Soft Tissue Special Issue: Giant Cell-Rich Lesions of the Head and Neck Region

Jen-Chieh Lee¹ · Hsuan-Ying Huang²

Received: 28 August 2019 / Accepted: 1 October 2019 / Published online: 16 January 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Giant cell-rich lesions represent a heterogeneous group of tumors and non-neoplastic lesions, usually arising in bone, which harbor varying number of reactive osteoclastic-type multinucleate giant cells as a common feature. Among these entities, some are confined to the head and neck region (e.g., central giant cell granuloma and mimicking lesions, i.e., peripheral giant cell granuloma and cherubism) or show a relative predilection for this region (e.g., aneurysmal bone cyst and brown tumor of hyperparathyroidism), while others are rare but associated with distinct underlying disease (e.g., giant cell tumor of bone) or histology (e.g., tenosynovial giant cell tumor of the temporomandibular joint and phosphaturic mesenchymal tumor of the jaws) when occurring in the head and neck. Collectively, these lesions pose great challenge in the pathologic diagnosis, which often requires combinatory assessment from the clinical, histopathologic, and/or molecular aspects. This review provides a summary of pertinent clinical and pathologic features and an update of recent molecular and genetic findings of these entities. The considerations in differential diagnosis as well as the effects of the emerging therapeutic RANKL-antagonizing antibody denosumab will also be addressed.

Keywords Giant cell tumor of bone · Aneurysmal bone cyst · Central giant cell granuloma · Tenosynovial giant cell tumor · Phosphaturic mesenchymal tumor · Brown tumor of hyperparathyroidism

Introduction

Osteoclast-like giant cells can be present in a broad range of benign and malignant bone and soft tissue neoplasms as a reactive component that varies widely in abundance but sometimes even constitutes the main tumor bulk. The clinicopathological characters, prevalence and behavior of these giant cell-rich neoplasms differ not only among individual tumor entities but also in various tumor locations within the same entity, hence requiring cautious consideration of sites of involvement in differential diagnosis. The head and neck represent a unique anatomical region accommodating vital organs and

structures within the confines of craniofacial bones and surrounding soft tissues from which a variety of giant cell-containing neoplasms may arise and pose diagnostic challenges, given their overlapping histology and demographic variations from their extracraniofacial counterparts. In this review, we elaborate the recent understanding of diagnostic classification in the contexts of both histomorphology and pertinent disease-defining genetic aberrations for essential giant cell-containing neoplasms of the head and neck as follows.

Giant Cell Tumor of Bone

Giant cell tumor of bone (GCTB) typically affects the epiphyses of long bones of skeletally mature young adults with a female predilection [1–3]. In the absence of underlying Paget's disease, GCTB is extremely rare in the craniofacial bones (< 1%), [4] whereas the de novo GCTBs in this region are predominantly located in the sphenoid bone with an older presenting age and a more apparent female predominance [4–7]. Laryngeal GCTBs are also rare and tend to arise in the thyroid cartilage, probably following osseous metaplasia [8].

✉ Hsuan-Ying Huang
a120600310@yahoo.com

¹ Department and Graduate Institute of Pathology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

² Department of Anatomical Pathology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 123 Ta-Pei Road, Niao-Sung District, Kaohsiung 833, Taiwan

Macroscopically, GCTB is usually a red-brown and friable tumor with a well-defined or locally infiltrative border. Histologically, GCTB comprises numerous osteoclast-like multinucleate giant cells and mononucleate cells (Fig. 1) [1, 9.] Compared with other giant cell-containing mimics, the giant cells in GCTBs are larger with abundant nuclei (> 20 in many) and more evenly distributed in the tumor. The mononucleate cells in GCTBs include macrophages and the mitotically active, mononucleate ‘stromal cells’ with ovoid to spindle nuclei. The latter population is considered the true neoplastic cells that recruit receptor activator of nuclear factor κ B (RANK)-expressing monocytes and then mediate the fusion and differentiation of monocytes into osteoclasts through expressing RANK ligand (RANKL) [10–12]. Notably, GCTB may manifest a broad range of histologic variations, such as a fibrous histiocytoma-like storiform pattern with aggregates of

foamy histiocytes, fibrosclerotic areas with collagenous stroma, secondary aneurysmal bone cyst with hemorrhage or hemosiderin deposition, osteoid deposition following fracture or biopsy, or giant cell-depleted areas dominated by mononucleate stromal cells (Fig. 1b). Brisk mitotic activity (up to 20 per 10 high-power fields) is not uncommon without prognostic relevance, while the presence of atypical mitotic figures should raise the suspicion of malignant GCTB or other sarcoma types. Malignant transformation of GCTB may develop de novo or secondarily (several years after surgical and/or radiation therapy of primary GCTB) and take the form of osteosarcoma, fibrosarcoma, or undifferentiated pleomorphic sarcoma [13–15]. Malignant GCTB in the head and neck region are exceedingly rare and include one laryngeal case that should be carefully distinguished from anaplastic thyroid carcinoma [16–18].

Fig. 1 Evenly distributed osteoclastic giant cells in most parts of this sinonasal giant cell tumor of bone (**a**). Note the ovoid to spindle “stromal” cells and a vascular stroma. Areas devoid of giant cells are also noticed in this case, where the tumor bulk is composed mainly of quite uniform ovoid to spindle tumor cells with pale cytoplasm (**b**).

This tumor contains a rare *H3F3B* p.G34L mutation instead of more common *H3F3A* mutations (**c**). A post-denosumab vertebral giant cell tumor exhibits complete depletion of giant cells and prominent woven bone deposition (**d**). Note the lack of conspicuous atypia and the generally low cellularity. The mitotic activity is also low

The groundbreaking genetic discovery of GCTB is the identification of the histone 3.3 gene *H3F3A* mutations in a vast majority of cases (> 95%) [19–22]. An estimate of >80% of GCTBs contain a mutation affecting the codon Gly34, mostly G34W (less commonly, G34V/R/L or mutations involving *H3F3B*, the other histone 3.3 gene) (Fig. 1c). The high sensitivity and specificity of these mutations render them valuable diagnostic adjuncts of GCTB, and immunohistochemistry using antibodies against these mutant proteins is robust in demonstrating respective mutations in the neoplastic mononuclear stromal cells [23, 24]. However, deletion of the mutant allele of the *H3F3A* gene associated with negative immunostaining for histone 3.3 G34W, probably during sub-clonal evolution, was recently reported in a subset of malignant GCTB, hence posing a diagnostic challenge [25].

Aneurysmal Bone Cyst

Aneurysmal bone cyst (ABC) typically manifests a frequently painful, multicystic and osteolytic lesion involving the metaphysis of long bones of children and adolescents [9]. CT and MRI studies demonstrate characteristic fluid-fluid levels, sometimes with perforation of the cortex and extension to adjacent soft tissue. More than 75% of ABCs occur in the first 2 decades of life without apparent sex predilection [26–28]. Twelve percent of cases occur in the head and neck region, where the preferential site is mandible, especially the posterior region (> 60%) [27, 29, 30].

Grossly, ABC mostly manifests as a well-circumscribed, tan-white, and sponge-like or multicystic lesion with variable solid components. Rarely, predominantly solid ABCs

have been reported to arise in the head and neck, which tended to be diagnosed as giant cell reparative granulomas in the past [31]. Microscopically, ABC exhibits multilocular cystic, blood-filled cystic spaces separated by fibrous septa containing bland fibroblast/ myofibroblast-like spindle cells of moderate cellularity, interspersed with osteoclastic giant cells and osteoblast-rimmed osteoid or delicate eggshell-like metaplastic woven bone, with occasional presence of prominently basophilic “blue bone”. The solid variant reveals essentially identical morphology with only a subtle incipient microcystic component (Fig. 2a) [32, 33]. Notably, ABC-like areas, or “secondary ABC” (a term to be discouraged), may occur in various benign or malignant bone tumors, which, given the remarkable difference in clinical behavior, should be clearly distinguished from *bona fide* ABC and include GCTB, osteblastoma, chondroblastoma, fibrous dysplasia, central giant cell granuloma, ossifying fibroma, and osteosarcoma, etc [26, 34, 35]. Among these, telangiectatic osteosarcoma represents the most critical differential and differs from ABCs in having frankly sarcomatous cells, despite their resemblances at the radiologic and macroscopic levels.

Genetically, primary ABCs harbor the rearranged *USP6* gene (ubiquitin specific peptidase 6), in the genuinely neoplastic (myo)fibroblast-like spindle cells (Fig. 2b) [36]. The most frequent 5' fusion partner is *CDH11* (cadherin 11), recurrently fused with *USP6* in 70% of ABCs, among many other alternative partner genes [37, 38]. Through a promoter swap mechanism, the fundamental biologic consequence of these genetic fusions is to drive the upregulation of the complete *USP6*-coding region that critically implicates various cellular processes, such as intracellular trafficking, matrix degradation and cell transformation [39].

Fig. 2 A solid aneurysmal bone cyst in the occipital bone shows the proliferation of bland spindle cells arranged in fascicular and storiform patterns, in a collagenous to fibromyxoid stroma (a). The picture is somewhat reminiscent of nodular fasciitis. Osteoclast-type giant

cells and inflammatory cells are focally present and unevenly distributed. Note a microscopic hemorrhagic cyst (middle lower field). The diagnosis is confirmed with FISH demonstrating break-apart of the *USP6* gene (b)

Central Giant Cell Granuloma and Mimicking Lesions

Central giant cell granuloma (CGCG) is a benign but sometimes locally aggressive tumor of the jaws, most commonly affecting the mandible of female pediatric patients [40]. Clinically, CGCG is usually a slowly growing expansile lesion. Aggressive clinical behavior is observed in about 20–30% of cases, characterized by pain, tooth absorption, and invasion of perignathic tissues, and a higher chance of recurrence [40]. Cortical bone perforation is present in up to 50% of cases [40]. Grossly, CGCG is red–brown, fleshy, and often hemorrhagic in appearance. Microscopically, CGCG is unencapsulated and composed of proliferative spindle cells admixed with osteoclastic multinucleate giant cells, in a vascular and hemorrhagic background (Fig. 3). Fibrous septa with osteoid deposition or woven bone formation are sometimes present.

A minority of CGCGs, especially in those with multiple lesions, harbor germline mutations targeting RAS/MAPK pathway as a manifestation of underlying Noonan syndrome, LEOPARD syndrome, or neurofibromatosis type 1 [41]. These genetic associations also imply a potential tumorigenic role of deregulated RAS/MAPK pathway in most sporadic CGCGs, as confirmed by the recent identification of mutations involving *TRPV4*, *KRAS*, and *FGFR1* in 72% of sporadic CGCG [42]. Intriguingly, 81% of non-ossifying fibromas of long bones, a tumor type histologically similar to CGCG, also harbor mutations in *KRAS*,

FGFR1, or *NF1*, suggesting a close relationship between these 2 entities [43].

Peripheral giant cell granuloma, usually occurring in the lower jaw, is a morphologically identical lesion outside the bone, which mostly manifests as a polypoid lump protruding and/or ulcerating the overlying gingival mucosa. It is generally considered a reactive lesion, and may spontaneously regress after removal of the irritants with a low recurrence rate.

Cherubism is a rare familial syndrome predominantly resulting from *SH3BP2* mutations in 80% of cases and inherited in an autosomal dominant fashion [44, 45]. Starting in early childhood, patients with Cherubism manifest symmetrical, bilateral expansion of both jaws, which usually regress after puberty. The histologic features are similar to CGCG, although eosinophilic cuff-like perivascular deposits are considered characteristic but inconsistent.

Tenosynovial Giant Cell Tumor

Tenosynovial giant cell tumor (TSGCT) often arises in or near the synovial tissue of a joint, bursa, or tendon sheath. It is currently classified under the WHO category of “so-called fibrohistiocytic tumours”, despite mounting evidence suggesting its synoviocyte differentiation [46, 47]. The localized type most commonly involves the hand (fingers in 85%), whereas knee is the most frequent site of involvement by the diffuse type. TSGCT rarely occurs in the head and neck region, preferentially affecting, among other sites, the temporomandibular joint (TMJ), where a vast majority of cases

Fig. 3 Central giant cell granuloma. Nodules of hemorrhagic areas surrounded by fascicles or whorls of bland spindle cells (a). The osteoclastic giant cells tend to aggregate near the hemorrhagic areas (b). Osteoid deposition is sometimes observed (c)

are of diffuse type [48–50]. Unlike a female predominance of TSGCTs outside the head and neck region, TSGCTs of TMJ are more common in males, with a wide age range (median, 45 years) [48, 51]. The most common presenting symptoms include pain, hearing loss, and impaired mouth opening, etc [48, 52–54]. TSGCT of TMJ frequently manifests bone destruction, often with intra-cranial extension and/or middle ear involvement [55, 56].

Grossly, localized-type TSGCT presents as a small and well-demarcated nodular or multilobular lesion, whereas the diffuse-type counterpart is larger and exhibits a villous growth pattern and infiltrative tumor border. Extra-articular lesions can show a multinodular appearance with a variegate color pattern [57]. Microscopically, TSGCT is composed of quite variable proportions of mononuclear cells, osteoclast-like multinucleate giant cells, foamy macrophages, and other inflammatory cells (Fig. 4a). There are two types of mononuclear cells: the smaller histiocytes, with reniform nuclei and pale cytoplasm, and the larger histiocytoid to epithelioid cells, with round to ovoid vesicular nuclei and amphophilic cytoplasm often loaded with hemosiderin pigments. Mitotic activity can be brisk.

Of note, TMJ lesions quite often demonstrate chondroid metaplasia (Fig. 4b), posing difficulty in distinction from chondroblastoma, synovial chondromatosis, or chondrosarcoma, particularly given that the temporal bone is traditionally considered a preferential site for craniofacial chondroblastomas [54, 58–61]. As such, it has been speculated that some previously reported temporal chondroblastomas

might have represented TSGCT with chondroid metaplasia [60]. Positive clusterin immunostaining in the large mononuclear cells, negative S100, and a wild-type *H3F3B* genotype favor TSGCT over chondroblastoma [46, 60, 62]. Malignant TSGCT may rarely occur in TMJ [47, 63–65], where the large mononuclear cells reveal increased mitoses, atypical mitoses, enlarged nuclei with prominent nucleoli, and/or spindling, or where areas resembling myxofibrosarcoma or undifferentiated pleomorphic sarcoma are observed.

Genetically, the neoplastic cells (i.e., the large mononuclear cells) harbor rearrangement of *CSF1* (colony stimulating factor 1), usually fused with *COL6A3* (collagen type VI alpha 3 chain) (Fig. 4c) [66–68]. The majority of cells in the lesion, e.g., mononuclear macrophages, do not harbor this fusion but instead express the CSF1 receptor, and are attracted by the relatively fewer neoplastic cells as a result of CSF1 overexpression driven by the fusion.

Phosphaturic Mesenchymal Tumor

Phosphaturic mesenchymal tumor (PMT) is a rare bone and soft tissue tumor that causes hypophosphatemia and osteomalacia as a paraneoplastic syndrome through secreting phosphatonins, FGF23 in particular, which lead to renal wasting of phosphate [69, 70]. PMT is considered the tumor type behind most instances of tumor-induced osteomalacia (TIO) [69]. PMT occurs in a wide variety of anatomic locations including the head and neck regions, and

Fig. 4 A temporomandibular joint tenosynovial giant cell tumor presents scattered giant cells, many small macrophages, and variable number of larger histiocytoid to epithelioid tumor cells often containing cytoplasmic hemosiderin pigment, which tend to be located near the periphery of the cytoplasm (a). Chondroid metaplasia with cal-

cification, a common feature of tenosynovial giant cell tumor in this location (b). FISH reveals *CSF1* rearrangement, which is present in a small subset of cells (genuine neoplastic cells) among abundant non-neoplastic macrophages and inflammatory cells (c)

most commonly affects the middle-aged, male and female alike [71]. The presenting symptoms are mostly related to TIO and hypophosphatemia, including myalgia, muscle weakness, bone pain, and fracture (quite often multiple); rare examples presenting with psychotic symptoms were also reported [69, 72, 73]. The causative tumors are usually occult and require careful clinical and imaging examinations to localize, including radionuclide scans (preferably ^{68}Ga DOTATATE-PET/CT) [74–76].

The macroscopic features of PMT are often nondistinctive. Some tumors may contain a fatty component, and others may be heavily calcified. Microscopically, PMT is so widely variable that it has been misdiagnosed as many other entities, including hemangioma, hemangiopericytoma, giant cell tumor, non-ossifying fibroma, osteoblastoma, chondroma, etc [77]. Some previously reported osteomalacia-inducing “hemangiopericytoma-like tumors of nasal passages”

probably represented sinonasal PMT mimicking sinonasal hemangiopericytoma/glomangiopericytoma [69]. PMT usually consist of bland spindle cells, which deposit a hyalinized to smudgy matrix (Fig. 5). Focal to prominent presence of osteoclastic giant cells is observed in many cases (Fig. 5c). A rich capillary network and/or “staghorn” pericytoma-like vasculature is commonly present. The matrix typically calcifies in a characteristic “grungy” or flocculent fashion, and may sometimes exhibit an appearance resembling chondroid or osteoid [69, 78–80]. Other morphologic variations include mature adipose tissue, “fibrohistiocytic” spindled cells, microcystic change, and a peripheral shell of woven bone. Malignancy in PMT is rare and shows high nuclear grade, marked pleomorphism, high cellularity, necrosis and elevated mitotic activity, resembling undifferentiated pleomorphic sarcoma or fibrosarcoma [69, 81, 82]. Of note, in the jaws, PMT with admixed odontogenic epithelial elements

Fig. 5 Phosphaturic mesenchymal tumors arising in the soft part of nasal cavity (**a**) and in the mandible bone (**b**), respectively. Both tumors are composed of bland spindle cells, with grungy calcification, osteoid-like matrix deposition (in **b**), and a rich vasculature which is somewhat hemangiopericytoma-like. Note the absence of

osteoclastic giant cell in these two examples. By contrast, other phosphaturic mesenchymal tumors often harbor variable number of giant cells, sometimes so numerous that they can mimic giant cell tumor of bone (**c**). The tumor in **a** contains *FN1-FGFR1* fusion (**d**)

and a predilection for young males have been described [83]. By immunohistochemistry, most PMT express CD56, ERG, FGFR1, SATB2, and/or somatostatin receptor 2A [84–87]. Antibodies to FGF23 have shown questionable specificity, whereas chromogenic in situ hybridization (CISH) assay may be more useful in revealing *FGF23* mRNA overexpression [69, 88].

Nearly half of PMT contain either *FNI-FGFR1* or, uncommonly, *FNI-FGF1* fusion [86, 89], suggesting a central role for the FGFR1 pathways in tumorigenesis of PMT (Fig. 5d).

Brown Tumor of Hyperparathyroidism

Brown tumor is a rare non-neoplastic bone lesion associated with primary and, more commonly, secondary hyperparathyroidism (particularly in chronic renal disease) [9]. Brown tumor can occur in any bone of all ages, with craniofacial (especially jaw) bones being one of the preferential sites [90, 91]. The excessively secreted parathyroid hormone (PTH) causes bone resorption through overactive osteoclasts, leading to microfractures, hemorrhage, and subsequent formation of tumorlike lesion composed of osteoclastic giant cells, reactive fibrovascular tissue, hemosiderin deposition, and sometimes calcification (Fig. 6). The adjacent bone shows osteoclastic dissection and tunneling of the cancellous bone, a hallmark remodeling pattern of hyperparathyroidism, as well as fibrosis and osteopenia (Fig. 6c) [9]. With the PTH

status corrected, brown tumors regress with normal ossification resumed.

Treatment Effect of Denosumab in Giant Cell Tumors and Other Giant Cell-Rich Lesions

Given the crucial role of RANK/RANKL pathways in the GCTB pathogenesis, denosumab, a monoclonal antibody antagonizing RANKL, has increasingly been used to treat surgically uncontrollable tumors with promising efficacy [92, 93]. As such, the treatment-induced dramatic histologic alterations, usually manifesting marked depletion of giant cells and increased deposition of woven bone, can bewilder the pathologists unaware of this treacherous pitfall and potentially lead to the wrongful diagnosis of osteosarcoma (Fig. 1d) [15, 22]. Useful features that can help distinguish treated GCTB from osteosarcoma include distinct bone deposition patterns, at most mild cellular atypia, lower mitotic activity or Ki-67 index, and no permeation into adjacent host bones [15].

Similar to GCTB, other giant cell-rich bone tumors also often express high levels of RANKL [94, 95]. Therefore, denosumab has also been administered to treat non-GCTB giant cell-rich lesions, including ABC and CGCG, and demonstrated some symptom-relieving and/or tumor-regressing effect. Histologically, the treatment depletes osteoclastic giant cells and elicits bone deposition; in ABC, the marked decrease in cellularity of both multinucleate and

Fig. 6 Brown tumor of hyperparathyroidism. Note hemorrhage, hemosiderin deposition, and a fibrovascular stroma (a). Harboring numerous osteoclastic giant cells (especially near the hemorrhagic cyst), this example is quite difficult to distinguish from other giant cell-rich lesions. Focal calcification, possibly representing metaplas-

tic calcification in the context of hyperparathyroidism, may also raise the suspicion of phosphaturic mesenchymal tumor (b). Osteoclastic tunneling of the trabecular bone (dissecting osteitis) is a hallmark feature of hyperparathyroidism sometimes identifiable in or adjacent to a brown tumor (c)

Table 1 Differential diagnosis of giant cell lesion of the head and neck region

	Peak age	Sex predilection	Preferential site	Giant cell features	Other important clinical/ microscopic features	Molecular/genetic features
Giant cell tumor of bone	3rd–4th decades	Female	Sphenoid	Large in size, with many nuclei; numerous; evenly distributed	Mononucleated macrophages and ovoid to spindle neoplastic cells	<i>H3F3A</i> G34W/N/R/L or rarely <i>H3F3B</i> mutations in most cases. Head and neck tumors often associated with underlying Paget's disease
Aneurysmal bone cyst	1st–2d decades	F≅M	Mandible (posterior)	More abundant near hemosiderin or cystic spaces	Commonly multilocular cystic with fluid-fluid level; slender myofibroblast-like cells; osteoid deposition	<i>USP6</i> fusion genes (usually with <i>CDH11</i>) in most cases
Central giant cell granuloma	2nd–3rd decades	Female	Jaws (mandible)	More abundant near hemosiderin or cystic spaces	Plump to slender spindle cells; fibrotic to hemorrhagic background; osteoid or woven bone deposition	<i>TRPV4</i> , <i>KRAS</i> , or <i>FGFR1</i> mutations in 72% of sporadic cases. Manifested in Noonan syndrome, LEOPARD syndrome, and neurofibromatosis type 1 (often multiple)
Tenosynovial giant cell tumor	5th decade	Male	Temporo-mandibular joint	Variable number	Often diffuse-type; smaller macrophages and larger, usually outnumbered histiocytoid/epithelioid neoplastic cells with cytoplasmic hemosiderin; chondroid metaplasia common in head and neck	<i>CSF1</i> fusion gene (usually with <i>COL6A3</i>) in most cases. Clusterin immunoreactivity
Phosphaturic mesenchymal tumor	Middle-aged	F≅M	Jaws & sinonasal	Variable (sometimes absent)	Hypophosphatemia and osteomalacia; secondary hyperparathyroidism in some. Bland spindle cells; “grungy” calcification and matrix deposition; hemangiopericytoma-like vasculature. Biochemical abnormalities corrected with complete tumor excision	<i>FN1-FGFR1</i> or <i>FN1-FGF1</i> fusions in ~50% of cases. Immunoreactive to CD56, ERG, FGFR1, SATB2, and somatostatin receptor 2A. FGF23 overexpression
Brown tumor of hyperparathyroidism	Any age	F≅M	Jaws	More abundant near hemosiderin	Severe primary or secondary hyperparathyroidism. Reactive fibrovascular tissue with bland spindle cells, hemorrhage, and hemosiderin; dissecting osteitis in adjacent bone may be found. Cured with PTH correction	Non-neoplastic lesion

mononucleate cells may impart a picture mimicking simple bone cyst [96–99].

Differential Diagnosis of Giant Cell-Rich Lesions

As compared with CGCGs, brown tumors tend to have prominent compartmentalized lobulated architecture and features suggestive of hyperparathyroidism (e.g., dissecting osteitis) in the adjacent bones. However, these two entities may closely resemble each other in histologic appearances, especially in biopsy specimens. Although brown tumors can manifest as a solitary lesion in the head and neck, this diagnostic consideration should be particularly kept in mind when facing multiple concurrent, histologically similar giant cell-containing lesions, and biochemical survey for elevated parathyroid hormone and calcium levels is useful to identify underlying hyperparathyroidism. Despite the recent discovery of mutations in RAS/MAPK pathway in CGCGs, the actual prevalence rates need independent validation and the performance of individual molecular testing appears cumbersome for most pathology laboratories. Notably, PMT may also cause secondary or even tertiary hyperparathyroidism along with constitutional and bone symptoms similar to those manifested with brown tumor [100]. Different from the latter context, the biochemical alterations associated with PMT are chiefly severe hypophosphatemia with a high FGF23 serum level and variable calcium status, which, however, are quite often ill-characterized pre-operatively and quickly corrected (and therefore missed) post-operatively. Histologically, the presence of grungy calcification and staghorn vasculature, typical of PMT, is usually absent in CGCGs and brown tumors. Documentation of high FGF23 expression with RNA CISH or *FNI-FGFR1/FGF1* fusions (albeit not very sensitive) is confirmatory for the diagnosis of PMT where necessary. In terms of incidence rates, both GCTB and solid ABCs are rare in the head and neck, while Paget-associated GCTBs represent a unique clinical manifestation to be considered in the differential diagnosis of head and neck giant cell-containing lesions. Unlike other mimics, adequately sampled GCTBs usually contain diagnostic foci composed of evenly distributed giant cells admixed with mononuclear cells where spindled fibroblasts are inconspicuous. Further, sequencing for various *H3F3A* mutations and/or employment of the derived antibody against the most frequent mutant *H3F3A* G34W protein can provide confirmatory evidence for difficult cases, such as biopsy samples. Analogously, *USP6* rearrangement detected by FISH is diagnostic of solid ABC in the head and neck that may treacherously simulates CGCGs. Table 1 lists some of the useful differential features of the respective entities.

Conclusion

The contemporary differential diagnostic approach of giant cell-containing neoplasms of the head and neck is multifaceted and should integrate the information of demographic data, biochemical measurements, radiologic imaging studies, and histologic evaluations in conjunction with logical employment of proper immunohistochemical panels and molecular testing to arrive at the accurate diagnosis. Apart from the conventional clinical, biochemical, radiologic, and morphological correlations, we recommend the inclusion of at least *H3F3A* sequencing or immunohistochemistry for derived mutant proteins as well as *USP6* FISH assay in the diagnostic armamentarium of head and neck giant cell-containing lesions so as to prevent the misdiagnosis of other rare but distinct entities as CGCGs.

Acknowledgement The authors thank Drs. Yu-Chien Kao, Wan-Shan Li, Chih-Hsueh Chen, and Yo-Chun Lin for providing kind assistance and precious cases.

Funding This work was not supported by any research fund.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

References

1. Athanasou NA, Bansal M, Forsyth R, Reid RP, Sapi Z. Giant cell tumour of bone. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. World Health Organization classification of tumours of soft tissue and bone. Lyon: IARC Press; 2013. p. 321–4.
2. Dahlin DC, Cupps RE, Johnson EW Jr. Giant-cell tumor: a study of 195 cases. *Cancer*. 1970;25(5):1061–70.
3. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. *J Bone Joint Surg Am*. 1987;69(1):106–14.
4. Unni KK, Inwards CY. Dahlin's bone tumors. 6th ed. Philadelphia: LWW; 2010.
5. Huvos AG. Bone tumors: diagnosis, treatment, and prognosis. 2nd ed. Philadelphia: WB Saunders; 1991.
6. Bertoni F, Unni KK, Beabout JW, Ebersold MJ. Giant cell tumor of the skull. *Cancer*. 1992;70(5):1124–32.
7. Czerniak B. Dorfman and Czerniak's bone tumors. 2nd ed. Philadelphia: Saunders; 2016.
8. Wieneke JA, Gannon FH, Heffner DK, Thompson LD. Giant cell tumor of the larynx: a clinicopathologic series of eight cases and a review of the literature. *Mod Pathol*. 2001;14(12):1209–15.
9. Vigorita VJ. Orthopaedic pathology. 3rd ed. Philadelphia: LWW; 2016.
10. Zheng MH, Robbins P, Xu J, Huang L, Wood DJ, Papadimitriou JM. The histogenesis of giant cell tumour of bone: a model of interaction between neoplastic cells and osteoclasts. *Histol Histopathol*. 2001;16(1):297–307.
11. Wuelling M, Engels C, Jesse N, Werner M, Kaiser E, Delling G. Histogenesis of giant cell tumors. *Pathologe*. 2002;23(5):332–9.

12. Lau YS, Sabokbar A, Gibbons CL, Giele H, Athanasou N. Phenotypic and molecular studies of giant-cell tumors of bone and soft tissue. *Hum Pathol.* 2005;36(9):945–54.
13. Meis JM, Dorfman HD, Nathanson SD, Hagggar AM, Wu KK. Primary malignant giant cell tumor of bone: “dedifferentiated” giant cell tumor. *Mod Pathol.* 1989;2(5):541–6.
14. Brien EW, Mirra JM, Kessler S, Suen M, Ho JK, Yang WT. Benign giant cell tumor of bone with osteosarcomatous transformation (“dedifferentiated” primary malignant GCT): report of two cases. *Skelet Radiol.* 1997;26(4):246–55.
15. Wojcik J, Rosenberg AE, Bredella MA, Choy E, Hornicek FJ, Nielsen GP, et al. Denosumab-treated Giant cell tumor of bone exhibits morphologic overlap with malignant giant cell tumor of bone. *Am J Surg Pathol.* 2016;40(1):72–80.
16. Chan J, Gannon FH, Thompson LD. Malignant giant cell tumor of the sphenoid. *Ann Diagn Pathol.* 2003;7(2):100–5.
17. Karamanakis PN, Jaaskelainen JE, Alafuzoff I, Pirinen E, Vanninen R, Silvennoinen S, et al. Malignant giant cell tumor in the posterior fossa of a neonate. *J Neurosurg Pediatr.* 2010;5(3):277–82.
18. Vivero RJ, Dave SP, Gomez CR, Weed DT. Giant cell tumor of the larynx: a case of malignant sarcomatous transformation. *Ear Nose Throat J.* 2013;92(6):E59.
19. Behjati S, Tarpey PS, Presneau N, Scheipl S, Pillay N, Van Loo P, et al. Distinct H3F3A and H3F3B driver mutations define chondroblastoma and giant cell tumor of bone. *Nat Genet.* 2013;45(12):1479–82.
20. Cleven AH, Hocker S, Briaire-de Bruijn I, Suzhai K, Cleton-Jansen AM, Bovee JV. Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. *Am J Surg Pathol.* 2015;39(11):1576–83.
21. Al-Ibraheemi A, Inwards CY, Zreik RT, Wenger DE, Jenkins SM, Carter JM, et al. Histologic spectrum of giant cell tumor (GCT) of bone in patients 18 years of age and below: a study of 63 patients. *Am J Surg Pathol.* 2016;40:1702–12.
22. Girolami I, Mancini I, Simoni A, Baldi GG, Simi L, Campanacci D, et al. Denosumab treated giant cell tumour of bone: a morphological, immunohistochemical and molecular analysis of a series. *J Clin Pathol.* 2016;69(3):240–7.
23. Amary F, Berisha F, Ye H, Gupta M, Gutteridge A, Baumhoer D, et al. H3F3A (Histone 3.3) G34W Immunohistochemistry: a reliable marker defining benign and malignant giant cell tumor of bone. *Am J Surg Pathol.* 2017;41(8):1059–68.
24. Yamamoto H, Iwasaki T, Yamada Y, Matsumoto Y, Otsuka H, Yoshimoto M, et al. Diagnostic utility of histone H3.3 G34W, G34R, and G34V mutant-specific antibodies for giant cell tumors of bone. *Hum Pathol.* 2018;73:41–50.
25. Yoshida KI, Nakano Y, Honda-Kitahara M, Wakai S, Motoi T, Ogura K, et al. Absence of H3F3A mutation in a subset of malignant giant cell tumor of bone. *Mod Pathol.* 2019;32:1751–61.
26. Vergel De Dios AM, Bond JR, Shives TC, McLeod RA, Unni KK. Aneurysmal bone cyst. A clinicopathologic study of 238 cases. *Cancer.* 1992;69(12):2921–31.
27. Bataineh AB. Aneurysmal bone cysts of the maxilla: a clinicopathologic review. *J Oral Maxillofac Surg.* 1997;55(11):1212–6.
28. Mankin HJ, Hornicek FJ, Ortiz-Cruz E, Villafuerte J, Gebhardt MC. Aneurysmal bone cyst: a review of 150 patients. *J Clin Oncol.* 2005;23(27):6756–62.
29. Fennessy BG, Vargas SO, Silvera MV, Ohlms LA, McGill TJ, Healy GB, et al. Paediatric aneurysmal bone cysts of the head and neck. *J Laryngol Otol.* 2009;123(6):635–41.
30. Song W, Suurmeijer AJH, Bollen SM, Cleton-Jansen AM, Bovee J, Kroon HM. Soft tissue aneurysmal bone cyst: six new cases with imaging details, molecular pathology, and review of the literature. *Skelet Radiol.* 2019;48(7):1059–67.
31. Li HR, Tai CF, Huang HY, Jin YT, Chen YT, Yang SF. USP6 gene rearrangement differentiates primary paranasal sinus solid aneurysmal bone cyst from other giant cell-rich lesions: report of a rare case. *Hum Pathol.* 2018;76:117–21.
32. Sanerkin NG, Mott MG, Roylance J. An unusual intraosseous lesion with fibroblastic, osteoclastic, osteoblastic, aneurysmal and fibromyxoid elements “Solid” variant of aneurysmal bone cyst. *Cancer.* 1983;51(12):2278–86.
33. Bertoni F, Bacchini P, Capanna R, Ruggieri P, Biagini R, Ferruzzi A, et al. Solid variant of aneurysmal bone cyst. *Cancer.* 1993;71(3):729–34.
34. Martinez V, Sissons HA. Aneurysmal bone cyst. A review of 123 cases including primary lesions and those secondary to other bone pathology. *Cancer.* 1988;61(11):2291–304.
35. Gnepp D. Diagnostic surgical pathology of the head and neck. 2nd ed. Philadelphia: Saunders; 2009.
36. Oliveira AM, Perez-Atayde AR, Inwards CY, Medeiros F, Derr V, Hsi BL, et al. USP6 and CDH11 oncogenes identify the neoplastic cell in primary aneurysmal bone cysts and are absent in so-called secondary aneurysmal bone cysts. *Am J Pathol.* 2004;165(5):1773–80.
37. Dal Cin P, Kozakewich HP, Goumnerova L, Mankin HJ, Rosenberg AE, Fletcher JA. Variant translocations involving 16q22 and 17p13 in solid variant and extraosseous forms of aneurysmal bone cyst. *Genes Chromosomes Cancer.* 2000;28(2):233–4.
38. Blackburn PR, Davila JJ, Jackson RA, Fadra N, Atiq MA, Pitel BA, et al. RNA sequencing identifies a novel USP9X-USP6 promoter swap gene fusion in a primary aneurysmal bone cyst. *Genes Chromosomes Cancer.* 2019;58(8):589–94.
39. Oliveira AM, Chou MM. The TRE17/USP6 oncogene: a riddle wrapped in a mystery inside an enigma. *Front Biosci (Schol Ed).* 2012;4:321–34.
40. Chrcanovic BR, Gomes CC, Gomez RS. Central giant cell lesion of the jaws: an updated analysis of 2270 cases reported in the literature. *J Oral Pathol Med.* 2018;47(8):731–9.
41. Vered M, Buchner A, Dayan D. Central giant cell granuloma of the jawbones—new insights into molecular biology with clinical implications on treatment approaches. *Histol Histopathol.* 2008;23(9):1151–60.
42. Gomes CC, Gayden T, Bajic A, Harraz OF, Pratt J, Nikbakht H, et al. TRPV4 and KRAS and FGFR1 gain-of-function mutations drive giant cell lesions of the jaw. *Nat Commun.* 2018;9(1):4572.
43. Baumhoer D, Kovac M, Sperveslage J, Ameline B, Strobl AC, Krause A, et al. Activating mutations in the MAP-kinase pathway define non-ossifying fibroma of bone. *J Pathol.* 2019;248(1):116–22.
44. Mangion J, Rahman N, Edkins S, Barfoot R, Nguyen T, Sigurdsson A, et al. The gene for cherubism maps to chromosome 4p16.3. *Am J Hum Genet.* 1999;65(1):151–7.
45. Flanagan AM, Speight PM. Giant cell lesions of the craniofacial bones. *Head Neck Pathol.* 2014;8(4):445–53.
46. Boland JM, Folpe AL, Hornick JL, Grogg KL. Clusterin is expressed in normal synoviocytes and in tenosynovial giant cell tumors of localized and diffuse types: diagnostic and histogenetic implications. *Am J Surg Pathol.* 2009;33(8):1225–9.
47. Al-Ibraheemi A, Ahrens WA, Fritchie K, Dong J, Oliveira AM, Balzer B, et al. Malignant tenosynovial giant cell tumor: the true “Synovial Sarcoma?” A clinicopathologic, immunohistochemical, and molecular cytogenetic study of 10 cases, supporting origin from synoviocytes. *Mod Pathol.* 2019;32(2):242–51.
48. Verspoor FGM, Mastboom MJL, Weijs WLJ, Koetsveld AC, Schreuder HWB, Flucke U. Treatments of tenosynovial giant cell tumours of the temporomandibular joint: a report of three cases and a review of literature. *Int J Oral Maxillofac Surg.* 2018;47(10):1288–94.

49. Cho JM, Chang JH, Kim SH, Lee KS. Pediatric giant cell tumor of the tendon sheath of the craniocervical junction involving the occipital condyle. *Childs Nerv Syst*. 2016;32(1):175–9.
50. Gelinne A, Akture E, Tranmer B. Tenosynovial giant cell tumor of the clinoid: rare condition. *World Neurosurg*. 2018;118:168–71.
51. Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. *Acta Orthop*. 2017;88(6):688–94.
52. Romanach MJ, Brasileiro BF, Leon JE, Alves DB, de Almeida OP, Vargas PA. Pigmented villonodular synovitis of the temporomandibular joint: case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111(3):e17–28.
53. Chow LT, Kumta SM, King WW. Extra-articular pigmented villonodular synovitis of the temporomandibular joint. *J Laryngol Otol*. 1998;112(2):182–5.
54. Carlson ML, Osetinsky LM, Alon EE, Inwards CY, Lane JJ, Moore EJ. Tenosynovial giant cell tumors of the temporomandibular joint and lateral skull base: review of 11 cases. *Laryngoscope*. 2017;127(10):2340–6.
55. Safaee M, Oh T, Sun MZ, Parsa AT, McDermott MW, El-Sayed IH, et al. Pigmented villonodular synovitis of the temporomandibular joint with intracranial extension: a case series and systematic review. *Head Neck*. 2015;37(8):1213–24.
56. Herman CR, Swift JQ, Schiffman EL. Pigmented villonodular synovitis of the temporomandibular joint with intracranial extension: a case and literature review. *Int J Oral Maxillofac Surg*. 2009;38(7):795–801.
57. Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. *Radiographics*. 2008;28(5):1493–518.
58. Wang JG, Liu J, He B, Gao L, Zhang L, Liu J. Diffuse tenosynovial giant cell tumor around the temporomandibular joint: an entity with special radiologic and pathologic features. *J Oral Maxillofac Surg*. 2019;77(5):1022e1–e39.
59. Cai XY, Yang C, Chen MJ, Yun B. Simultaneous pigmented villonodular synovitis and synovial chondromatosis of the temporomandibular joint: case report. *Int J Oral Maxillofac Surg*. 2009;38(11):1215–8.
60. Oda Y, Izumi T, Harimaya K, Segawa Y, Ishihara S, Komune S, et al. Pigmented villonodular synovitis with chondroid metaplasia, resembling chondroblastoma of the bone: a report of three cases. *Mod Pathol*. 2007;20(5):545–51.
61. Kurt AM, Unni KK, Sim FH, McLeod RA. Chondroblastoma of bone. *Hum Pathol*. 1989;20(10):965–76.
62. Hoch BL, Garcia RA, Smalberger GJ. Chondroid tenosynovial giant cell tumor: a clinicopathological and immunohistochemical analysis of 5 new cases. *Int J Surg Pathol*. 2011;19(2):180–7.
63. Yoon HJ, Cho YA, Lee JI, Hong SP, Hong SD. Malignant pigmented villonodular synovitis of the temporomandibular joint with lung metastasis: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111(5):e30–6.
64. Bertoni F, Unni KK, Beabout JW, Sim FH. Malignant giant cell tumor of the tendon sheaths and joints (malignant pigmented villonodular synovitis). *Am J Surg Pathol*. 1997;21(2):153–63.
65. Li CF, Wang JW, Huang WW, Hou CC, Chou SC, Eng HL, et al. Malignant diffuse-type tenosynovial giant cell tumors: a series of 7 cases comparing with 24 benign lesions with review of the literature. *Am J Surg Pathol*. 2008;32(4):587–99.
66. West RB, Rubin BP, Miller MA, Subramanian S, Kaygusuz G, Montgomery K, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proc Natl Acad Sci USA*. 2006;103(3):690–5.
67. Cupp JS, Miller MA, Montgomery KD, Nielsen TO, O'Connell JX, Huntsman D, et al. Translocation and expression of CSF1 in pigmented villonodular synovitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. *Am J Surg Pathol*. 2007;31(6):970–6.
68. Mastboom MJL, Hoek DM, Bovee J, van de Sande MAJ, Suzhai K. Does CSF1 overexpression or rearrangement influence biological behaviour in tenosynovial giant cell tumours of the knee? *Histopathology*. 2019;74(2):332–40.
69. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol*. 2004;28(1):1–30.
70. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA*. 2001;98(11):6500–5.
71. Boland JM, Tebben PJ, Folpe AL. Phosphaturic mesenchymal tumors: what an endocrinologist should know. *J Endocrinol Invest*. 2018;41(10):1173–84.
72. Hodgson SF, Clarke BL, Tebben PJ, Mullan BP, Cooney WP 3rd, Shives TC. Oncogenic osteomalacia: localization of underlying peripheral mesenchymal tumors with use of Tc 99m sestamibi scintigraphy. *Endocr Pract*. 2006;12(1):35–42.
73. Shih YH, Chen HC, Liao SC, Tseng MC, Lee MB. Psychotic disorder due to phosphaturic mesenchymal tumor with mixed connective tissue variant. *Psychosomatics*. 2012;53(1):96–7.
74. Garcia CA, Spencer RP. Bone and In-111 octreotide imaging in oncogenic osteomalacia: a case report. *Clin Nucl Med*. 2002;27(8):582–3.
75. Siegel HJ, Rock MG. Occult phosphaturic mesenchymal tumor detected by Tc-99m sestamibi scan. *Clin Nucl Med*. 2002;27(8):608–9.
76. El-Maouche D, Sadowski SM, Papadakis GZ, Guthrie L, Cottle-Delisle C, Merkel R, et al. (68)Ga-DOTATATE for tumor localization in tumor-induced osteomalacia. *J Clin Endocrinol Metab*. 2016;101(10):3575–81.
77. Sundaram M, McCarthy EF. Oncogenic osteomalacia. *Skelet Radiol*. 2000;29(3):117–24.
78. Bahrami A, Weiss SW, Montgomery E, Horvai AE, Jin L, Inwards CY, et al. RT-PCR analysis for FGF23 using paraffin sections in the diagnosis of phosphaturic mesenchymal tumors with and without known tumor induced osteomalacia. *Am J Surg Pathol*. 2009;33(9):1348–54.
79. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer*. 1987;59(8):1442–54.
80. Shelekhova KV, Kazakov DV, Hes O, Treska V, Michal M. Phosphaturic mesenchymal tumor (mixed connective tissue variant): a case report with spectral analysis. *Virchows Arch*. 2006;448(2):232–5.
81. Ogoe A, Hotta T, Emura I, Hatano H, Inoue Y, Umezumi H, et al. Recurrent malignant variant of phosphaturic mesenchymal tumor with oncogenic osteomalacia. *Skelet Radiol*. 2001;30(2):99–103.
82. Uramoto N, Furukawa M, Yoshizaki T. Malignant phosphaturic mesenchymal tumor, mixed connective tissue variant of the tongue. *Auris Nasus Larynx*. 2009;36(1):104–5.
83. Wu H, Bui MM, Zhou L, Li D, Zhang H, Zhong D. Phosphaturic mesenchymal tumor with an admixture of epithelial and mesenchymal elements in the jaws: clinicopathological and immunohistochemical analysis of 22 cases with literature review. *Mod Pathol*. 2019;32(2):189–204.

84. Agaimy A, Michal M, Chiosea S, Petersson F, Hadravsky L, Kristiansen G, et al. Phosphaturic mesenchymal tumors: clinicopathologic, immunohistochemical and molecular analysis of 22 cases expanding their morphologic and immunophenotypic spectrum. *Am J Surg Pathol*. 2017;41(10):1371–80.
85. Yamada Y, Kinoshita I, Kenichi K, Yamamoto H, Iwasaki T, Otsuka H, et al. Histopathological and genetic review of phosphaturic mesenchymal tumours, mixed connective tissue variant. *Histopathology*. 2018;72(3):460–71.
86. Lee JC, Su SY, Changou CA, Yang R-S, Tsai K-S, Collins MT, et al. Characterization of FN1-FGFR1 and Novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. *Mod Pathol*. 2016;29(11):1335–46.
87. Tajima S, Fukayama M. Fibroblast growth factor receptor 1 (FGFR1) expression in phosphaturic mesenchymal tumors. *Int J Clin Exp Pathol*. 2015;8(8):9422–7.
88. Carter JM, Caron BL, Dogan A, Folpe AL. A novel chromogenic in situ hybridization assay for FGF23 mRNA in phosphaturic mesenchymal tumors. *Am J Surg Pathol*. 2015;39(1):75–83.
89. Lee JC, Jeng YM, Su SY, Wu CT, Tsai KS, Lee CH, et al. Identification of a novel FN1-FGFR1 genetic fusion as a frequent event in phosphaturic mesenchymal tumour. *J Pathol*. 2015;235(4):539–45.
90. Grulois V, Buysschaert I, Schoenaers J, Debruyne F, Delaere P, Vander Poorten V. Brown tumour: presenting symptom of primary hyperparathyroidism. *B-ENT*. 2005;1(4):191–5.
91. Hong WS, Sung MS, Chun KA, Kim JY, Park SW, Lee KH, et al. Emphasis on the MR imaging findings of brown tumor: a report of five cases. *Skelet Radiol*. 2011;40(2):205–13.
92. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res*. 2012;18(16):4415–24.
93. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. *Curr Opin Oncol*. 2012;24(4):397–403.
94. Stagner AM, Sajed DP, Nielsen GP, Ebb DH, Faquin WC, Chebib I, et al. Giant cell lesions of the maxillofacial skeleton express RANKL by RNA in situ hybridization regardless of histologic pattern. *Am J Surg Pathol*. 2019;43(6):819–26.
95. Won KY, Kalil RK, Kim YW, Park YK. RANK signalling in bone lesions with osteoclast-like giant cells. *Pathology*. 2011;43(4):318–21.
96. O'Connell JE, Bowe C, Murphy C, Toner M, Kearns GJ. Aggressive giant cell lesion of the jaws: a review of management options and report of a mandibular lesion treated with denosumab. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;120(5):e191–8.
97. Schreuder WH, Coumou AW, Kessler PA, de Lange J. Alternative pharmacologic therapy for aggressive central giant cell granuloma: denosumab. *J Oral Maxillofac Surg*. 2014;72(7):1301–9.
98. Palmerini E, Ruggieri P, Angelini A, Boriani S, Campanacci D, Milano GM, et al. Denosumab in patients with aneurysmal bone cysts: a case series with preliminary results. *Tumori*. 2018;104(5):344–51.
99. Kurucu N, Akyuz C, Ergen FB, Yalcin B, Kosemehmetoglu K, Ayvaz M, et al. Denosumab treatment in aneurysmal bone cyst: evaluation of nine cases. *Pediatr Blood Cancer*. 2018. <https://doi.org/10.1002/pbc.26926>.
100. Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia. *Bone Rep*. 2017;7:90–7.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.