Skeletal Radiology (2022) 51:747–762
https://doi.org/10.1007/s00256-021-03870-0

REVIEW ARTICLE

Update on the imaging features of the enchondromatosis syndromes

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Received: 13 March 2021 / Revised: 12 July 2021 / Accepted: 14 July 2021 / Published online: 24 July 2021

Abstract
Ollier disease and Maffucci syndrome are the commonest enchondromatosis subtypes, arising from non-hereditary mutations in the *IDH1* and *IDH2* genes, presenting in childhood and being characterised by multiple enchondromas. Maffucci syndrome also includes multiple soft tissue haemangiomas. Aside from developing bony masses, osseous deformity and pathological fracture, ~ 40% of these patients develop secondary central chondrosarcoma, and there is increased risk of non-skeletal malignancies such as gliomas and mesenchymal ovarian tumours. In this review, we outline the molecular genetics, pathology and multimodality imaging features of solitary enchondroma, Ollier disease and Maffucci syndrome, along with their associated skeletal complications, in particular secondary chondrosarcoma. Given the lifelong risk of malignancy, imaging follow-up will also be explored. Metachondromatosis, a rare enchondromatosis subtype characterised by enchondromas and exostoses, will also be briefly outlined.

Keywords Enchondromatosis · Ollier disease · Maffucci syndrome · Enchondroma · Chondrosarcoma

Introduction

Solitary enchondromas are benign central chondrogenic neoplasms exhibiting hyaline cartilaginous differentiation with a predilection for the metadiaphysial regions of the short and long tubular bones of the hands, feet and limbs [1, 2]. They are the second commonest benign chondrogenic tumours following osteochondroma, representing 3–17% of all primary bone tumours in a large biopsy series [2–5]. The true prevalence of enchondromas is likely underestimated, as these lesions tend to be asymptomatic and present as incidental findings in the 3rd–4th decades of life with no gender predilection [2]. The true rate of malignant transformation of solitary enchondroma to secondary central chondrosarcoma (CS) is unknown but has been estimated at 4.2% [6, 7]. Conversely, malignant transformation occurs in ~ 40% of patients with enchondromatosis syndromes [1, 2], and such patients are on average 10–15 years younger than those with primary CS [8]. Ollier and Maffucci syndrome are the commonest enchondromatosis subtypes and will be explored in detail in this article, along with an overview of metachondromatosis. The remaining enchondromatosis syndromes are extremely rare and beyond the scope of this review.

Molecular genetics

Superti-Furga et al. suggested that enchondromatosis syndromes could be classified according to their underlying molecular defects [9]. Both Ollier disease and Maffucci syndrome are mosaic disorders caused by non-hereditary mutations in *IDH1* and *IDH2*, resulting in a mosaic phenotype. Mutations in these genes are present in ~ 85% of enchondromas. Different non-synonymous single nucleotide variant mutations have also been described, including *IDH1* p.R132C, *IDH1* p.R132H, *IDH1* p.R132G and very rarely *IDH2* p.R172S. In patients with Maffucci syndrome, only the *IDH1* p.R132C genotype is present [10].

Analysis of the genomics of different tumours from the same patient demonstrates that identical mutations are present in 95% of cases, and the same mutations can also be seen in normal tissues (e.g. blood), indicating somatic mosaicism (a somatic mutation acquired early in development, i.e. post-zygotic, leading to a mosaic phenotype) [11].

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Thus, these alterations are acquired early in development, rather than representing inherited germline mutations. At the molecular level, mutations in *IDH1/2* result in intra-cellular accumulation of D-2-hydroxyglutarate, an oncometabolite, which then acts as an inhibitor of α-KG dependent dioxygenases, involved in DNA and histone demethylation [12]. Other somatic mutations, in addition to those in *IDH1/2*, have been seen in chondrosarcoma, including *COL21A1*, *TP53*, *RB1* and genes involved in the Sonic Hedgehog signalling pathway [13].

Other forms of enchondromatosis are described and associated with germline (as opposed to post-zygotic somatic mutations in the case of *IDH1* and *IDH2*) mutations in other genes, for example metachondromatosis (*PTPN11* mutations) [14].

Interestingly, 50% of primary central atypical cartilaginous tumours (ACT)/central chondrosarcoma grade I (Gd I CS), and 50% of grades II and III CS share the same mutations in IDH1 and IDH2 [15], which suggests progression from enchondroma and ACT/Gd I CS to higher grade disease [15].

In Maffucci syndrome, 70% of spindle cell haemangiomas are associated with mutations in *IDH1* and more rarely *IDH2*, a finding not identified in other benign vascular neoplasms [16]. These are benign vascular tumours with a propensity for local recurrence, characterised by ectatic vascular spaces lined by bland endothelial cells with an associated spindle cell component. The spindle cells are slender and tapering, and epithelioid areas may also be identified. This histological feature may assist in the important distinction from Kaposi sarcoma. Additionally, there is no significant cytological atypia [16].

Histopathological features

The histopathological features of both enchondroma and central ACT/central Gd I CS, chondrosarcoma grades II and III are similar to those arising in non-syndromic individuals, but with some important differences as outlined below.

Enchondroma

Enchondromas are hypocellular and composed of oval chondrocytes with a closed chromatin pattern embedded in a hyaline matrix, and host bone permeation is not identified. Enchondromas occurring in the syndromic setting of Ollier disease and Maffucci syndrome often have a higher degree of cellularity than those seen in sporadic tumours, and taken in isolation, this feature cannot be used to make a definitive diagnosis of ACT/Gd I CS. For this, other factors such as the presence of host bone permeation (characterised by host lamellar bone surrounded by tumour with features of tumour-induced osteolysis and formation of Howship's lacunae), destruction of the bony cortex and extra-osseous extension are required. Correlation with the radiological impression is also important in making this often challenging distinction.

Central ACT/grade I chondrosarcoma and high-grade chondrosarcoma

Central ACT/Gd I CS is associated with a higher degree of cellularity than that seen in enchondroma [15]. There is also more cytological atypia, and importantly, host bone permeation and destruction are present. Significantly, central ACT is regarded as an intermediate grade locally aggressive chondrogenic tumour, rather than a sarcoma in the WHO 2020 classification [17].

CS grade II is associated with a higher degree of cellularity, spindling of the chondrocytes, an open chromatin pattern and conspicuous nucleoli, and the matrix is more myxoid in quality. Chondrosarcoma grade III has an even higher degree of cellularity and cytological atypia, and mitoses are increasingly conspicuous (> 2/10HPF). Dedifferentiated chondrosarcoma is a high-grade subtype of chondrosarcoma, which has a bi-morphic histologic appearance with a conventional chondrosarcomatous component and an abrupt transition to a high-grade, non-cartilaginous sarcoma [17].

Ollier disease

Ollier disease is the commonest enchondromatosis subtype, with an estimated prevalence of 1:100,000 (18), and affects both sexes equally [1]. Some authors make a distinction between Ollier disease and enchondromatosis on the basis of distribution of enchondromas. Ollier disease is defined by multiple (3 or more) asymmetrically distributed enchondromas either exclusively or predominantly involving one side of the body [19], although bilateral, asymmetrically distributed disease also occurs [9, 18, 20]. The term 'enchondromatosis' has also been used to describe more symmetric distribution of enchondromas. For the purpose of this review, Ollier disease and enchondromatosis are used interchangeably. The tubular long bones are most commonly involved, namely the femur, tibia, humerus and fibula, which are typically shortened and deformed [20]. The small tubular bones of the hands and feet and the flat bones of the pelvis may also be involved. Involvement of the ribs [21], spine and skull is rare but possible [9].

Patients with Ollier disease present in childhood, with the number and size of enchondromas increasing until skeletal maturity [22, 23]. Patients can present with pathological fracture, palpable painless bony masses, osseous deformity such as asymmetric upper or lower limb shortening and

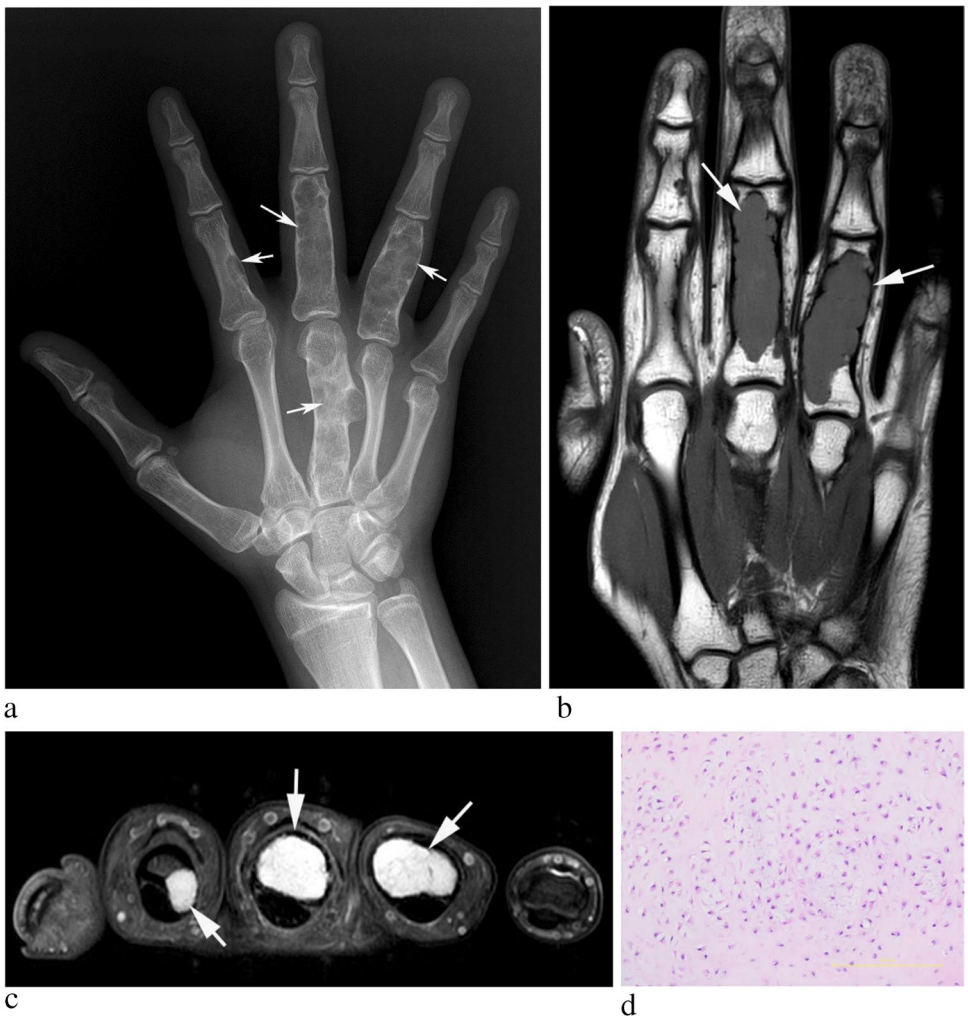

Fig. 1 A 16-year-old boy with Ollier disease. **a** Dorso-palmar radiograph of the right hand showing multiple lytic lesions (arrows) expanding the middle finger metacarpal and index, middle and ring finger proximal phalanges. There is no appreciable chondroid matrix mineralisation. **b** Coronal T1W TSE and **c** axial SPAIR MR images show well-defined central enchondromas with homogeneous intermediate T1W SI (arrows-**b**) and heterogeneous hyperintensity on the fat suppressed sequence (arrows-**c**). **d** (H&E × 20). Enchondroma arising in the setting of Ollier disease. Note a higher degree of cellularity compared to simple enchondroma, which can represent a diagnostic pitfall. However, there is no significant cytological atypia, and host bone permeation is not identified

asymmetric/varying finger lengths, joint malalignment and reduced joint mobility [18, 22]. Growth arrest, deformity and angulation occur in the upper and lower limbs, which may require surgery [24]. Initial diagnosis can also be made on imaging as an incidental finding [24].

Approximately 30–40% of cases undergo sarcomatous transformation to CS [1, 20], this occurring in adulthood and most frequently in the long tubular and flat bones. In addition, multifocal malignant transformation has been reported in both Ollier disease and Maffucci syndrome [8, 20]. Patients with Ollier disease are at further risk of non-skeletal malignant lesions such as gliomas and ovarian mesenchymal tumours, while non-small cell lung cancer and leukaemia have also been described [1, 25].

Maffucci syndrome

Maffucci syndrome is an extremely rare disease, fewer than 200 cases having been reported worldwide [26]. It is usually diagnosed in the first decade of life and often at birth [27]. It is characterised by the presence of multiple enchondromas combined with multiple haemangiomas which are most commonly of a spindle cell type, these having malignant potential to transform into secondary CS and angiosarcoma, respectively [27–29]. The haemangiomas are usually found in the upper extremity (particularly the hands), followed by the lower extremity and axial skeleton [30]. These appear as areas of bluish discolouration which blanch on pressure [31]. Vascular anomalies have also been described in the meninges, tongue, oral mucosa and visceral organs [30].

Maffucci syndrome has a higher reported risk of malignant transformation than Ollier disease [20, 32, 33], although one recent study found no difference [30]. The average age for neoplastic change from enchondroma to CS in Maffucci syndrome is 40 years [34], while a further study found the average age at first surgery for CS in Maffucci syndrome was 30 years [20]. Similar to Ollier disease, patients with Maffucci syndrome are susceptible to the development of extra-skeletal malignant lesions such as gliomas, astrocytomas, mesenchymal ovarian tumours, cholangiocarcinoma, pancreatic adenocarcinoma and hepatocellular carcinoma [10,

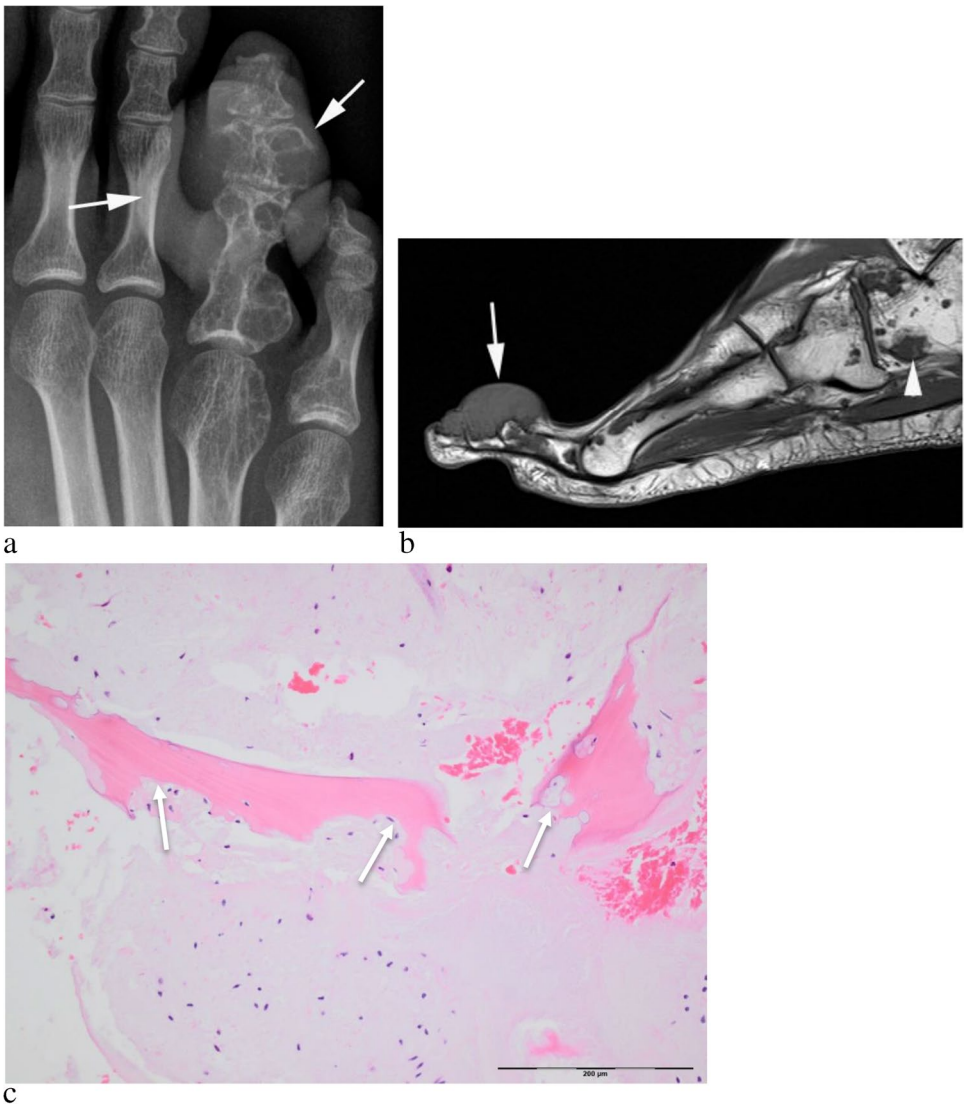

Fig. 2 A 29-year-old male with Ollier disease. **a** Dorso-plantar radiograph and **b** sagittal T1W TSE MR image of the right foot showing multiple lobular lytic lesions expanding the fourth toe metatarsal head and phalanges. A large extra-medullary mass (arrows) arising from the middle phalanx proved to be an atypical cartilaginous tumour. There are also multiple small enchondromas in the tarsal bones (arrowhead-**b**). **c** (H&E×20). Atypical cartilaginous tumour. A cartilaginous tumour composed of chondrocytes with a closed chromatin pattern, but displaying definite host bone permeation with formation of Howship's lacunae (arrows)

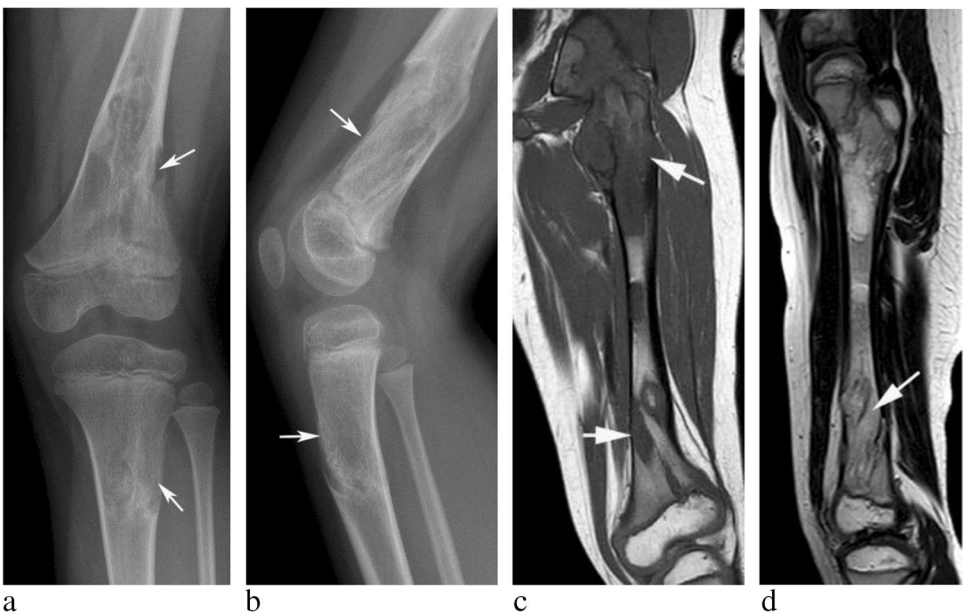

Fig. 3 A 4-year-old girl with Ollier disease. **a** AP and **b** lateral radiographs of the left knee demonstrate mild expansion and deformity of the distal femoral and proximal tibial metaphyses by poorly defined elongated lytic lesions (arrows) extending from the growth plates. **c** Coronal T1W TSE and **d** sagittal T2W FSE MR images demonstrate multiple intra-medullary chondral tumours (arrows) in the proximal and distal femoral metaphyses

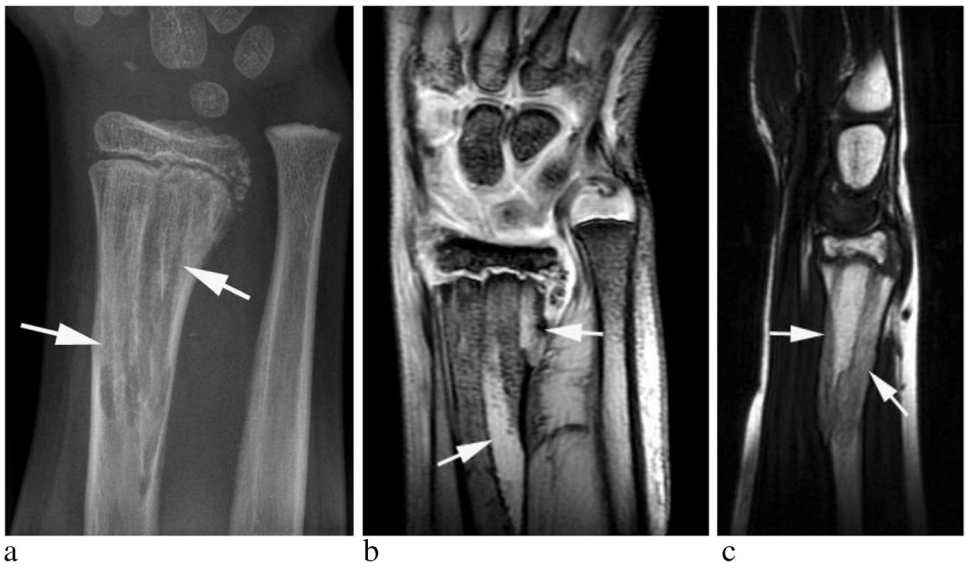

Fig. 4 A 9-year-old boy with Ollier disease. **a** AP radiograph, **b** coronal T2*W GrE and **c** sagittal T2W FSE MR images of the distal forearm show multiple elongated chondral tumours (arrows) extending from the distal radial growth plate into the metaphysis

20, 26, 30]. Intracranial lesions occur in 5–10% of patients with Ollier disease and Maffucci syndrome, which includes skull base CS, glial tumours and various non-sarcomatous lesions [35, 36].

Verdegaal et al. [17] and El Abiad et al. [27] found that unlike in Ollier disease, enchondromas were bilateral in Maffucci syndrome. For both Ollier disease and Maffucci syndrome, Verdegaal et al. also identified 3 patterns of distribution of enchondromas. In group I (18%), only the hands and/or feet were affected. In group II (40%), enchondromas were located in the long tubular bones and/or the flat bones. In group III (42%), both the long and flat bones, as well as the small tubular bones of the hands and/or feet, were involved [20].

Ollier and Maffuci syndrome are diagnosed based on clinical, radiological and histological evaluation [20]. El Abiad et al. [27] and Ahmed et al. [34] recommended whole-body magnetic resonance imaging (WB-MRI)/magnetic resonance angiography (MRA) at the time of diagnosis to assess for chondral lesions and vascular anomalies in visceral organs. They also advocated gene sequencing at the time of diagnosis.

As yet, there is no specific curative treatment available for these syndromes. Surgical therapy is available when complications occur such as pathological fracture, growth defects/

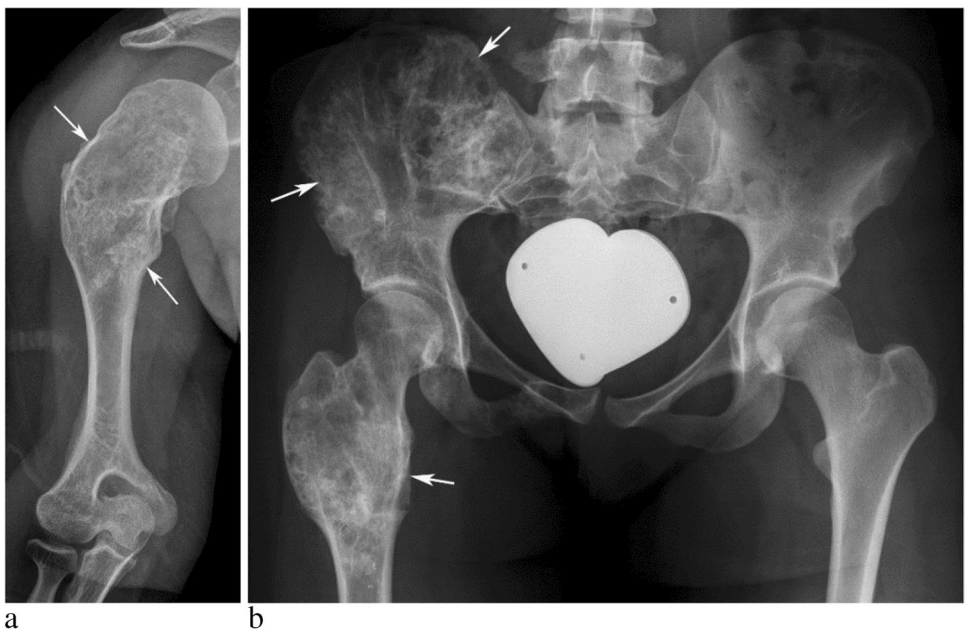

Fig. 5 A 25-year-old female with Ollier disease. **a** AP radiograph of the right arm demonstrates prominent expansion and deformity of the proximal humeral shaft together with multiple areas of ring-like chondroid matrix calcification (arrows). **b** AP radiograph of the pelvis and hips shows extensive involvement of the right ilium and proximal femur (arrows)

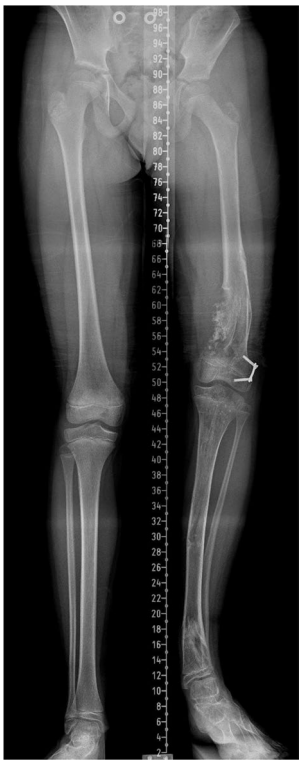

Fig. 6 An 11-year-old boy with Ollier disease. Long leg radiograph demonstrates involvement of the left femur and tibia with consequent leg length discrepancy and metaphyseal bowing

deformities or malignant transformation [20]. Leg lengthening procedures can be performed for leg length discrepancy, while osteotomy and debulking surgery or amputation can be performed to correct disabling enlargement of the fingers and toes [20]. Disease-related mortality rate for Ollier disease and Maffucci syndrome was found to be 6.8% in a study of 161 patients, the majority of deaths being due to CS and related complications, while a small number of deaths were due to other malignancies [20].

Imaging features

Solitary enchondroma

The radiographic appearance of enchondromas is variable depending upon the location and extent of calcification [38]. Radiographs of enchondromas in the small bones of the hands and feet demonstrate a well-demarcated lobular lytic lesion typically centrally located in the metaphysis and diaphysis [2, 18]. There is usually associated endosteal scalloping, which can be quite deep and extensive in this region [2]. A chondroid matrix with ring and arc, flocculent or stippled calcification can be difficult to appreciate in enchondromas of the hands and feet. Cortical expansion and thickening may be present, but cortical disruption and periosteal reaction should not be seen unless there is an associated pathological fracture [2]. Enchondromas of the long tubular bones tend to be centrally or eccentrically located, well-defined lytic lesions in the metaphysis or diaphysis, measuring < 5 cm longitudinally [2, 39]. There is associated evenly distributed chondroid matrix calcification [2, 25, 38, 40], and shallow endosteal scalloping (< 1/3 cortical thickness and along < 1/3 of the lesion extent) with minor cortical thickening may be demonstrated [2, 39].

There have been reports of solitary enchondroma in the pubic rami [41, 42], which appear purely lytic with slight fusiform expansion of the bone, thinning of the cortex, and a well-defined zone of transition without a sclerotic margin [41]. Calcification, soft tissue mass and cortical destruction should not be present, and lesions should measure no more than 3–5 cm in size [2, 40, 41, 43].

Enchondromas in Ollier disease *and* Maffucci syndrome

In Ollier disease and Maffucci syndrome, enchondromas are initially located close to the growth plate cartilage and migrate progressively towards the metaphysis or diaphysis with skeletal growth (Fig. 1). The epiphyseal region adjacent to the affected metaphysis may demonstrate irregularities [18]. However, 10% of enchondromas may be located within the epiphysis. Surface lesions known as periosteal chondromas can also occur in enchondromatosis syndromes [44, 45], these being eccentric and sub-periosteal with distinct cortical defects (Fig. 2) [38].

Radiographs typically demonstrate multiple linear or pillar-shaped radiolucent, homogeneous oval or elongated lesions with a thin rim of radiodense bone. These run parallel to the long axis of the bone from the metaphysis to diaphysis, are most typically seen in the skeletally immature and are common in Ollier disease and Maffucci syndrome (Figs. 3 and 4) [18, 46–48]. With time, these lesions demonstrate stippled or punctate calcification. Enchondromas are frequently assembled as clusters resulting in asymmetric enlargement and flaring of the metaphysis (Fig. 5) [18, 49]. Bone erosion and/or hypertrophy of the cortical surface can be observed (Fig. 2a) [48]. Enchondromas result in severe growth abnormalities, with the affected diaphysis being short, enlarged and possibly demonstrating bending close to the metaphysis (Figs. 5a and 6) [18], and pathological fracture may occur. Despite reports of enchondromas occurring in the flat bones of patients with enchondromatosis (Figs. 5b and 7), the imaging appearances are not well-described.

Radiographs of the hands and feet are often pathognomonic and demonstrate multiple well-demarcated radiolucent lesions with expansile remodelling of the affected bone, thinning of the cortex and endosteal scalloping (Figs. 1 and 2). Chondroid matrix mineralisation may be present [34], while patients with Maffucci syndrome may demonstrate multiple small round calcifications in the soft tissues due

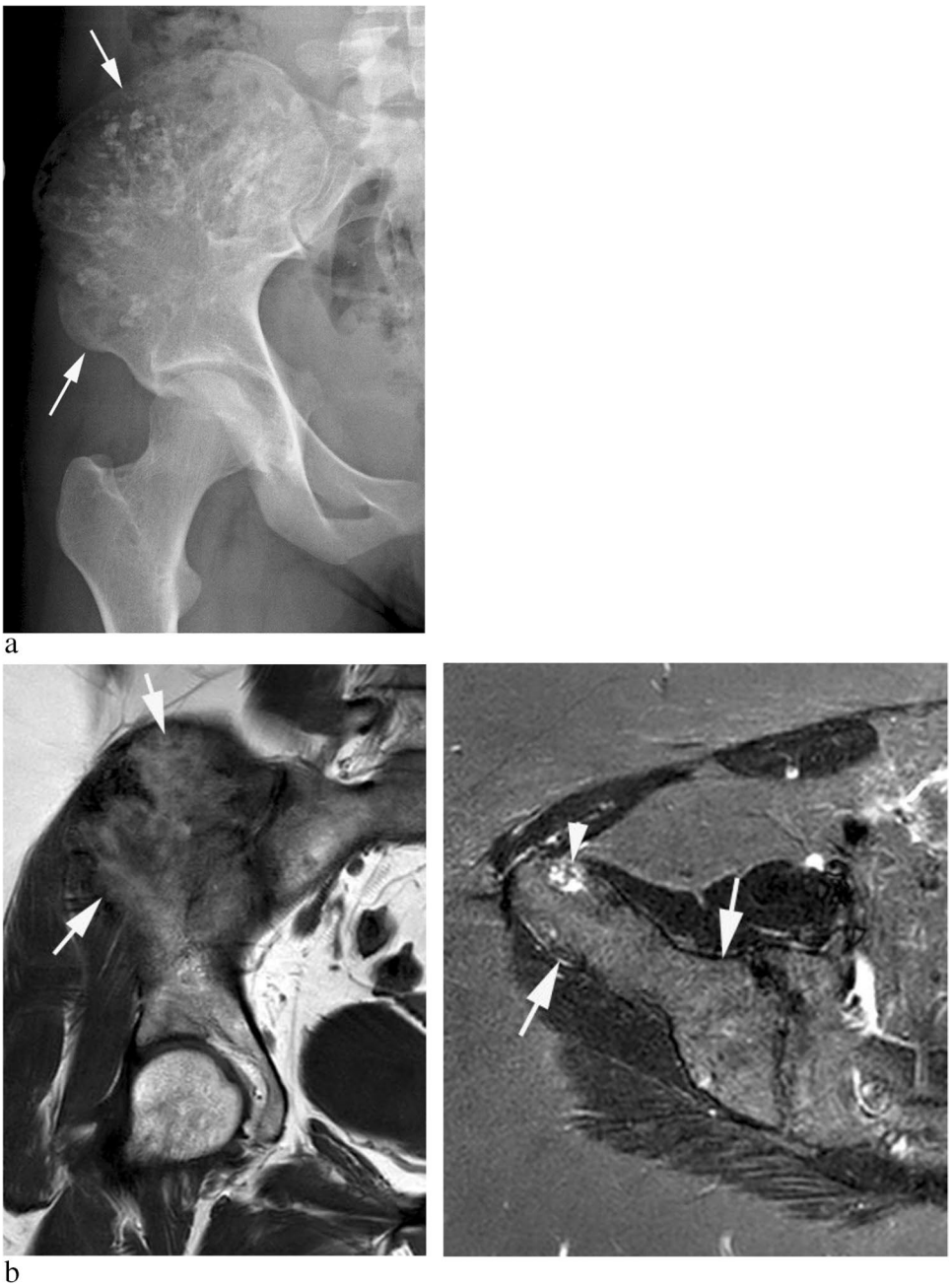

Fig. 7 A 15-year-old female with Ollier disease. **a** AP radiograph of the right hemipelvis demonstrates generalised enlargement of the right ilium (arrows) which contains multiple foci of punctate calcification consistent with chondroid matrix mineralisation. **b** Coronal T1W TSE and **c** axial STIR MR images confirm the bony enlargement (arrows) and also small islands of chondral tissue (arrowhead-**b**)

to phleboliths within vascular malformations (Fig. 8) [27, 31, 34].

Computed tomography (CT) is superior to radiography in detecting matrix mineralisation, the pattern of calcification and lesion margins [35]. CT is especially helpful in assessing suspected enchondromas in complex areas of anatomy such as the pelvis [2, 25]. CT can better assess the extent of endosteal scalloping [2], the presence of an associated soft tissue mass and complications such as pathological fracture with associated haematoma, or secondary CS [38]. Multiplanar reconstructed CT can be used for surgical planning in patients with enchondromatosis syndromes.

On MRI, enchondromas appear as lobular chondral islands of variable size surrounded by marrow fat. The cartilage islands are of low-to-intermediate signal intensity (SI) on T1-weighted (T1W) sequences (Figs. 1b, 2b, 3c and 7b) and hyperintense on T2W and fat suppressed T2W or short tau inversion recovery (STIR) sequences (Figs. 1c, 3d, 4b, c and 7c). Foci of hyperintense T1W SI representing marrow fat are typically demonstrated within and around the cartilage islands [2, 50], while intra-lesional hypointense linear SI may be demonstrated on T2W images representing fibrous septa [39]. Focal areas of hypointense SI on T1W and T2W sequences may also be seen, representing chondroid matrix

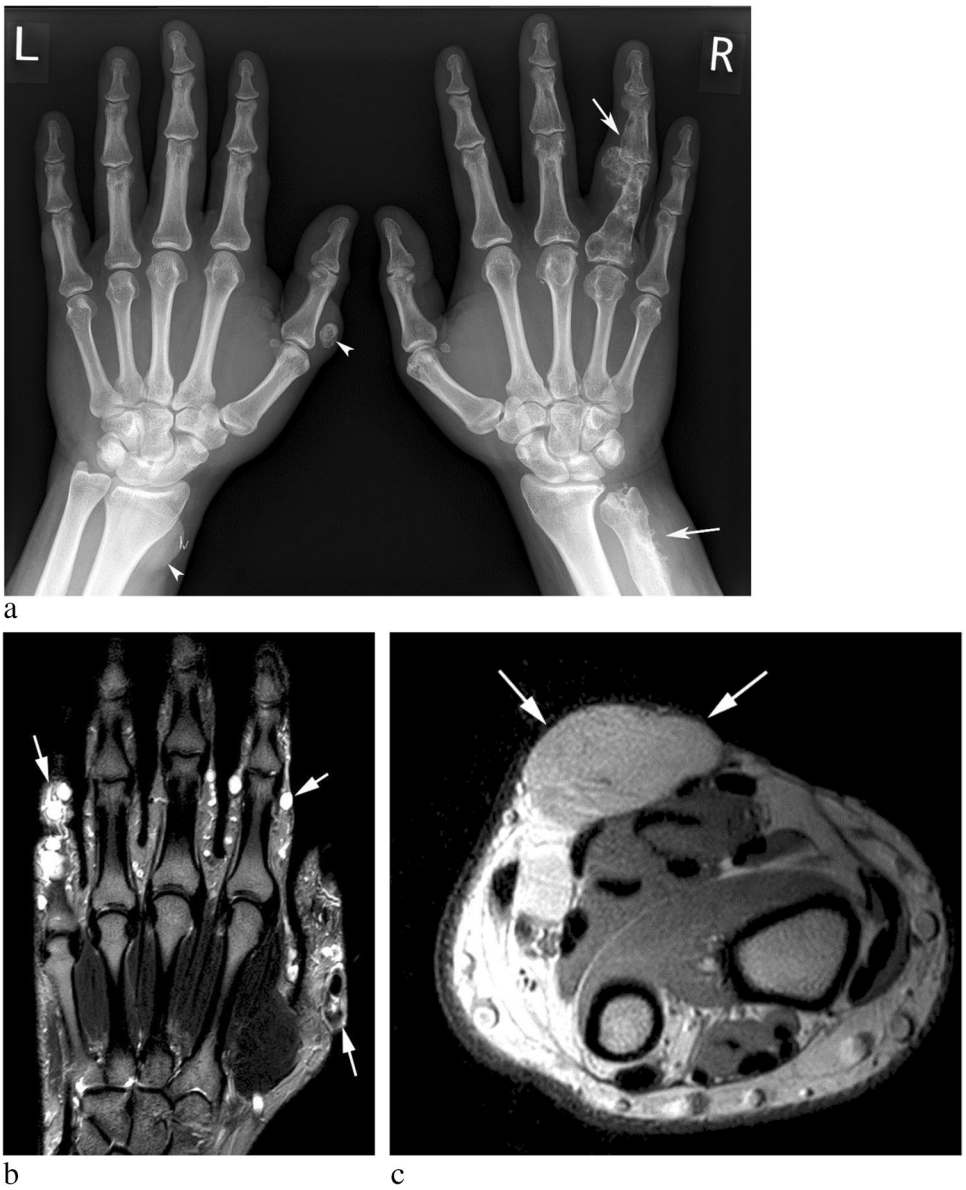

Fig. 8 A 42-year-old male with Maffucci syndrome. **a** Dorso-palmar radiograph of both hands demonstrates widespread enchondromas (arrows) on the right side and several soft tissue masses (arrowheads) on the left side, one of which is heavily ossified compatible with a phlebolith. **b** Coronal STIR and **c** axial PDW FSE MR images demonstrate multiple lobular soft tissue masses (arrows) in the fingers and volar distal forearm consistent with haemangiomas

mineralisation [2]. Following contrast, peripheral and septal enhancement may be demonstrated [39, 51, 52].

Enchondromas can demonstrate radiotracer uptake on bone scintigraphy which is typically homogenous and mild compared to the physiologic uptake in the anterior iliac crest [2, 53]. However, children can have active lesions that show more intense uptake [37].

Imaging features suggesting malignant transformation

Malignant transformation of enchondroma in Ollier disease and Maffucci syndrome should be suspected clinically if any osseous lesion demonstrates growth after skeletal maturity [2], particularly if associated with pain [14]. Malignant transformation of enchondroma is more common in the long tubular bones and flat bones than in the hands and feet, with a risk of 44–50% and 14%, respectively. [20]. In addition, the diagnostic threshold for CS in the hands and feet is higher than that of CS elsewhere in the body [54]. A recent study found that high-grade CS was more likely to occur in tumours arising from the pelvis in enchondromatosis syndromes [33]. Previously reported radiographic features suggestive of the development of CS in enchondromatosis syndromes include cortical destruction and the presence of a soft tissue mass (Fig. 9a) [20]. However, the inherent skeletal deformities in Ollier disease and Maffucci syndrome make assessment of suspicious or aggressive radiographic features challenging [27].

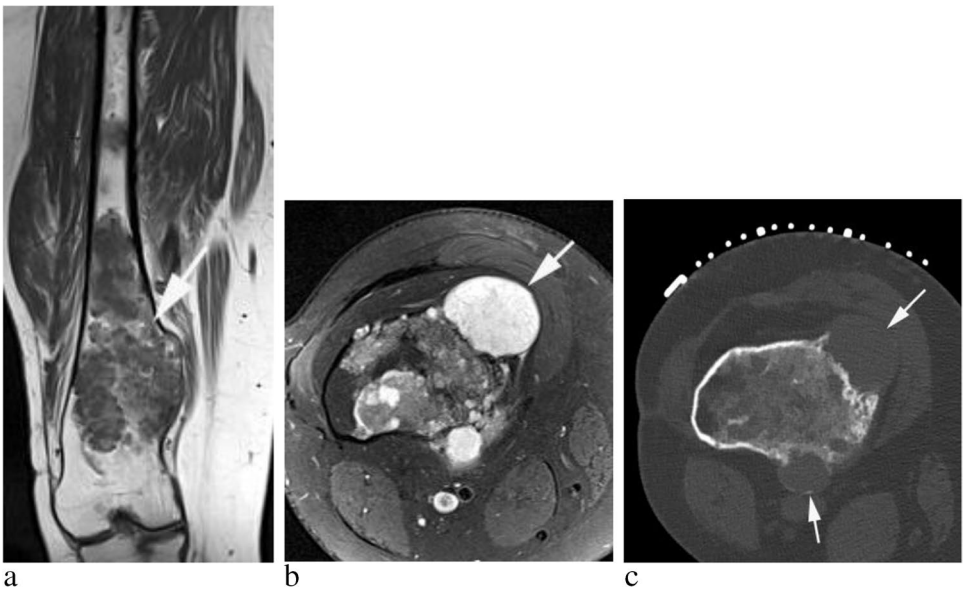

Fig. 9 A 28-year-old female with Ollier disease. **a** Coronal T1W TSE MR image of the right femur shows an extensive distal diaphyseal lesion (arrow) resulting in marked medial cortical expansion. **b** Axial STIR and **c** CT images show well-defined surface chondral masses (arrows). Histologically confirmed atypical cartilaginous tumour

General radiographic features suggestive of ACT in the long bones include larger size (> 5 cm), deep endosteal scalloping, cortical remodelling, cortical thickening and periosteal reaction [39, 51, 52, 55, 56]. On CT and MRI, the presence of deep and extensive endosteal scalloping involving > 2/3 of the cortical thickness and tumour length, cortical remodelling and thickening, periosteal reaction and peri-tumoural soft tissue oedema are more frequently observed in ACT (Fig. 9) [51, 52, 55, 57]. A recent study found endosteal scalloping was more significantly associated with grade I CS than enchondroma in the pelvis, and calcification, soft tissue mass and cortical disruption were only found in grade I CS [43].

Radiographic features suggestive of high-grade CS (grades II and III) include permeative bone destruction, bone expansion, cortical destruction and aggressive periosteal reaction (Fig. 10). Less extensive matrix mineralisation may also be demonstrated [58]. MRI findings in keeping with high-grade CS comprise greater tumour length, cortical thickening, cortical destruction, bone expansion, bone and soft tissue oedema, periosteal reaction and the presence of a soft tissue mass [44, 58–61]. A recent study found that the presence of bone marrow oedema, periosteal reaction and soft tissue oedema on MRI may indicate high-grade malignant transformation of enchondromas in the long bones in patients with enchondromatosis syndromes (Fig. 10c, d) [33]. However, no specific features could be identified to suggest high-grade CS in the hands or feet (Fig. 11).

Dedifferentiated CS may demonstrate bi-phasic features at radiography and aggressive features such as progressive bone destruction, cortical destruction, reduced bone mineralisation and a large soft tissue mass [58, 62]. CT and MRI may demonstrate bi-phasic tumour morphology with an intermediate-to-low SI T2W non-chondroid component contrasting with the relatively hyperintense chondral tissue, the former often demonstrating uniform enhancement following contrast [62, 63]. However, it should be noted that dedifferentiated CS can have a range of MRI features. The SI of the non-chondroid component will reflect its basic morphology, its vascularity and degree of haemorrhage and necrosis. Combinations of chondrosarcoma and fibroblastic osteosarcoma have been described in Ollier disease [64]. Dedifferentiated CS has also been reported in Mafucci syndrome, the dedifferentiated component in 1 case containing 3 mesenchymal elements, osteosarcoma, fibrosarcoma and malignant fibrous histiocytoma [65].

Bone scintigraphy cannot reliably distinguish between enchondroma and CS; however, it can be used to evaluate the extent of the disease in enchondromatosis syndromes (Fig.10b) [32]. Increased uptake in a lesion may be due to other reasons such as insufficiency fractures [46]. F-18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) may be useful in identifying intermediate or high-grade CS at SUVmax values of > 4.5, although at SUVmax values of 2–4.5, it is difficult to differentiate between benign and malignant tumours [66, 67]. FDG-PET-CT can be used to identify regions of greatest SUVmax to guide percutaneous biopsy [68], assess for metastatic disease and identify tumour recurrence at follow-up [6, 69].

In summary, the clinical criteria for malignant transformation are as follows: pain and growth of an enchondroma beyond

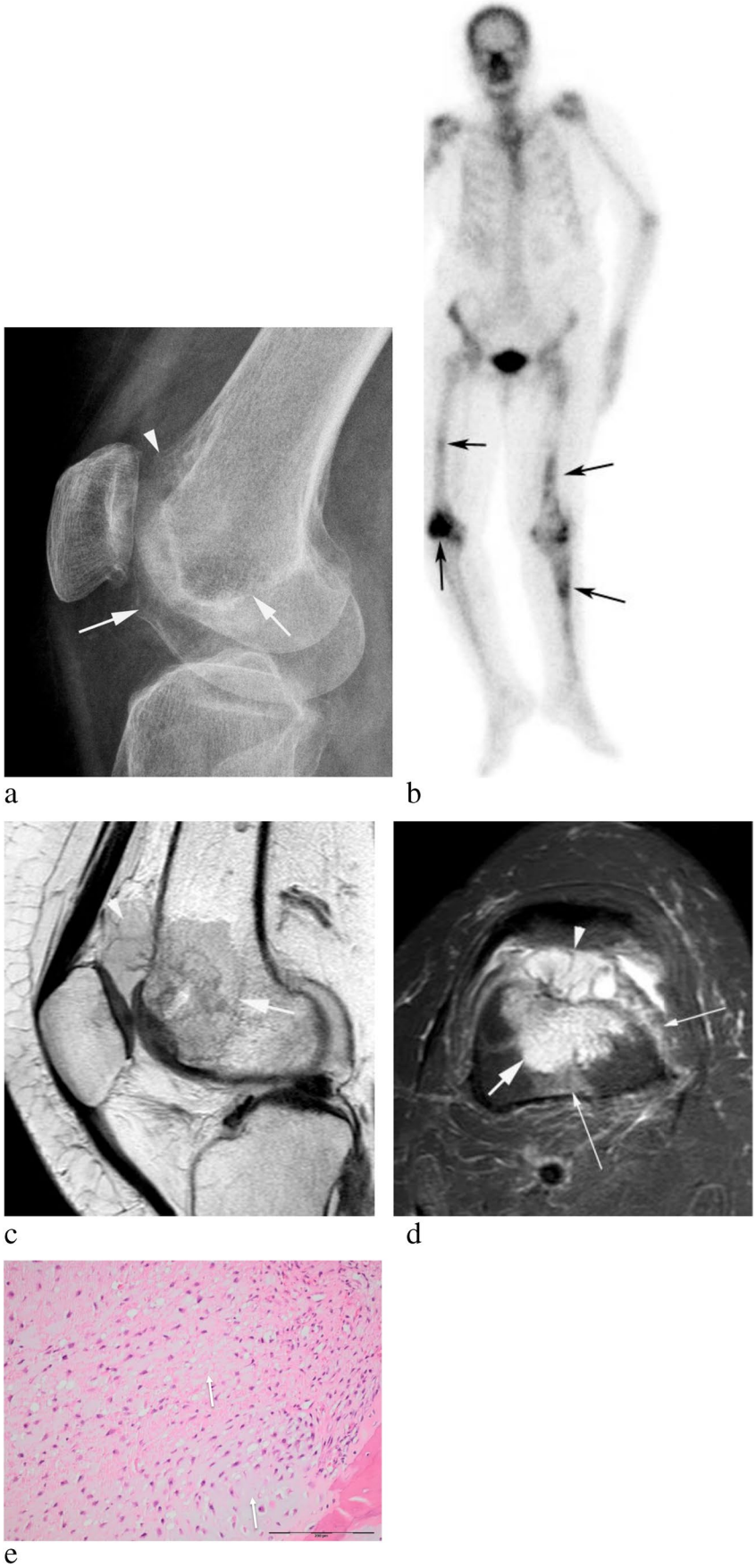

Fig. 10 A 66-year-old female with Ollier disease. **a** Lateral radiograph demonstrates a poorly defined lytic lesion (arrows) in the distal femur which has broken through the anterior cortex (arrowhead). **b** Whole-body bone scan shows multifocal areas of abnormal skeletal uptake in the femora of variable intensity consistent with enchondromas (arrows), although a particularly intense right distal femoral lesion is noted. **c** Sagittal PDW FSE and **d** axial STIR MR images of the right knee show an intra-medullary lesion (arrows) with a lobular anterior extra-osseous extension (arrowheads) and mild marrow and soft tissue oedema (thin arrows-**d**). (H&E × 20). **e** Central chondrosarcoma grade II. A cartilaginous tumour with a higher degree of cellularity, composed of spindled chondrocytes with moderate nuclear atypia and an open chromatin pattern. The stroma has a myxoid quality (arrow)

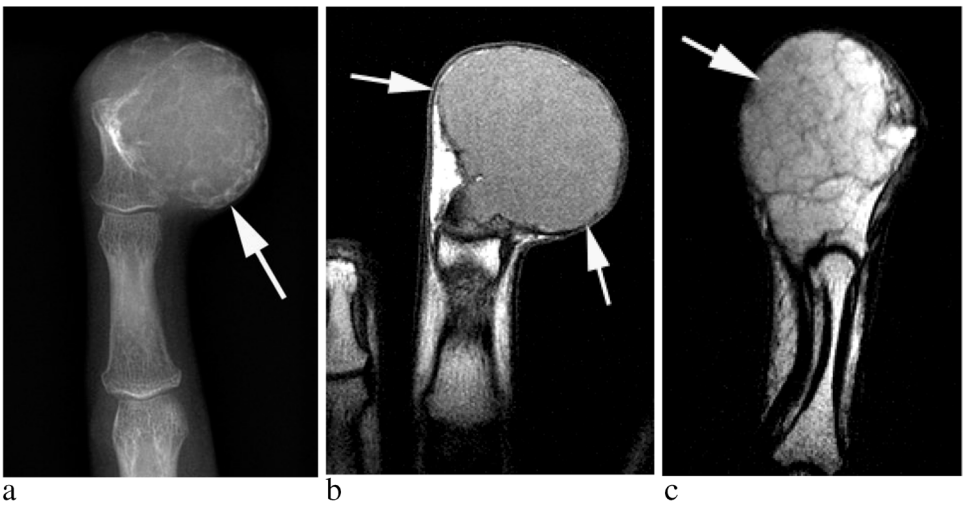

Fig. 11 A 19-year-old female with Ollier disease. **a** Dorsopalmar radiograph, **b** coronal T1W TSE and **c** sagittal T2W FSE MR images show a huge chondral tumour (arrows) expanding the distal phalanx. Despite the aggressive imaging appearances, this was a histologically confirmed enchondroma

skeletal maturity. Imaging criteria include cortical destruction, presence of a soft tissue mass, bone expansion, deep endosteal scalloping, less extensive matrix mineralisation and aggressive periosteal reaction on radiography, CT and MRI. In addition, the presence of bone marrow oedema and soft tissue oedema on MRI also suggests malignant transformation.

Metachondromatosis

Metachondromatosis is a rare autosomal dominant disorder with incomplete penetrance caused by mutations in the *PTPN11* gene [9, 14], approximately 50 cases having been reported worldwide [70]. It has a prevalence of < 1:1,000,000, is characterised by the presence of enchondromas and exostoses and usually presents in the 1st decade of life [71–73]. It is distinct from multiple hereditary osteochondromas (MHO) in that the exostoses in metachondromatosis point towards the joint, are mainly located in the hands and feet [1, 9, 70] and have a predominantly fibrous cap with a core of disorganised cartilage surrounded by trabecular bone [14]. In addition, metachondromatosis is not linked to the *EXT1* and *EXT2* genes responsible for MHO (14). Exostoses can arise from the metaphysis or epiphysis and are typically located in the phalanges and metacarpals of the hands (Figs. 12a–c), although exostoses have also been reported in the femur, tibia (Figs. 12d–f), fibula, anterior aspects of the vertebral bodies and scapular blades [70]. There may be associated peri-articular soft tissue calcification (Figs.12g, h) [70].

Enchondromas typically involve the iliac crests and long bone metaphyses of the lower extremities [1], other reported locations including the proximal humerus, distal radius and small bones of the hands and feet [74–76]. There has been one reported case of metachondromatosis occurring without enchondromas, suggesting multiple and variable phenotypes of the condition [74]. On radiographs, metaphyseal enchondromas can appear striated, while along the iliac crest and superior femoral neck, they can be punched-out or lacunar-like [70, 77]. Lesions are reportedly not associated with axial deformity or shortening of affected bones [70, 78]. However, they can result in secondary reduced range of motion [79], and deformity of the small joints of the hands, such as hyperextension, subluxation or valgus deformity, which may persist even after regression of an exostosis [70]. Peri-articular soft tissue calcifications are often present and are due to peripheral enchondral ossification of epiphysis-based exophytic enchondromas [70, 75].

A diagnosis of metachondromatosis is based on clinical signs, radiographic findings and familial history. If a molecular diagnosis is confirmed, this can be used to aid diagnosis in other family members [71, 72]. The clinical course of metachondromatosis is unpredictable, with simultaneous growth of some lesions and regression of others [71, 73]. Metachondromatosis is thought to spontaneously regress during childhood, although some lesions persist into adulthood [70, 78]. Similar to other enchondromatoses, new lesions do not appear after skeletal maturation [70]. However, unlike other enchondromatosis syndromes, metachondromatosis has low malignant potential, only 2 cases of secondary CS having been reported in the literature, both of which had arisen from an enchondroma [72, 80]. Complications include nerve compression, femoral head avascular necrosis, necrosis of overlying skin and pathological fracture [70, 75, 76]. Avascular necrosis of the femoral head is a particularly frequent complication and is thought to be caused by exostoses or enchondromas in the femoral neck interfering with the integrity of the lateral epiphyseal vessels [81]. Management of metachondromatosis depends upon clinical presentation, with surgical excision of exostoses advocated for symptomatic patients [79].

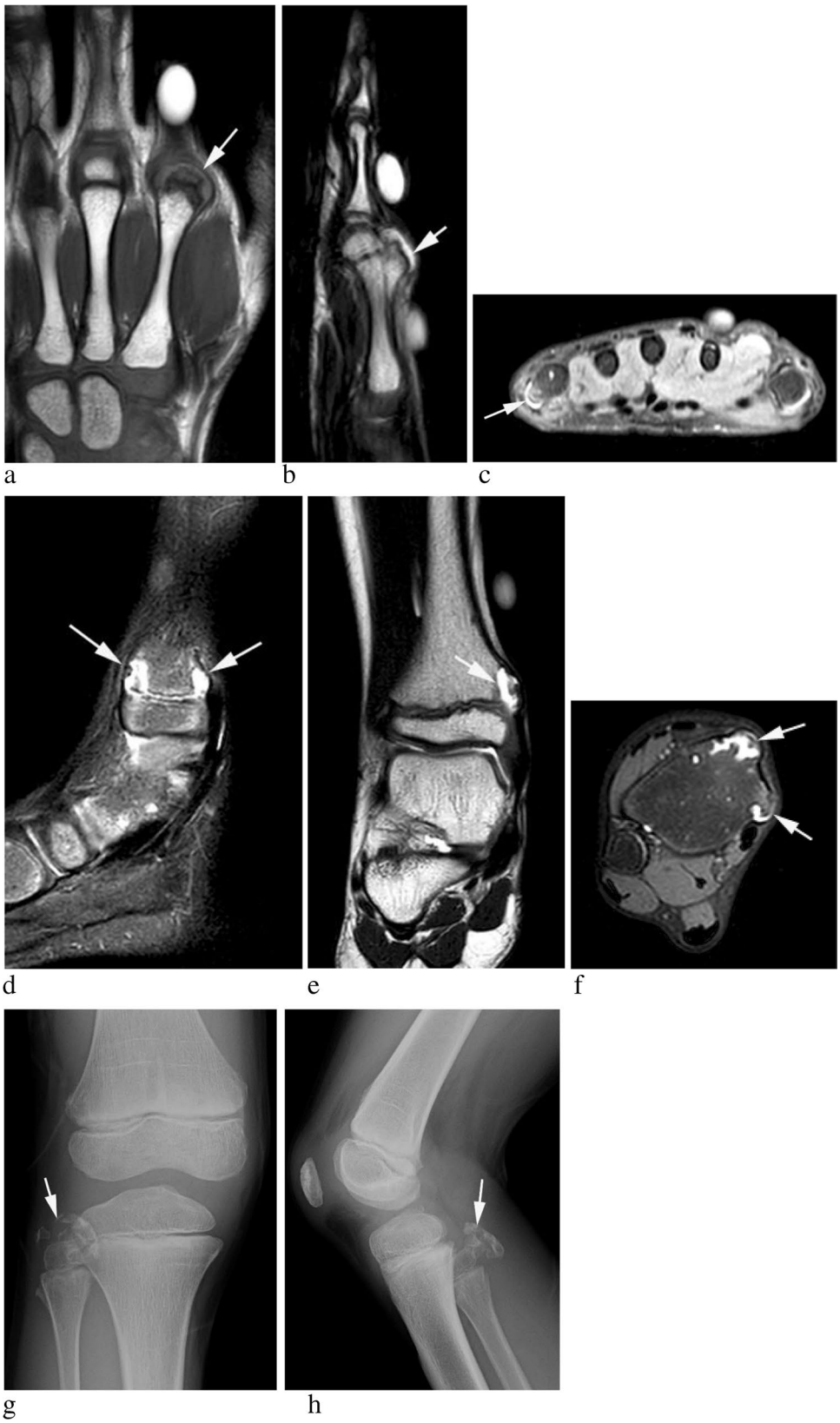

Fig. 12 A 6-year-old boy with metachondromatosis. **a** Coronal T1W TSE and **b** sagittal T2W FSE MR images show a sessile osteochondroma of the index finger metacarpal head (arrows) pointing towards the MCP joint. **c** Axial SPAIR MR image shows a further exostosis arising from the little finger metacarpal head (arrow). **d** Sagittal STIR, **e** coronal T2W FSE and **f** axial SPAIR MR images of the ankle show a combination of small exostoses and intra-medullary chondral lesions (arrows) in the distal tibial metaphysis. **g** AP and **h** lateral radiographs of the right knee demonstrate peri-articular soft tissue ossifications (arrows) around the proximal tibiofibular joint

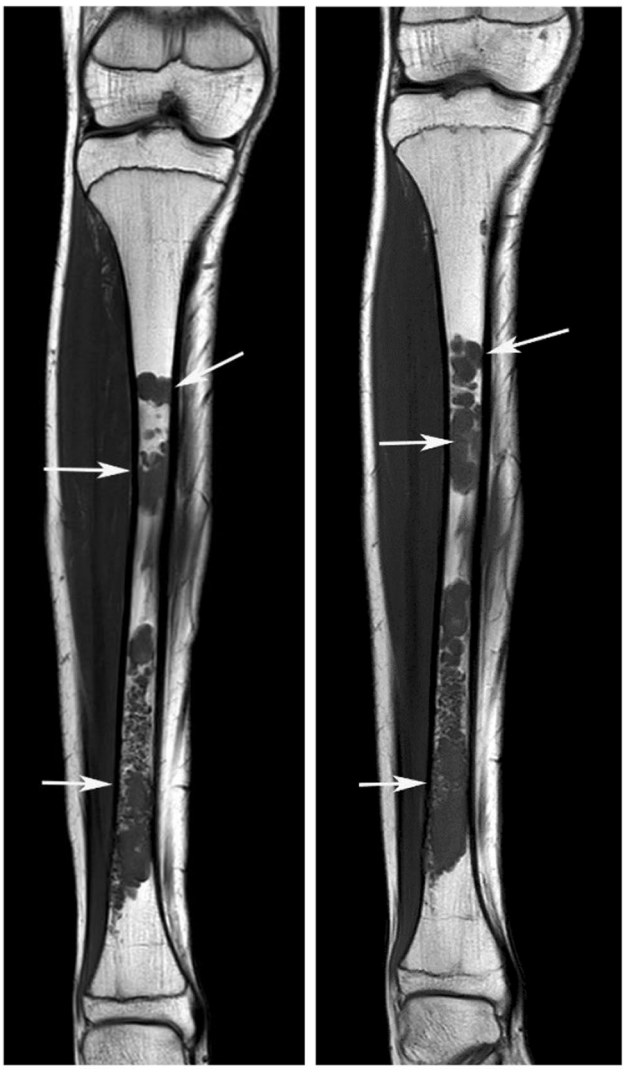

Fig. 13 A 13-year-old boy with Ollier disease. **a** Coronal T1W TSE MR image of the tibia shows multiple intra-medullary enchondromata (arrows). **b** Repeat coronal T1W TSE MR image of the tibia 7 months later shows growth of all of the lesions (arrows)

Follow-up of patients with enchondromatosis syndromes

Given the significant increased risk of malignant transformation in certain enchondromatosis syndromes and various other CNS and soft tissue malignancies, follow-up of such patients must be performed. However, there is currently no agreed consensus or standard protocol. Several studies and literature reviews have advocated annual physical examination [6, 23, 30], with varied imaging follow-up techniques and intervals. Verdegaal et al. advocate screening radiographs for patients with enchondromas in the long and/or flat bones when complaints of pain, swelling or neurological disorders arise or increase [20]. El Abiad et al. recommend plain radiography of known enchondromas measuring < 5 cm every 2–3 years [30], while Lin et al. recommend skeletal surveys every 1–2 years with localised radiographs of symptomatic areas. However, radiography is limited in certain anatomical areas and the frequency of skeletal surveys must be weighed against the risk of cumulative radiation exposure [82]. Herget et al. advise annual MRI of affected areas or WB-MRI for patients with chondral tumours that measure > 5–6 cm in size (Fig. 13), or those located in the pelvis, femur, humerus or scapula [8].

Due to the increased risk of gliomas and skull base CS in Ollier disease and Maffucci syndrome, regular cranial MRI at annual or 3-yearly intervals has been recommended, although one study advocated head CT in symptomatic patients [20, 36, 83]. In patients with Maffucci syndrome, abdominal CT in symptomatic patients or annual abdominal ultrasound has been recommended, with further investigation in the form of CT or MRI should any abnormality be detected [20, 23].

Follow-up with annual or biennial WB-MRI has been suggested by several authors [26, 30, 83, 84]. One study used the following protocol: coronal and axial STIR sequences, along with a coronal T1-weighted sequence [84]. The benefits of WB-MRI include the ability to monitor the size of enchondromas, detect soft tissue lesions and extra-skeletal malignancy (Fig. 14) and the avoidance of multiple exposures to ionising radiation over the course of a lifetime [83]. However, it may be difficult to diagnose changes in the hands and feet with WB-MRI, and WB-MRI is also relatively time consuming and expensive [84]. Where WB-MRI is not available, bone scintigraphy is recommended as an alternative, while CT may be helpful in anatomically difficult regions such as the scapula or pelvis [30].

Due to the rarity of metachondromatosis, it is difficult to establish formal monitoring recommendations. Mavrogenis et al. advised monitoring and follow-up in patients with large, growing long bone exostoses due to the risk of neural and vascular compression, and in patients with femoral head involvement due to the risk of avascular necrosis [75].

Taking into account the various recommendations in the literature, for patients with Ollier disease and Maffucci syndrome, we advise annual clinical examination and WB-MRI from the age of 25 years considering that El Abiad et al. identified the median age at cancer diagnosis was 25 years in Ollier disease and 30 years in Maffucci syndrome [30]. While this is costly, particularly WB-MRI, this is offset by the rarity of these disorders and the significant lifetime risk of multi-centric CS occurring in a metachronous pattern. For patients with metachondromatosis, we advocate biennial or triennial clinical review, which can be adjusted depending upon the patient's clinical status [70, 73, 75].

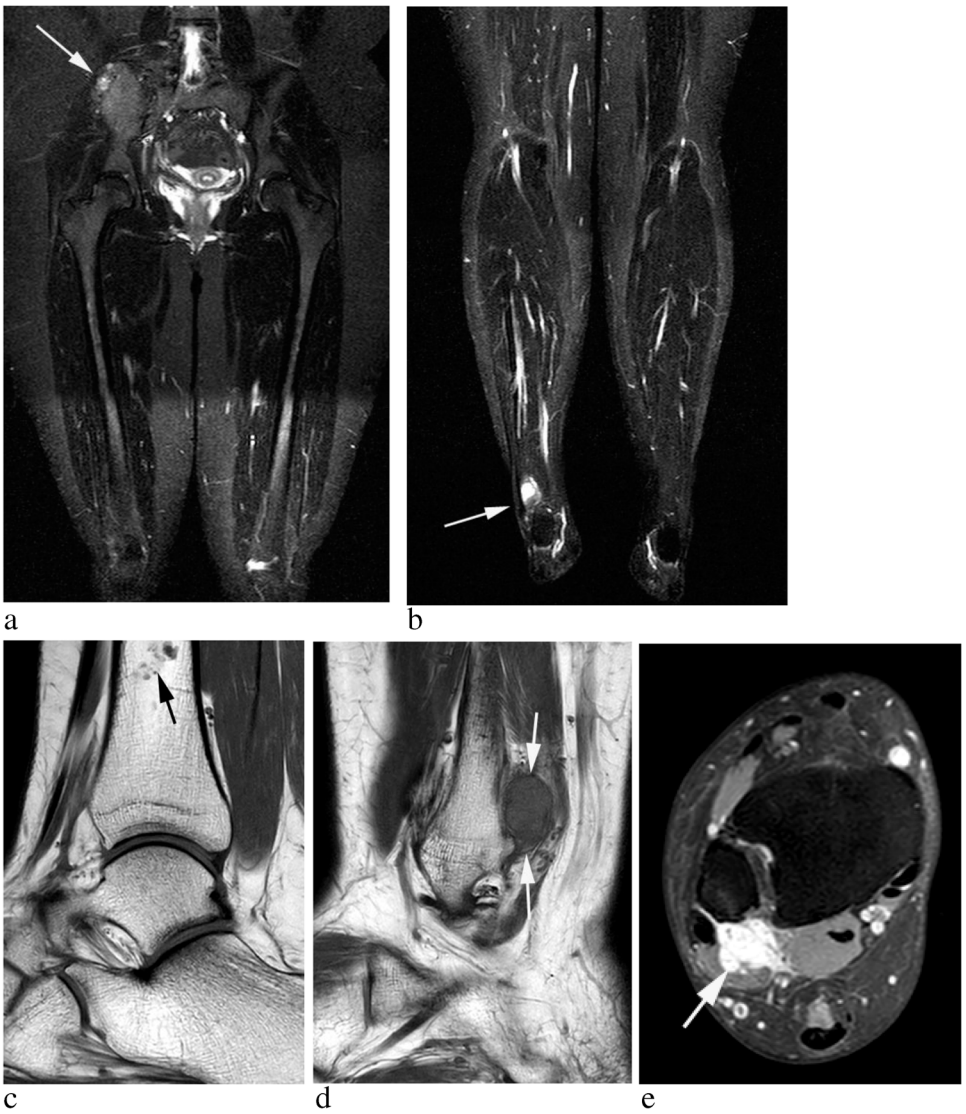

Fig. 14 A 15-year-old female with known enchondromatosis involving the right iliac blade. **a**, **b** Coronal STIR MR images from a WB-MRI study show small intra-medullary chondral lesions (arrow-**a**) in the expanded right ilium, and a small hyperintense soft tissue mass (arrow-**b**) in the right ankle region. **c**, **d** Sagittal T1W TSE and **e** axial SPAIR MR images of the right ankle show further small intra-medullary chondral lesions (arrow-**c**) in the distal tibial metadiaphysis and a lobular fluid SI soft tissue mass (arrows-**d**, **e**) posterior to the lateral malleolus consistent with a haemangioma indicating a diagnosis of Maffucci syndrome

Conclusions

Ollier disease and Maffucci syndrome are the commonest of the enchondromatosis syndromes, characterised by multiple enchondromas in the small tubular bones of the hands and feet, the long tubular bones and flat bones. Patients typically develop deformities in the hands, feet and lower limbs and are at significant risk of secondary CS and non-skeletal malignancies. Multimodality imaging of such patients aids diagnosis, can allow for pre-operative planning and can identify malignant transformation. Clinical and imaging follow-up is necessary in these patients, although as yet there is no agreed national or international consensus on protocol.

Declarations

Conflict of interest The authors declare no competing interests.

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