Giant Cell-Rich Tumors of Bone

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KEYWORDS

- Giant cell tumor • Giant cell granuloma • Non-ossifying fibroma • Aneurysmal bone cyst
- USP6-rearranged lesions

Key points

- Multinucleated giant cells can be found in a distinct group of bone tumors and generally represent bystanders of the actual neoplastic population
- Most giant cell-rich bone tumors show characteristic molecular alterations that can aid in the differential diagnosis and primarily involve mutations of the *H3.3*, *KRAS*, and *FGFR1* genes as well as rearrangements of the *USP6* gene
- Benign fibrous histiocytoma (BFH) is no longer listed as a separate entity in the latest WHO classification and believed to represent giant cell tumor with regressive changes
- Giant cell lesion of the small tubular bones has also been eliminated as a distinct entity in the latest WHO classification and thought to represent solid aneurysmal bone cyst
- Rearrangements of the *USP6* gene are not limited to classical aneurysmal bone cysts but occur in a variety of formerly "difficult to classify" lesions

ABSTRACT

The term *giant cell-rich tumors of bone* refers to a shared morphologic pattern in a group of different osseous lesions, that is, the abundance of osteoclastlike giant cells. Fitting with a broad spectrum of clinical presentations and biological behavior, the recent detection of characteristic molecular alterations in giant cell tumor of bone (*H3-3*), nonossifying fibroma (*KRAS*, *FGFR1*), giant cell granuloma of the jaws (*KRAS*, *FGFR1*, *TRPV4*), and aneurysmal bone cyst (*USP6*) have contributed significantly to the biological understanding of these morphologically related but clinically distinct lesions and their systematic classification, highlighting differences and pathogenic relationships.

GIANT CELL TUMOR OF BONE

INTRODUCTION

Conventional giant cell tumor constitutes 4% to 5% of all primary bone tumors. This tumor is considered a locally aggressive and rarely metastasizing neoplasm that can undergo malignant transformation into a high-grade sarcoma.¹ Giant cell tumor of bone (GCT) predominantly develops in the epiphyseal/metaphyseal region of long tubular bones after skeletal maturity (>20 years). In less than 10% of cases, tumors occur while the growth plates are still open and are then centered more proximally in the metaphyses.² Most commonly involved sites include the distal femur, the proximal tibia, and the distal radius. In

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the spine, the vertebral bodies are affected. GCT is exceptionally rare in the craniofacial bones.

IMAGING FEATURES

As GCTs lack formation of mineralized matrix, they appear purely lytic in radiographs and computed tomographic (CT) scans without sclerotic margins. GCTs are usually large, intramedullary, eccentrically located, and well defined (**Fig. 1A**). Cortical scalloping and penetration can occur in advanced lesions, but aggressive periosteal reactions are usually absent. MRI of GCT shows nonspecific, usually heterogeneous signal intensity on T1-weighted images before and after contrast administration; T2-weighted images are also nonspecific but can demonstrate (pseudo-)cystic change (fluid-fluid levels, see **Fig. 1C**).

GROSS AND MICROSCOPIC FEATURES

Tumors are mostly solid and consist of friable brown tissue with varying amounts of hemorrhage, cystic change, and necrosis. Tumors usually measure 5 to 15 cm in diameter.

Microscopically, abundant and remarkably large multinucleated giant cells are the hallmark of the

disease. Although intermingled smaller giant cells can occur in a variety of different lesions, the amount and size of giant cells demonstrating more than 50 nuclei per tissue section is typical for GCT (**Fig. 1B**). The neoplastic cell population, however, is composed of mostly monomorphic oval or polygonal cells arranged in a haphazard manner; it shows ill-defined cell borders and a slightly eosinophilic cytoplasm. Nuclei tend to appear round to ovoid with vesicular chromatin and central nucleoli; they are practically identical to the nuclei of the giant cell component. Mitotic activity, mild to moderate cytologic atypia, and areas of necrosis can be observed, as well as vascular invasion. GCT can undergo regressive changes with prominent accumulation of siderophages and foam cells; other secondary changes include (pseudo-)cystic change and reactive new bone formation.

Following antiresorptive therapy (eg, with denosumab), the microscopic appearance markedly changes. The multinucleated giant cells disappear, and the lesional mononuclear cells decrease and partly transform into osteoblasts forming varying amounts of immature woven bone trabeculae.^{3,4} This observation is in line with gene expression profiles of the mononuclear component of GCT that

Fig. 1. GCT in the distal radius of a 17-year old boy. The conventional radiograph shows a well-demarcated, slightly expansile lytic lesion extending to the subchondral bone (A) with heterogeneous enhancement in a T1-weighted, fat-saturated MRI sequence after contrast administration (C). Microscopically, multiple (nonneoplastic) large giant cells are embedded in a background of monomorphic mononuclear spindle cells arranged in a haphazard manner (B) [hematoxylin-eosin, original magnification, 50x]. H3.3 G34W immunoreactivity can be observed in the mononuclear spindle cells (D) [original magnification, 100x].

resemble those of cells with early osteoblastic differentiation.⁵ In some cases, reactive atypia can be striking and mimic malignant transformation.³

Malignant GCT can show different kinds of presentation. Typically, parts of a regular GCT can be found adjacent to a high-grade sarcoma, similar to dedifferentiated liposarcoma or chondrosarcoma. The characteristic histone H3.3 mutation of GCT usually remains detectable in the sarcomatous component, and malignant transformation can occur in the primary manifestation or after local recurrences of the GCT. Osteosarcoma (OS) or undifferentiated pleomorphic sarcoma (UPS) comprise the most common histologic patterns found in malignant GCT. OS or UPS without a detectable GCT component but revealing an H3.3 mutation most likely also represent malignant GCT. Genetically, malignant GCT resembles OS and UPS and shows a high degree of aneuploidy.⁶

IMMUNOPHENOTYPE AND MOLECULAR PATHOLOGY FEATURES

Virtually all GCTs (96%) harbor mutations in the *H3-3A* gene specifically involving Glycine 34, with G34W (p.Gly34Trp) accounting for 90% of cases and G34L (p.Gly34Lys) for a smaller minority.^{7–9} The G34W mutation can be detected reliably by immunohistochemistry showing nuclear positivity in the mononuclear cell population only (Fig. 1D). The functional impact is still largely unknown so far, but recent studies point to a massive effect on the global epigenetic landscape that seems to impair normal osteogenic differentiation.¹⁰ Apart from this driver mutation, GCTs show a relatively low mutation burden and a flat copy number profile.

DIFFERENTIAL DIAGNOSIS

The histology in the typical clinical and imaging context is fairly diagnostic for GCT without additional analyses, whereas H3.3 testing confirmed that *giant cell granulomas of the jaws*, *aneurysmal bone cyst (ABC)*, *giant cell lesions of the small tubular bone*, and *non-ossifying fibroma* are not related to GCT. On the other hand, lesions formerly classified as *BFH*, histologically resembling non-ossifying fibroma but mainly occurring later in life and centered in the epiphyses of long tubular bones, turned out to represent giant cell tumors with marked regressive changes and are no longer listed as a separate entity in the current World Health Organization (WHO) classification (Fig. 2). In case of doubt, immunohistochemical testing for the G34W mutation is usually sufficient to

confirm GCT. The detection of rarer mutations still requires sequencing.¹¹

SUMMARY AND PROGNOSIS

Conventional GCT recurs locally following curettage in 15% to 50%, usually within 2 years. Tumors can occasionally metastasize to the lungs, which is believed to result from embolization of intravascular growth. Metastases occur in 3% to 7% of cases, often following local recurrence; show limited growth dynamics; and can regress spontaneously. The prognosis of malignant GCT is similar to those of other high-grade sarcomas of bone.

CLINICS CARE POINTS

- Most cases present as lytic mass lesions in the epiphyseal region of long tubular bone in patients older than 20 years
- Abundant large multinucleated giant cells distributed evenly among mononuclear spindle cells are characteristic; H3.3 testing can confirm the diagnosis
- Regressive changes, either following denosumab or without prior treatment (formerly known as BFH), can significantly alter the histologic and radiologic appearance of GCT
- Metastases can occur but often follow an indolent clinical course; primary/secondary malignant GCTs represent high-grade bone sarcomas requiring a multidisciplinary treatment approach

NON-OSSIFYING FIBROMA OF BONE (NOF)

INTRODUCTION

NOF is the most common benign tumor of bone.¹² As it usually follows an asymptomatic course and undergoes spontaneous resolution, most cases are clinically not recognized, which is why the actual incidence of NOF is difficult to determine. It has been estimated, however, that 30% to 40% of children develop one or even multiple occult lesions during skeletal growth.¹³ The first edition of the WHO classification of bone tumors published in 1972 described NOF as a nonneoplastic bone lesion of “obscure etiology”; the second edition from 1993 continued to recognize NOF as a tumorlike lesion, probably representing a developmental anomaly.^{14,15} In 2002 the third edition of the WHO classification was published and did not list NOF as a separate bone tumor entity; in the fourth edition from 2013 NOF was described together with benign fibrous histiocytoma as a fibrohistiocytic lesion.¹⁶ After recurrent pathogenic

Fig. 2. GCT with regressive changes (former BFH). Conventional radiographs (A) and coronal CT reconstruction (B) of the proximal femur of a 33-year old woman show a well-demarcated osteolysis of the femoral head with a peripheral sclerotic rim. Microscopically, a dense spindle cell proliferation with only few intermingled multinucleated giant cells (C) and extensive foam cell change [hematoxylin-eosin, original magnification, 50x] (D) is visible, resembling non-ossifying fibroma (NOF) of bone [hematoxylin-eosin, original magnification, 50x]. (E) The tumor cells are consistently positive for H3-3A (G34W mutation 50x).

mutations in the mitogen-activated protein (MAP) kinase signaling pathway were identified recently, NOF was finally recognized as a benign neoplasm and is now listed under the osteoclastic giant cell-rich tumors in the current and fifth edition of the WHO blue book.

NOF exclusively develops in the first 2 decades of life and generally affects the metaphyses of long tubular bones, mainly around the knee and in the distal tibia. Multiple lesions can occur sporadically and also in distinct syndromes, mostly belonging to the spectrum of RASopathies and including neurofibromatosis type 1 (NF1) and Jaffe-Campanacci syndrome.

IMAGING FEATURES

The presentation of NOF on plain radiographs is usually so characteristic that no biopsy

confirmation is required. Lesions appear well defined, polylobulated (grapeliike), and lytic. Lesions are centered in the cortex and show sclerotic and scalloped borders (Fig. 3A, B). Remarkably, (residual) NOF is only rarely encountered in adults, which is probably caused by spontaneous regression and resolution over time.

GROSS AND MICROSCOPIC FEATURES

Most NOFs consist of solid brown tissue with variable amounts of hemorrhage and (pseudo-) cystic change. Necrosis is usually only present after a prior pathologic fracture.

Histologically, the tumors are composed of histiocytelike spindle cells arranged in storiform patterns. Mitoses can be found but are usually scant. There is no significant cytologic atypia. Throughout the lesion, intermingled

Fig. 3. Plain radiographs of non-ossifying fibroma in the distal femur of a 16-year old girl (A) and in the distal tibia of a 14-year old boy (B) displaying well-defined, eccentric, and lobulated radiolucent lesions with sclerotic borders. Microscopically, histiocytelike spindle cells are arranged in storiform patterns with intermingled osteoclastlike giant cells (C) [hematoxylin-eosin, original magnification, 50x]. (D) Mandibular central giant cell granuloma in a 28-year old woman presenting as a well-circumscribed lytic lesion. Microscopically, monomorphic mononuclear spindle cells and scattered multinucleated giant cells can be observed in association with areas of hemorrhage (E) [hematoxylin-eosin, original magnification, 50x].

multinucleated giant cells can be observed that appear rather small (>10 nuclei per tissue section) and cluster around areas of hemorrhage (Fig. 3C). Aggregations of siderophages and foam cells are other typical findings, the background can be rich in collagen fibers. Reactive new bone formation is rare (*non-ossifying* fibroma) but can be seen following a fracture. The histology of NOF strongly resembles that of giant cell granuloma of the jaws.

IMMUNOPHENOTYPE AND MOLECULAR PATHOLOGY FEATURES

In the vast majority of cases, NOF can be reliably diagnosed without additional analysis but requires radiologic correlation. The immunophenotype is nonspecific and highlights the histiocytic differentiation of the lesional cells. Sequencing revealed mutually exclusive hotspot mutations affecting *KRAS* and *FGFR1* in greater than 80% of cases, which strongly argues for a neoplastic nature.¹¹ The reason why NOF ceases to grow at some point and completely resolves over time without leaving a trace remains unclear. A similar

mechanism like in fibrous dysplasia in which the lesional cells carrying the *GNAS* mutation get diminished over time by undergoing apoptosis might be a possible explanation.¹⁷

DIFFERENTIAL DIAGNOSIS

In the appropriate clinical and imaging context, the diagnosis of NOF is usually straightforward. A nearly identical morphology in the jaws can be found in *giant cell granuloma* (GCG), which is outlined in more detail later discussion. Solid parts of ABC can appear similar microscopically but lack the typical radiologic appearance of NOF. In case of doubt, a fluorescence in situ hybridization (FISH) analysis of the *USP6* gene is helpful to support the diagnosis of ABC. Another histologic mimic is GCT with regressive changes, which was formerly believed to represent a distinct lesion designated as *benign fibrous histiocytoma* (BFH). The histology can appear identical to NOF, but age and the involved sites mirror the distribution of GCT. Immunohistochemical detection of the *H3.3* mutation is an easy way to diagnose or rule out GCT with regressive changes.

SUMMARY AND PROGNOSIS

Surgical pathologists only infrequently encounter NOF in their daily routine because it is only biopsied or curetted in case of (imminent) fracture. The prognosis is excellent, and local recurrences are rare. Malignant transformation has not been described so far. As the *KRAS* and *FGFR1* mutations found in NOF are virtually absent in conventional OS, a relationship between these 2 lesions seems highly unlikely.

CLINICAL CARE POINTS

- Most common benign tumor of bone
- Pathognomonic presentation on plain radiographs showing a well-defined, grapelike osteolysis with a sclerotic rim centered in the cortex of the metaphysis of long tubular bones
- Mutations in the MAP kinase signaling pathway drive NOF
- Histologic mimics can be easily ruled out by radiologic correlation and few molecular tests (H3.3, USP6)

GIANT CELL GRANULOMA OF THE JAWS (GCG)

INTRODUCTION

Giant cell granuloma is a benign and sometimes locally aggressive tumor of the jaws; it can develop inside the bone (central giant cell granuloma of the jaws [GCG]) or in the gingival/alveolar mucosa (peripheral GCG). Central GCG most commonly affects patients in the first 2 decades of life and accounts for 10% of all benign tumors of the jaws. The anterior aspects of the mandible (and maxilla) are most frequently involved.¹⁸ Peripheral GCG (synonym giant cell epulis) usually occurs later in life (fifth and sixth decades) and most commonly develops in the mandible.¹⁹

GCG has long been considered to be of reactive nature, and central GCG has also been referred to as reparative GCG. In the current WHO classification of head and neck tumors published in early 2017, central GCG is defined as a benign “lesion” and peripheral GCG is described to result from chronic irritation. In 2018, Gomes and colleagues,²⁰ however, discovered recurrent mutations in the MAP kinase signaling pathway in both central and peripheral GCG, strongly arguing in favor of a neoplastic origin.

Imaging Features

Central GCG typically presents as a slowly growing, well-delineated, and expansile osteolysis with cortical thinning (Fig. 3D). If large, a multilobulated and/or soap bubble appearance can be

observed. Locally aggressive lesions show cortical penetration and soft tissue infiltration. Tooth resorption or displacements are sometimes evident. Peripheral GCG can erode the underlying bone, which can be visible on radiographs or sectional images.

GROSS AND MICROSCOPIC FEATURES

GCGs have a similar morphology independent of their site of origin. The tissue is brittle and brown with varying amounts of hemorrhage and (pseudo-)cystic change.

Microscopically, GCGs consist of monomorphic and histiocytelike spindle cells arranged in haphazard lobules. Multinucleated giant cells are usually abundant and unevenly distributed throughout the tumor. These cells are rather small (<10 nuclei per tissue section) and cluster around areas of hemorrhage (Fig. 3E). The tumor is incompletely subdivided by fibrous septa containing woven bone trabeculae. Secondary changes include accumulation of siderophages, and a thin peripheral rim of reactive new bone formation may be present. Mitotic activity can vary but is usually low. Significant cytologic atypia is not a typical feature of GCG. With the exception of the fibrous septa, the histology is very similar to non-ossifying fibroma (NOF) of the peripheral skeleton.

IMMUNOPHENOTYPE AND MOLECULAR PATHOLOGY FEATURES

Immunohistochemistry is unspecific and not useful. The mononuclear cells express histiocytic markers including CD68 and CD163. Sequencing analyses have revealed recurrent *KRAS* and *FGFR1* mutations, similar to non-ossifying fibroma of bone, in both central and peripheral GCG. In addition, *TRPV4* mutations have been exclusively detected in central GCG (and neither in peripheral GCG nor in NOF so far).²⁰ This finding is in line with the fact that GCGs can develop in several syndromes, all belonging to the spectrum of RASopathies, including NF1 as well as Noonan, LEOPARD, and Jaffe-Campanacci syndromes. Notably, some patients develop both GCG and NOF. Multiple GCGs point to a syndrome-related pathogenesis.

DIFFERENTIAL DIAGNOSIS

Brown tumors caused by hyperparathyroidism are rare in the Western population but can appear histologically identical to GCGs.

Syndrome-related GCGs are also virtually indistinguishable from sporadic cases and can be the initial presenting symptom. Even in the absence of more specific signs of Noonan syndrome or

NF1, a thorough clinical examination or screening for the relevant germline alterations should be considered, particularly in patients with multiple GCGs. Histologically, some cases show a more prominent spindle cell component with lesser giant cells and a notably storiform pattern of growth without being specific. Lesions tend to reach a considerable size and behave locally aggressive.²¹

Cherubism is a rare benign disease characterized by symmetric enlargement of all 4 quadrants of the jaws. Cherubism is caused by a mutation of the SH3BP2 gene with approximately 50% being inherited in an autosomal dominant trait and 50% arising as de novo mutations. The disease manifests before the age of 6 years and is usually easy to diagnose in the appropriate clinical and imaging contexts. Histologically, however, cherubism appears similar to (syndrome-related) GCG.

ABC is generally characterized by a multicystic architecture composed of blood-filled spaces subdivided by fibrous septa containing multinucleated giant cells. Imaging shows expansile lesions with fluid-fluid levels in MRI. Some ABCs, however, lack the defining cystic appearance and strongly resemble GCGs microscopically; they are referred to as solid ABCs. If this differential diagnosis is considered, USP6 FISH analysis might be helpful to substantiate it.

Conventional GCT practically does not exist in the jaws. Histologically, it shows a higher number and more evenly distributed giant cells that contain more than 50 nuclei per tissue section. H3-3A mutations are absent in GCG.

SUMMARY AND PROGNOSIS

Peripheral GCGs are usually excised and recur only infrequently, particularly if the underlying periosteum is included in the excision. Central GCGs are frequently treated by curettage. Recurrence rates differ depending on the aggressiveness of individual lesions.

CLINICAL CARE POINTS

- Benign tumors exclusively occurring in the craniofacial skeleton and can be clinically classified as nonaggressive and locally aggressive types
- Sporadic cases are usually solitary and commonly affect the anterior mandible; multiple lesions point to a syndrome-related cause
- Mutations in the MAP kinase signaling cascade drive GCG (*KRAS*, *FGFR1*, *TRPV4*)
- Histologic mimics can be ruled out by thorough clinical/imaging correlation and

laboratory tests (parathormone). Molecular tests are rarely needed (*USP6* FISH)

ANEURYSMAL BONE CYST

INTRODUCTION

ABC is another lesion of bone that has originally been assumed to be of reactive nature. In the first 2 editions of the WHO classification, it was listed under the tumorlike lesions; in the third and fourth editions it was listed under the category of tumors of undefined neoplastic nature. The first evidence of underlying genetic rearrangements involving the *USP6* gene date back to 1991 and have been described in the WHO blue book since its third edition.²² However, it is only since the fourth edition published in 2013 that ABC has been defined as a true neoplasm and regarded to be of intermediate biological potential (locally aggressive). In the current and fifth edition, ABC is listed under the osteoclastic giant cell-rich tumors; disputably the editors have revised the biological behavior from locally aggressive to benign.²³

ABC usually affects children and adolescents; 80% of cases occur in the first 2 decades of life. Typically, the metaphyses of long tubular bones and the posterior elements of the vertebrae are involved; patients present with pain and swellings.

IMAGING FEATURES

Radiologically, ABCs appear expansile, lytic, and eccentric with well-defined margins and commonly a thin shell of reactive bone. Highly aggressive features and periosteal reactions are not typical for ABC, but ill-defined margins, penetration of the cortex, and an extraosseous extension are also possible. MRI highlights fluid-fluid levels that are highly characteristic (**Fig. 4A**); contrast administration primarily shows septal enhancement. Solid components can be present but are usually not predominating and should raise suspicion of other differential diagnoses, including telangiectatic osteosarcoma (TAEOS).

GROSS AND MICROSCOPIC FEATURES

The multicystic architecture of ABC shows blood-filled spaces of varying size that are separated by thin, tan-white septa. Solid areas appear brown and fragile.

Microscopically, the cyst walls are composed of monomorphic and fibroblastlike spindle cells and scattered multinucleated giant cells. Mitotic activity can be brisk, but high-grade atypia and atypical mitoses do not occur in ABC. Both giant cells and mononuclear spindle cells form smooth and

Fig. 4. Different tumors with USP6 rearrangement. Conventional ABC of the right proximal humerus of a 10-year-old boy showing multiple fluid-fluid levels on T2-weighted MRI (A). Histologically, solid and (pseudo-)cystic areas can be distinguished. The lesion contains an immature and reactive new bone formation that appears partly basophilic (so-called blue bone) (B) [hematoxylin-eosin, original magnification, 25x]. CT scans of intracortical ABC in the left tibia of a 19-year-old man (C) and in the right tibia of a 13-year old girl (E) appear lytic and locally aggressive but show a typical morphology of partly solid ABC (D, F) [hematoxylin-eosin, original magnification, 50x]. Juxtacortical ABC in the third metatarsal bone of a 13-year old boy presenting with a broad ossification (G, radiograph). Histologically, only minor parts of the lesion resemble ABC adjacent to abundant and reactive new bone formation (H) [hematoxylin-eosin, original magnification, 50x].

continuous flattened layers that line the (pseudo-)cystic spaces filled by blood and serous fluid (Fig. 4B). Siderophages can be numerous, and reactive new bone formation is another common finding. In at least a third of cases, the woven bone is mineralized in an irregular fashion and

appears bluish (so-called blue bone, see Fig. 4B). This peculiar matrix is not specific but a highly characteristic feature of ABC. Necrosis is uncommon if not secondary to pathologic fracture. Solid components show a similar cellular composition.

IMMUNOPHENOTYPE AND MOLECULAR PATHOLOGY FEATURES

Immunohistochemistry of ABC is nonspecific and generally not helpful in the diagnosis. Approximately 70% of ABCs show rearrangements of the *USP6* gene that fuses with various partner genes including *CDH11* (most common, 30% of cases), *THRAP3*, *CNBP*, *OMD*, *COL1A1*, *CTNNB1*, *STAT3*, *FOSL2*, *EIF1*, *SPARC*, *PAFAH1B1*, *USP9X*, and *RUNX2*.²³ The translocations result in upregulation of *USP6* transcription and are only present in the mononuclear spindle cell component. So far individual rearrangements have not been associated with a distinct clinical behavior. Notably, *USP6* rearrangements have not been reported in malignant tumors so far.

DIFFERENTIAL DIAGNOSIS

Various soft tissue, bone, and gnathic tumors can show secondary changes that mimic ABC. This phenomenon has formerly been referred to as *secondary ABC* and is not associated with *USP6* rearrangements. As it only represents reactive and nonspecific changes and not a separate entity or a collision tumor, the WHO recommends using the term *ABC-like changes*.

TAEOS is an important differential diagnosis that can mimic ABC. However, in *TAEOS* there is frank high-grade atypia with pleomorphic high-grade nuclei and usually abundant atypical mitoses. Imaging usually shows more aggressive features and a greater amount of solid areas, but there is an overlap in imaging features with those of ABC. *TAEOS* does not show *USP6* rearrangements.

In the jaws, solid ABC can virtually be indistinguishable from GCG. However, ABC is rather rare in the jaws and usually shows the classic (pseudo-)cystic presentation. Testing for *USP6* rearrangements can help in ambiguous cases.

In the small tubular bones, lesions with a similar histology like GCGs have formerly been classified as *giant cell lesions of the small bones*.²⁴ As most of those tumors were shown to harbor *USP6* rearrangements they are no longer listed in the current WHO classification as a separate entity but considered to constitute solid ABC²⁵ (Fig. 5).

SUMMARY AND PROGNOSIS

ABC is a benign bone tumor usually occurring in children and adolescents. Recurrence rates vary significantly in the literature but probably range between 15% and 30%. Malignant transformation has been described but most likely represented unusual *TAEOS*; so far, no convincing case of

malignant transformation and underlying *USP6* rearrangement has been reported.

CLINICS CARE POINTS

- Benign, expansile, and eccentrically located bone tumor developing in the metaphyses of long tubular bones and the posterior elements of the vertebrae
- Usually well defined and lytic on imaging; can show an (incomplete) sclerotic rim; aggressive imaging features are not typical, but possible; primarily cystic appearance on MRI with characteristic fluid-fluid levels
- *USP6* rearrangements in 70% of cases

OTHER TUMORS OF BONE WITH *USP6* REARRANGEMENTS

INTRODUCTION

With increasing molecular testing more and more soft tissue and bone lesions that have formerly been regarded as reactive pseudotumors or tumorlike lesions were shown to harbor recurrent genetic alterations and are now considered true neoplasms. Highly specific findings such as *H3.3* mutations in GCT and chondroblastoma can be extremely helpful in routine diagnostics and often warrant a reliable diagnosis even in smaller core needle biopsies. Other genes are involved in a variety of neoplasms so a mutation or rearrangement itself limits the spectrum of differential diagnoses but is not specific for a distinct lesion per se. Remarkably, several mutations that have been considered the driver genes of highly malignant tumors have recently been shown to also drive benign and sometimes even self-limiting lesions including pathogenic *KRAS* hotspot mutations in non-ossifying fibroma (NOF) and *EWSR1* rearrangements in simple bone cyst.^{11,26}

USP6 rearrangements are one prominent example of highly promiscuous alterations occurring in several but so far unequivocally benign neoplasms. The consecutive discovery in distinct lesions caused confusion in the nomenclature prompting the question if a shared molecular alteration is sufficient to assume a direct relation between lesions that otherwise appear distinct from each other. As the first cases of myositis ossificans (MO) were reported to harbor *USP6* rearrangements, those lesions were temporarily suggested to represent *soft tissue variants of ABC*, although clinical and microscopic features were distinct from ABC. In the meantime, it has been increasingly accepted that MO as well as fibro-osseous pseudotumor of digits both belong to the

Fig. 5. Solid ABC (former giant cell lesion of the small bones). CT shows a well-defined and expansile lytic lesion in the third right metatarsal of a 29-year-old woman (A). Microscopically, the tumor presents uniformly solid with foam cell changes (B) [hematoxylin-eosin, original magnification, 50x] and areas resembling giant cell granuloma of the jaws (C) [hematoxylin-eosin, original magnification, 50x].

spectrum of *USP6*-related neoplasms.^{27,28} The term *solid ABC* is somehow contradictory in itself (as is giant cell tumor without giant cells) but now introduced in the WHO classification to designate lesions in the small tubular bones formerly classified as a separate entity (giant cell lesions of the small bones). ABC can also develop inside and on the surface of cortical bone, which both can appear highly unusual on imaging. *USP6*-rearranged juxtacortical lesions can cause massive new bone formation and have been designated as *periostitis ossificans*, *periosteal fasciitis*, *juxtacortical ABC*, and *cranial fasciitis*, all with markedly distinct clinical presentation and behavior.^{29,30}

IMAGING FEATURES

Intracortical ABCs are usually lytic and well defined but can extend into the adjacent soft tissues (Fig. 4C, E). Periosteal reactions sometimes appear aggressive, indicating rapid growth; still,

tumors usually present thin shells of reactive woven bone at their periphery. Solid tumors often reveal homogeneous contrast enhancement prompting a broad spectrum of differential diagnoses. The presentation of lesions developing on the surface of tubular bones varies but can be characterized by abundant new bone formation (Fig. 4G, H).

GROSS, MICROSCOPIC, AND MOLECULAR PATHOLOGY FEATURES

The macroscopic and microscopic aspects of *USP6*-related lesions are mostly similar to ABC or nodular fasciitis. However, secondary changes can predominate and obscure the more characteristic findings. Searching for an *USP6* rearrangement by FISH or RNA sequencing should be considered in unusual intracortical and juxtacortical bone tumors that at least have some resemblance to conventional ABC or nodular fasciitis (Fig. 4).

SUMMARY AND PROGNOSIS

The spectrum of *USP6*-related tumors is increasing and includes rare manifestations at unusual sites. If any peculiar lesion of bone with an underlying *USP6* fusion transcript should be classified as (intracortical, juxtacortical, or solid) ABC will need to be decided as soon as larger series become available and potentially highlight differences in presentation and clinical behavior; currently, only few case reports have been published. In any case, the identification of *USP6* rearrangements appears particularly important because, at least so far, they do not seem to occur in malignant tumors.

CLINICS CARE POINTS

- *USP6*-related neoplasms can show unusual presentation in bone and include solid, intracortical, and surface-related manifestations
- *USP6* rearrangements have not been described in malignant tumors so far
- *USP6* testing is advocated in any lesion of bone that shows at least some morphologic similarity to conventional ABC or nodular fasciitis

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DISCLOSURE

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