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Diagnostic Approach to Giant Cell Lesions in the Oral and Maxillofacial Region: A Proposed Algorithm

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Abstract

Giant cells with multiple nuclei are frequently observed in histopathological examinations and are often crucial for diagnosis, though they can occasionally lead to diagnostic challenges. This study highlights a series of cases involving giant cell lesions (GCL), focusing on the differential diagnosis and the additional diagnostic methods used to reach a conclusive diagnosis. The aim was to develop a diagnostic approach to more accurately characterize these lesions. We reviewed all cases from January 2018 to June 2019 in the department, including those where giant cells were either a primary or secondary finding. Of 1000 biopsies, 25 cases were identified based on the presence of giant cell morphology. The most common lesions included central giant cell granuloma, cherubism, hyperparathyroidism, peripheral giant cell granuloma, tuberculosis, and hybrid lesions. A step-by-step approach for differential diagnosis was created, and a diagnostic algorithm was established, which is now in use for GCL cases. The use of radiological imaging, serological tests, and sometimes special staining techniques is crucial for accurate histopathological diagnosis. This proposed algorithm streamlines the diagnostic process, helping to quickly narrow down the necessary investigations for effective diagnosis.

Keywords: Histopathology, Jaws, Multinucleated giant cells, Central giant cell lesions, Oral and maxillofacial region

Introduction

Multinucleated giant cells (MGCs) are larger than typical cells, exhibiting a unique structure and function. These cells contain multiple nuclei distributed within the cytoplasm, which is a characteristic feature. MGCs are frequently found in histopathological studies of a variety of oral and maxillofacial conditions. The first description of these cells in granulomas associated with tuberculosis was made by Rokitansky and Langhans over a century ago. Giant cell lesions (GCLs) refer to a group of conditions that feature numerous multinucleated cells, resembling osteoclasts, in the connective tissue stroma. These lesions are categorized as peripheral when located in soft tissues or central when found in jawbone tissues [1-3].

According to a report by Mohajerani *et al*. [4], 6.36% of oral biopsies involved lesions containing multinucleated giant cells. These cells are easily identified under a microscope and serve as a diagnostic feature in certain conditions, such as peripheral giant cell granuloma (PGCG) and giant cell fibroma. However, some lesions present a diagnostic challenge because of their atypical

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histopathological appearance. This necessitates a comprehensive diagnostic approach involving clinical, radiological, and other investigation methods. In certain instances, the presence of giant cells may merely be a coincidental finding that does not contribute to the diagnosis [5-7].

This study focuses on the prevalence of GCLs in the oral and maxillofacial regions in our department. It explores their differential diagnosis, the role of special stains, and other diagnostic techniques while proposing a preliminary algorithm for their diagnosis.

This case series is the first to examine the significance of giant cells in diagnosing oral lesions, whether they are pathognomonic, lead to diagnostic confusion, or are incidental findings.

Materials and Methods

Following the ethical guidelines set by the Helsinki Declaration, we analyzed records from the Department of Oral Pathology and Microbiology between January 2018 and June 2019. The study included all cases showing giant cells in histopathology with available clinical, radiological, and additional diagnostic data. Six pathologists conducted a retrospective review of these cases, categorizing them according to a classification system used in our department. The classification considered whether giant cells were diagnostic, coexisted with other lesions (hybrid lesions), caused diagnostic ambiguity or were non-diagnostic findings **(Table 1)**. Cases with insufficient data on clinical history, photographs, radiological images, or other relevant investigations were excluded from the study.

Table 1. Classification of giant cell lesions based on diagnostic role in oral and maxillofacial pathology

Classification	Conditions
Lesions with pathognomonic giant cells	- Microbial giant cell lesions: tuberculosis, histoplasmosis, herpetic infections - Peripheral reactive giant cell lesions: peripheral giant cell granuloma, orofacial granulomatosis - Central giant cell lesions: central giant cell granuloma, hyperparathyroidism, cherubism, aneurysmal bone cyst - Neoplastic Lesions: - Benign: giant cell tumor, giant cell fibroma - Malignant: malignant giant cell tumor, Hodgkin's lymphoma (reed-sternberg cells) - Other conditions: foreign body granuloma, fibrous histiocytoma, Paget's disease
Hybrid or diagnostic dilemma lesions	- Giant cell granuloma (GCG) may coexist with: - Aneurysmal bone cyst - Odontogenic keratocyst - Fibrous dysplasia - Ossifying fibroma - Central odontogenic fibroma - Florid cemento-osseous dysplasia - Neurofibromatosis type 1 - Noonan Syndrome
Lesions with non-diagnostic giant cells	- Periapical granuloma or cyst - Unicystic ameloblastoma - Squamous cell carcinoma

Results and Discussion

A summary of 23 giant cell lesion cases is presented in **Table 2**.

Table 2. Summary of 23 giant cell lesion cases

Case No.	Age/ Sex	Location	Clinical presentation	Radiological findings	Additional tests	Diagnosis
1	42/M	Buccal mucosa	Ulcer	MRI shows an enhanced lesion in the right masseteric area	ZN stain, Mantoux, culture, Interferon-gamma assay – all negative, ESR elevated	Tuberculosis
2	22/M	Hard palate	Swelling	Osteolytic lesion spanning from 16 to 21	Mantoux, Interferon assay, chest X-ray – all negative, ESR raised	Chronic granulomatous inflammation
3	70/M	Mandibular alveolus	Soft tissue mass	-	PAS-positive, GMS positive	Histoplasmosis
4	23/M	Retromolar	Soft tissue mass	-	-	Peripheral giant cell granuloma
5	28/F	Buccal vestibule	Soft tissue mass	-	-	Peripheral giant cell granuloma
6	46/M	Lower lip	Swelling	-	Normal ACE, ZN staining, Mantoux test negative	Orofacial granulomatosis
7	40/M	Mandible	Swelling	Multilocular radiolucency crossing midline	Normal serum PTH, and Ca levels	Central giant cell granuloma
8	10/M	Bilateral mandible	Cherubic appearance	Mixed radiolucent-radiopaque lesion	-	Cherubism
9	37/F	Bilateral mandible, clivus	Swelling	Osteolytic lesions	Increased serum PTH, and Ca levels	Hyperparathyroidism
10	55/M	Mandible	Swelling	Osteolytic lesion	-	Central giant cell granuloma
11	14/M	Mandible	Swelling	-	-	Central giant cell granuloma
12	34/F	Maxilla	Swelling	Osteolytic lesion in anterior maxilla	-	Central giant cell granuloma
13	18/F	Mandible	Swelling	Osteolytic lesion 34-37	-	Central giant cell granuloma
14	52/M	Mandible	Swelling	Osteolytic lesion protruding from the lower border	-	Central giant cell granuloma
15	42/M	Mandible	Swelling	Osteolytic lesion crossing midline	-	Central giant cell granuloma
16	17/F	Mandible	Swelling	Osteolytic lesion at 24-26	-	Central giant cell granuloma
17	37/F	Posterior mandible	Swelling	Osteolytic lesion	Normal serum PTH	Central giant cell granuloma
18	23/M	Anterior maxilla	Swelling	Osteolytic lesion	Normal serum PTH	Central giant cell granuloma
19	21/M	Posterior mandible	Swelling	Osteolytic lesion	Normal serum PTH	Central giant cell granuloma

20	30/F	Mandible	Swelling	Expansile osteolytic lesion	Serum PTH: 407.2 pg/ml	Hyperparathyroidism-related brown tumor
21	06/M	Bilateral mandible	Cherubic appearance	Mixed radiolucent-radiopaque lesion	-	Cherubism
22	13/M	Bilateral mandible	Cherubic appearance	Mixed radiolucent-radiopaque lesion	-	Cherubism
23	05/M	Maxilla and mandible	Cherubic appearance	Mixed radiolucent-radiopaque lesion	-	Cherubism
24	51/M	Mandible	Swelling	Multilocular radiolucency	IHC panel – CD68+ve, panCK, Ki67, p53-ve	OKC with giant cell granuloma
25	06/M	Mandible	Swelling	Unilocular radiolucency	IHC panel – SATB2+ve, MDM2, CDK4-ve, Ki67 (15%)	Juvenile trabecular ossifying fibroma with giant cell granuloma

From our investigation of 1000 consecutive cases, we identified 25 cases where giant cells were crucial for the diagnosis and an additional 8 instances where giant cells were considered secondary findings. Among intra-osseous lesions, central giant cell granuloma (11 cases) was the most frequent, followed by cherubism (4 cases) and hyperparathyroidism (2 cases). One case of tubercular osteomyelitis was also included. On the peripheral side, we found two cases of peripheral giant cell granuloma, two microbial giant cell lesions (tuberculosis and histoplasmosis), one case of orofacial granulomatosis, and two hybrid lesions. Out of these, 18 were male and 7 female, aged between 10 and 70 years. Further discussion will focus on specific cases, illustrating their distinct clinical, radiological, and histopathological features.

Case report: central giant cell lesion

Patient overview

A 52-year-old male presented with a 1.5-year history of swelling in the mandibular anterior region. On clinical examination, a firm swelling was palpable, spanning from the 35th to the 46th tooth region. The orthopantomogram (OPG) demonstrated a large radiolucent lesion extending from the lower border of the anterior mandible, prompting consideration of central giant cell granuloma (CGCG) and ameloblastoma as potential diagnoses.

Microscopic findings

Histopathological examination revealed a well-organized fibrovascular stroma interspersed with multiple multinucleated giant cells, each containing between 4 and 20 nuclei. Additionally, the tissue displayed densely packed collagen fibers and a profusion of endothelial-lined capillaries, as seen in **Figure 1**.

Laboratory investigations

Serum analysis for parathyroid hormone (PTH), calcium, phosphorus, and alkaline phosphatase levels was within normal ranges, helping to rule out certain differential diagnoses.

Differential diagnosis

Several conditions were considered based on clinical and histopathological features:

Giant cell tumor (GCT): GCT is a benign but locally aggressive tumor primarily seen in long bones, though it can occasionally affect the jaws. It typically shows a diffuse distribution of osteoclast-like giant cells and macrophages with a background of stromal mononuclear cells. These cells may display increased mitotic activity but lack significant atypia. The absence of such features in this case excluded GCT as a diagnosis.

Hyperparathyroidism (HPT): The absence of elevated PTH and calcium levels ruled out the possibility of HPT, which commonly presents with brown tumors due to altered bone metabolism.

Cherubism: This condition, which generally presents with symmetrical, bilateral involvement of the mandible in young individuals, was ruled out due to the patient's age and the unilateral nature of the lesion.

Aneurysmal bone cyst: This cystic lesion is characterized by blood-filled spaces lined by connective tissue, often with multinucleated giant cells. The surgical

observations, including the lack of a blood-soaked sponge appearance, helped to exclude this diagnosis.

Malignant giant cell tumor: Given the absence of necrosis, abnormal mitosis, and other malignant features, the possibility of a malignant giant cell tumor was ruled out.

After excluding the above conditions, a diagnosis of central giant cell granuloma (CGCG) was confirmed.

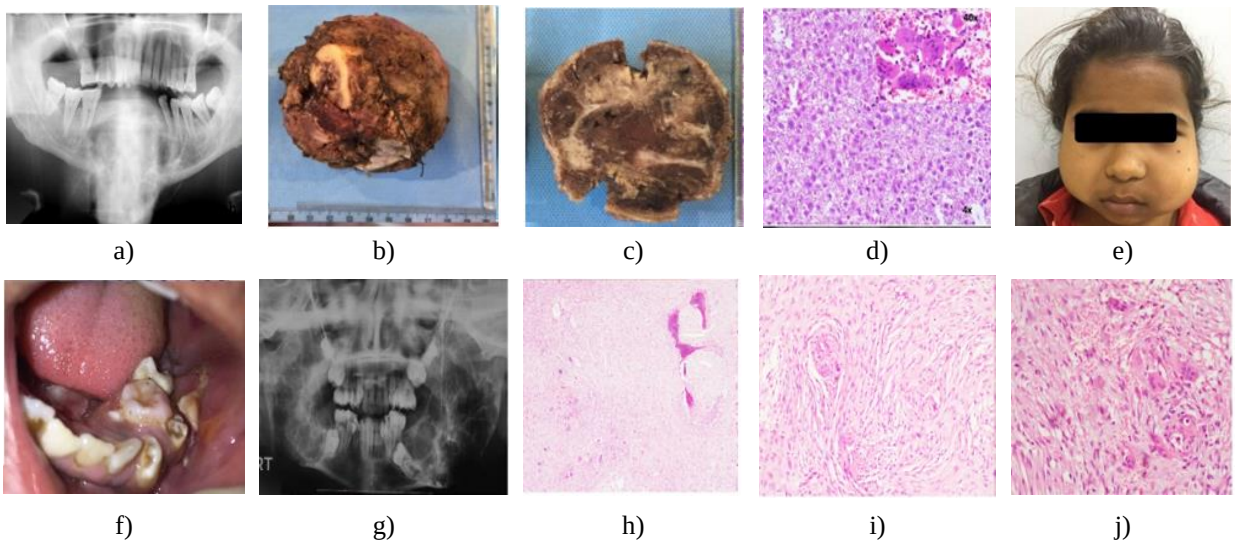

Figure 1. Case 1-Central giant cell granuloma (a-d) presenting as a radiolucent lesion of the anterior mandible (a), gross showed hemorrhagic areas (b, c), histopathology showed MGCs (H&E;4X;inset40X) (d), case 2-Cherubism (e-j), presented with bilateral swelling (e, f), mixed radiolucent-radiopaque lesion (h), histopathologicaly with osteoid (h; H&E; 4X), perivascular eosinophilic cuffing (i; 10X) and MGCs (j; 40X).

Case 2

A 10-year-old girl presented with gradual swelling in both the right and left cheek areas, resulting in a cherubic appearance that had developed slowly over the past year. Upon examination, a firm swelling was noted in the mandibular alveolus and both the mandibular rami. Radiographic images, including an orthopantomogram (OPG), showed a mixed radiolucent-radiopaque lesion in the rami of the mandible, with mixed dentition. A CBCT scan confirmed the same findings, with an additional developing lesion in the right maxillary molar region. A bilateral incisional biopsy revealed a fibrocellular stroma, with perivascular eosinophilic cuffs, multinucleated osteoclastic giant cells, minimal inflammatory cells, some myxomatous areas, and reactive osteoid formation lined by osteoblasts. Given the patient's young age and the bilateral nature of the lesion, other giant cell lesions were excluded, confirming the diagnosis of cherubism.

Case 3

A 37-year-old woman presented with several multilocular lesions affecting both the mandible and the clivus region. CT scans with contrast (CECT) and PNS views revealed a multiloculated cystic lesion in the body of both right and left mandibles, with evidence of bone destruction and remodeling near the first and second molars. An MRI showed another lesion in the anterior clivus, extending into the sphenoid sinuses, causing thinning of the diaphragmatic sellae. Microscopic examination of biopsies from the left and right mandibular lesions, as well as the clival tumor, revealed a fibrovascular stroma interspersed with numerous multinucleated giant cells. The stroma contained areas of hemorrhage and focal sinusoidal spaces, with several regions showing active osteoid formation in varying stages of maturation, with osteoblastic rimming **(Figure 2)**.

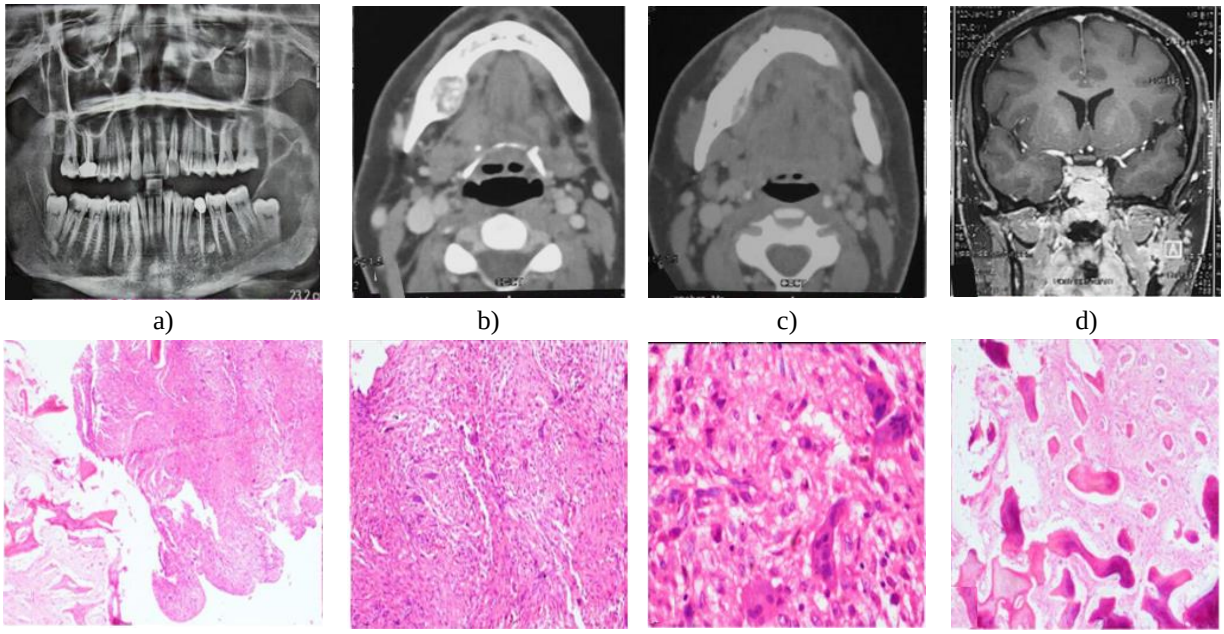

Figure 2. Case 3-hyperparathyroidism (a-h), OPG shows an osteolytic lesion in the left ramus (a) and CECT shows osteolytic lesions in the left and right mandible (b, c), MRI revealed a diffuse lesion in the clivus (d), histopathology showed giant cells with abundant bone formation (e-h; H&E; 4X, 10X, 40X, 4X).

Investigations

The serum parathormone (PTH) was elevated at 81.1 pg/ml, while serum calcium remained within normal limits.

Differential diagnosis

The case presented with multiple potential diagnoses, including hyperparathyroidism, aneurysmal bone cyst, and a hybrid lesion involving ossifying fibroma with giant cell granuloma. Additionally, the presence of lesions across both the mandible and skull raised the possibility of polyostotic fibrous dysplasia. However, radiological imaging did not reveal a well-defined mixed radiopaque-radiolucent lesion, which ruled out ossifying fibroma with giant cell granuloma. Furthermore, both the radiologic absence of a peau-d'orange pattern and the lack of "Chinese letter" woven bone appearance on histopathology helped eliminate the diagnosis of polyostotic fibrous dysplasia.

Ultimately, the diagnosis of hyperparathyroidism-related brown tumor was made based on the presence of multiple osteolytic lesions and elevated PTH levels.

Peripheral lesions

1. Microbial giant cell lesions

Case 4

A 42-year-old male presented with a non-painful ulcer on the right retromolar trigone, which had been present for three months. During examination, the right submandibular lymph nodes were found to be enlarged and firm. A preliminary diagnosis of traumatic ulcer was considered, with tuberculosis and malignancy as possible alternatives. MRI scans showed a lesion enhancing in the right masseteric space, involving the right medial pterygoid muscle. Histopathological examination revealed a cellular stroma containing several inflammatory cell clusters, interspersed with multinucleated giant cells resembling Langhans cells, all surrounded by fibrotic tissue. High magnification showed the giant cells had 7-15 nuclei, with accompanying histiocytes, lymphocytes, and plasma cells. The lesion also demonstrated a rich network of blood vessels with a perivascular inflammatory infiltrate primarily composed of plasma cells.

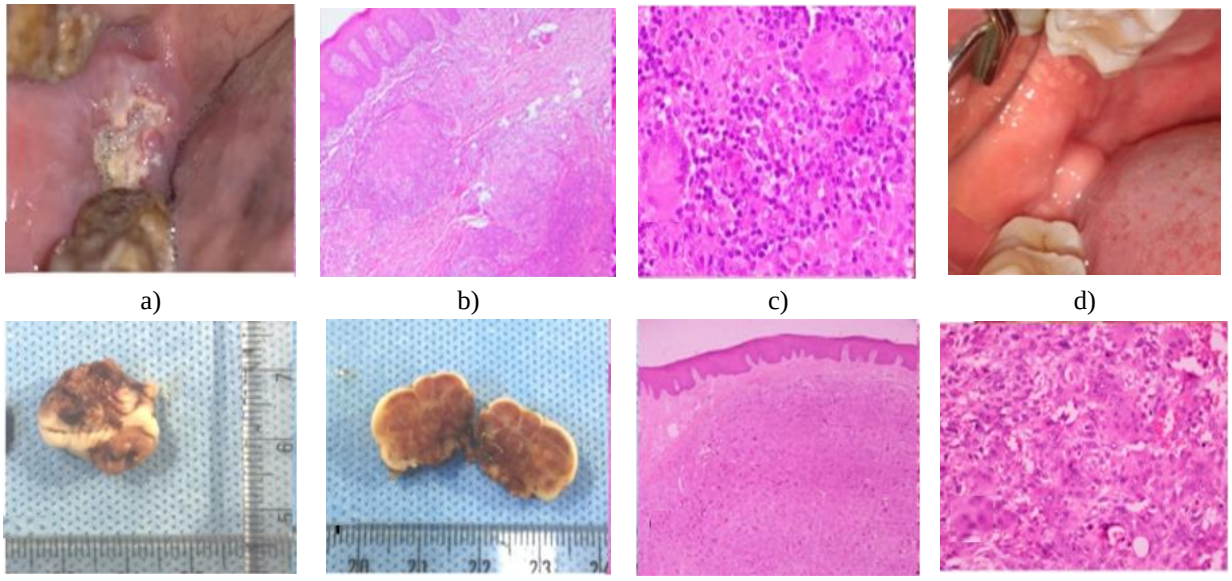

Figure 3. Case 4-tuberculosis ulcer (a-d), clinical presentation (a), photomicrograph showing Langhans-type giant cells (b,c; H&E; 4X, 40X), healed lesion (d), case 5-peripheral giant cell granuloma (e-h), lobular gross specimen and hemorrhagic cut surface (e, f), and photomicrograph showing epithelium with multinucleated giant cells (g, h; H&E; 4X, 40X).

Further testing

Ziehl-Neelsen staining came back negative for mycobacterium. Similarly, PAS staining showed no abnormalities.

Differential diagnoses

Granulomatous inflammation identified in the tissue sample excluded both traumatic and malignant ulcerations. Differential diagnoses considered included tuberculosis, sarcoidosis, foreign body granuloma, and fungal granulomas. The absence of foreign bodies and foreign-body giant cells helped rule out foreign-body granuloma. The lack of multi-system involvement, absence of eosinophilia, and normal ACE levels made sarcoidosis unlikely. Fungal granulomas were also excluded due to the absence of fungal elements under PAS staining. Based on the granulomatous findings, epidemiological data, and positive cultures, tuberculosis was diagnosed.

The patient was then referred to a pulmonologist for additional management. Follow-up tests, including the Mantoux test, culture, and interferon-gamma assays, confirmed the diagnosis of *M. tuberculosis*. Anti-tuberculosis treatment was initiated, and the lesion completely healed after regular monitoring **(Figure 3)**.

Peripheral giant cell lesions

Case 5

A 23-year-old male sought medical attention for a mass in the left retromolar area that had developed over the last six months. The lesion was well-defined and had a nodular surface. Histological analysis revealed parakeratinized epithelium surrounding a fibro-angiomatous stroma, which contained multinucleated giant cells. These cells were separated by bands of normal connective tissue. Under high magnification, there were numerous multinucleated giant cells (5-12 nuclei), surrounded by active fibroblasts, dilated blood vessels, and an intense chronic inflammatory cell response. The final diagnosis was peripheral giant cell granuloma **(Figure 3)**.

Hybrid lesions and giant cells

Case 6

A 51-year-old male presented with extensive swelling on the right side of his mandible. He had a history of cystic enucleations and tooth extractions (48th tooth in 2005 and 47th in 2012). Clinical examination revealed swelling in the mandibular angle, body, and ramus, causing displacement of the buccal vestibule. Histopathological examination showed areas of thickened, hyperplastic squamous epithelium with separation from the underlying collagenous capsule.

Some areas displayed basal cell proliferation and basal palisading. Another section showed a dense accumulation of histiocytes, multinucleated giant cells, and endothelial cells in the stroma. On higher magnification, histiocytes exhibited nuclear pleomorphism and hyperchromatism. Immunohistochemical staining was positive for CD68 and negative for p40, Pan-CK, and p53, while the Ki-67 index was low **(Figure 4)**.

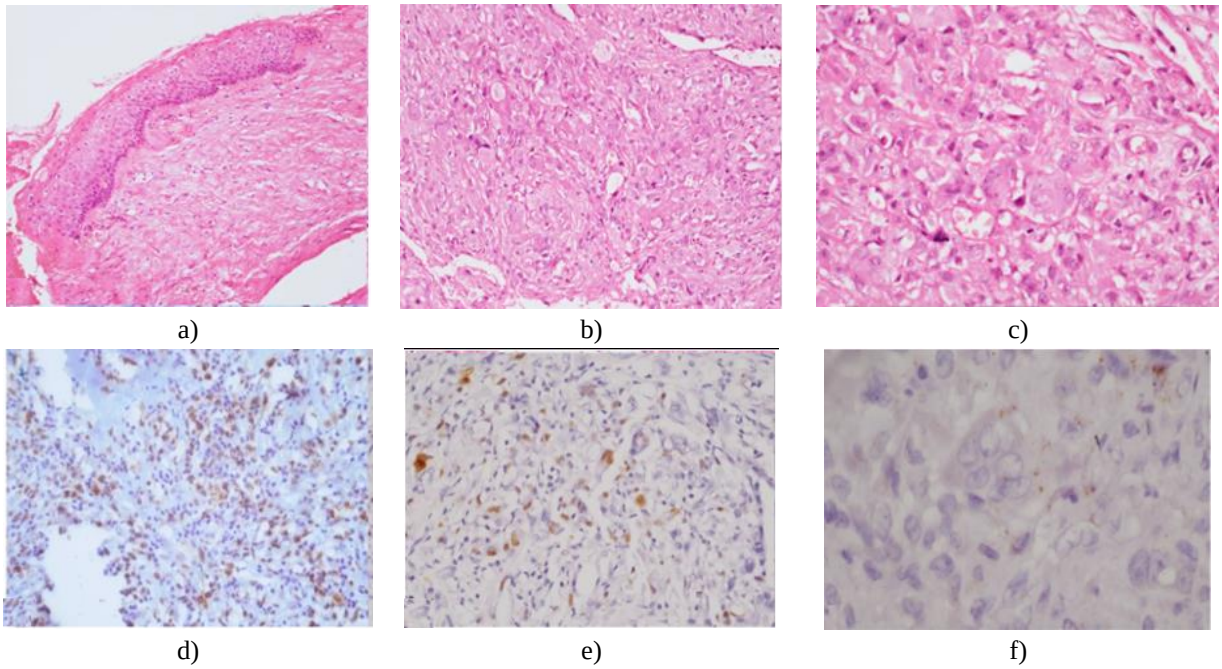

Figure 4. Case 6–hybrid lesion of Odontogenic keratocyst with giant cell granuloma displaying parakeratotic lining (a; H&E; 10X), highly cellular stroma with histiocytes, multinucleated giant cells (b, c; H&E; 20X, 40X), CD68 positive histiocytes (d), low Ki67 (e), and negativity to PanCK (f).

Differential diagnosis

Given the highly cellular nature of the lesion, squamous cell carcinoma and histiocytic sarcoma were considered in the differential diagnosis. The low Ki67 index suggested that the lesion exhibited benign characteristics, and the CD68 positivity was indicative of histiocytic cells. Ultimately, the lesion was diagnosed as an odontogenic keratocyst with a giant cell granuloma.

While giant cell lesions (GCLs) are relatively common in oral pathology, there has been limited systematic investigation into their diagnostic value. Current literature primarily consists of individual case reports or case series focused on one specific type of giant cell lesion. As far as we know, there has been no comprehensive study that aggregates multiple types of giant cell lesions while emphasizing the differential diagnosis and diagnostic approach. Individual reports are often insufficient for pathologists faced with challenging cases involving giant cell lesions. Thus, establishing a systematic diagnostic algorithm for these lesions is crucial. In our institution, GCLs accounted for 2.3% of cases, whereas Mohajerani *et al*. reported a higher prevalence of 6.2% in Iran [4]. This difference could be due to regional variations in the frequency of these lesions or differences in the types of biopsies submitted to pathologists.

Histologically, GCLs are divided into peripheral and central giant cell lesions, which help narrow down potential diagnoses **(Figure 5)**. Central lesions, which are giant cell-rich lesions of bone, include a variety of tumors that affect the skeleton. A summary of these central lesions within the jaws is presented in **Table 3**.

Table 3. Differential diagnosis of central giant cell lesions

Lesion	Age	Sex	Location	Clinical features	Radiographic appearance	Histopathology	Serum calcium (Ca)	Serum phosphorus (P)	Serum alkaline phosphatase (ALP)
Central giant cell granuloma (CGCG) (non-neoplastic)	< 30 years	F > M	Exclusively in the jaws, typically in the anterior mandible, crossing midline	Asymptomatic, detected during routine radiographic exam; non-aggressive form shows painless bone expansion; aggressive form shows pain, cortical perforation, and root resorption.	Expansile, well-defined, scalloped, non-corticated, multilocular (less commonly unilocular) radiolucency	Loose fibrous connective tissue with numerous proliferating fibroblasts, macrophages laden with hemosiderin, capillaries, and multinucleated giant cells in aggregates or diffusely scattered.	N	N	N
Giant cell tumor (osteoclastoma) (benign, locally destructive neoplasm)	3rd - 4th decades	M > F	Rare in skull; common in long bones (distal femur, proximal tibia, distal radius, proximal humerus, spine, and rare in flat bones)	Pain, swelling, and pathological fractures	Radiolucent with irregular, poorly defined borders	Prominent stromal component, high cellularity, mitotic figures present; larger giant cells with 40-60 nuclei; homogenous distribution pattern; may contain inflammatory cells and areas of necrosis, with little hemorrhage or hemosiderin pigment.	N	N	N
Primary hyperparathyroidism (PHPT)	F > M	Older age	Generalized skeletal disease	Stones, bones, groans, and moans	Osteolytic lesions resembling CGCG	Similar to CGCG	N or osteolytic lesions	N or osteolytic lesions	N

Secondary hyperparathyroidism (SHPT)	F > M	Older age	Same as PHPT	Same as PHPT	Same as PHPT	Same as PHPT	N or osteolytic lesions	N or osteolytic lesions	N
Cherubism (autosomal dominant, SH3BP2 mutation on chromosome 4)	F > M	2-4 years (regresses after puberty)	Mandible and maxilla	Characteristic "cherub" appearance with rounded jaws and upturned eyes; bilateral submandibular and cervical lymphadenopathy common	Bilateral, symmetrical, multilocular radiolucency with thick sclerotic borders; "floating tooth syndrome" with unerupted teeth	Numerous giant cells in a collagenous stroma with abundant fibroblasts; perivascular eosinophilic cuffing is characteristic.	N	N	N (physiological increase in ALP during active growth)
Noonan-like multiple giant cell lesion syndrome (autosomal dominant)	-	-	Congenital anomaly	Short stature, craniofacial dysmorphisms, and congenital heart defects	Multilocular radiolucency	Similar to cherubism with numerous giant cells in a collagenous stroma and perivascular eosinophilic cuffing	N	N	N (physiological increase in ALP during active growth)
Aneurysmal bone cyst	M = F	< 20 years	Affects nearly every part of the skeleton, with long bones and vertebrae being common; mandible > maxilla	Painful swelling, firm mass; can be primary or secondary (arising from other conditions)	Multilocular radiolucency with a "honeycomb" or "soap bubble" appearance, eccentric ballooning	Cavernous blood-filled spaces, no endothelial lining; giant cells (similar to CGCG) with varying amounts of hemosiderin pigment present.	-	-	-
Malignant giant cell tumor (very rare sarcoma)	-	-	Arises from benign giant cell tumors (primary) or previously diagnosed GCT (secondary)						

Various conditions, including central giant cell granuloma (CGCG), giant cell tumor, cherubism, brown tumor related to hyperparathyroidism (HPT), and malignant giant cell tumor, all present giant cells within

the affected tissue. Among these, CGCG is a non-cancerous granuloma where osteoclastic giant cells are embedded in fibro-cellular tissue. The case of CGCG described in this study (case 1), **(Figure 1)** aligns with typical presentations, though it lacks a trauma history, which is often seen with CGCG. The giant cell component might form in response to recent bleeding, while the fibroblastic part likely represents the lesion's older or healing portion [7]. The precise origin of the giant cells remains uncertain, but it has been suggested that they could arise from osteoblasts, mononuclear cells from the phagocytic system reacting to hemorrhage, endothelial cells, or other mesenchymal cells [8].

Brown's tumor, which shares histological features with CGCG, is characterized by multiple lesions, increased parathormone levels, and associated conditions like hypercalcemia and hypophosphatemia [9]. Techniques such as ultrasound or CT scans help identify abnormalities in the parathyroid glands [9, 10]. Case 3 in this report showed osteolytic lesions in the mandible and clivus, with giant cell granuloma on histopathology and significant hemorrhaging. Elevated PTH levels confirmed a Brown tumor related to hyperparathyroidism. Thus, CGCG should be a diagnosis of exclusion and evaluated for signs of primary hyperparathyroidism.

Cherubism, another possible diagnosis for intraosseous giant cell lesions, is marked by symmetrical jaw enlargement, typically involving the mandible and maxilla. It is inherited as an autosomal dominant trait due to a mutation in the SH3BP2 gene, which controls osteoblast and osteoclast activity during tooth eruption. Mutations in this gene can lead to abnormal osteoclast activity, causing osteolysis and delayed tooth eruption [11]. Case 2 **(Figure 1)** represents a typical cherubism case in a 10-year-old girl with bilateral lesions in the mandible, unerupted teeth, and giant cells in the histopathology.

Giant cell lesions (GCLs) can also occur peripherally, affecting the gingiva, buccal mucosa, and tongue. The most frequent lesion in these areas is peripheral giant cell granuloma (PGCG), which is most commonly seen in children with mixed dentition and adults in their 30s-40s. It is believed that the giant cells in PGCG may be a reactive response, originating from bone marrow mononuclear cells in response to an unspecified trigger from the surrounding tissue [12]. The idea that these cells originate from osteoclasts caused by deciduous tooth resorption explains their typical location in front of permanent molars [11]. Other types of GCLs that may occur in these areas include bacterial, fungal, and foreign-body granulomas. Tuberculosis, caused by *M. tuberculosis*, is the most common chronic bacterial infection in this region, with non-caseating granulomas occasionally found in such cases [13]. Case 3 **(Figure 2)** showed non-caseating granulomas. Special staining methods like Ziehl-Neelsen (ZN) are used to detect bacteria in tissue samples. This case, however, showed negative ZN staining, aligning with the fact that acid-fast bacilli are only detected in 27-60% of cases due to their low presence in tissue samples [6].

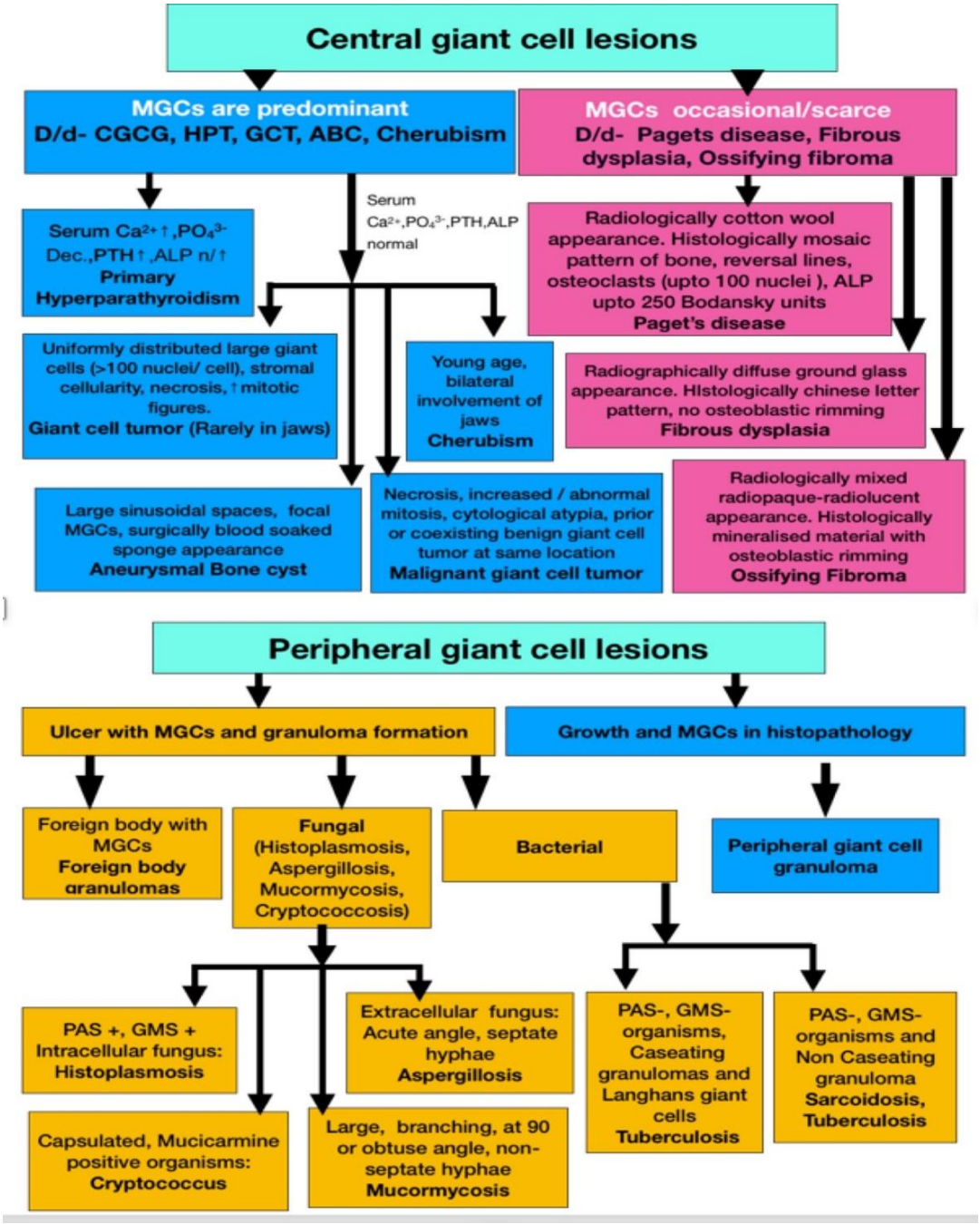

Figure 5. Diagnostic algorithm for the accurate pathological characterization of giant cell lesions

Brown's tumor is one of the closest histopathologic mimics of central giant cell granuloma (CGCG). However, it tends to present with multiple lesions, elevated parathyroid hormone (PTH) levels, hypercalcemia, and hypophosphatemia [9]. Imaging methods such as ultrasound, CT scans, or technetium scans can help in detecting abnormalities in the parathyroid glands [9, 10]. In Case 3 of the current study, multiple osteolytic lesions in the mandible and clivus showed features typical of CGCG, including significant hemorrhage. The elevated PTH levels supported the diagnosis of Brown's tumor resulting from hyperparathyroidism. Therefore, CGCG should always be considered after excluding the possibility of primary hyperparathyroidism.

Cherubism is another condition that can be confused with intraosseous giant cell lesions. It is marked by symmetrical jaw enlargement, usually affecting the mandible and maxilla. The condition is inherited as an autosomal dominant trait due to mutations in the SH3BP2 gene, which influences osteoblast and osteoclast activity during tooth eruption. Mutations in SH3BP2 lead to pathological osteoclast activation, causing osteolysis and the development of unerupted teeth [11]. Case 2 **(Figure 1)** from our study was a typical cherubism case in a 10-year-old girl with bilateral mandibular lesions, delayed tooth eruption, and histopathological evidence of giant cells.

In addition to central lesions, giant cell lesions (GCLs) can also be found peripherally, affecting areas like the gingiva, buccal mucosa, and tongue. Peripheral giant cell granuloma (PGCG) is the most common lesion in these regions, typically occurring in children during mixed dentition and in adults between 30 and 40 years of age. Some researchers suggest that the giant cells in PGCG may arise reactively from mononuclear cells circulating through the bloodstream, likely in response to an unidentified stimulus from the stroma [12]. These cells could also originate from osteoclasts after the resorption of deciduous teeth, which explains why PGCG commonly appears near the permanent molars [11]. Other types of GCLs in this area can include granulomas caused by bacterial, fungal, or foreign body reactions. Tuberculosis, caused by *M. tuberculosis*, is a frequent bacterial infection in the region, and while caseating granulomas are often found, non-caseating granulomas are also possible [13]. In Case 3 **(Figure 2)** of this study, non-caseating granulomas were observed, and Ziehl-Neelsen staining was negative, which aligns with the finding that acid-fast bacilli are only present in a small percentage (27-60%) of cases due to their scarcity in tissue samples [6].

Hybrid lesions involving giant cell formations have also been reported in connection with other conditions like fibro-osseous lesions, Noonan syndrome, neurofibromatosis type 1, odontogenic keratocysts, and central odontogenic fibromas, among others [7-13]. A rare hybrid lesion observed in our study (case 6), **(Figure 4)** involved an odontogenic keratocyst and giant cell granuloma, which might be due to either a collision tumor or a rare variant of the condition, or even a reactive giant cell formation within the odontogenic keratocyst [14].

Additionally, our study found giant cells without significant diagnostic relevance in a variety of other lesions, including radicular cysts, periapical granulomas, fibrous dysplasia, glandular odontogenic cysts, both conventional and unicystic ameloblastomas, and tumor giant cells in squamous cell carcinoma [14]. In these cases, the presence of multinucleated giant cells often represents a foreign body reaction to substances like cholesterol crystals in cystic lesions, keratin from neoplastic cells, or histiocytic material [15].

Conclusion

While histopathology remains a key diagnostic tool for giant cell lesions, the correct diagnosis often requires the integration of clinical findings, radiological images, serological tests, and other diagnostic methods. By using a classification system and a systematic approach as outlined in this paper, pathologists can more effectively narrow down the differential diagnoses for these rare lesions and design an optimal investigative approach.

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