and (b) lateral radiographs of the right leg showing anterolateral bowing of the tibia. Old fracture at the thinned right fibula with pseudarthrosis formation due to non-union.



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