

# Malignancy mimics- diagnostic perplexities for oral and maxillofacial pathologists

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## Abstract

**Objective:** In pathology practice, one frequently encounters benign lesions which superficially resemble malignancy clinically and histopathologically. The diagnostic pitfalls can be avoided if the approach exemplified in the present study is followed. We expect that familiarity of these cases will be helpful for pathologists at the beginning of their career.

**Methods:** Clinical case records of all the pathological specimens reported in our laboratory from January 2018 to September 2019 were queried. Cases displaying pseudotumor features were reviewed along with the special stains were performed and immunohistochemistry (IHC) studies. A working classification of pseudotumors presenting in the oral cavity was proposed.

**Results:** Immunoglobulin G4-related disease, nodular fasciitis, fibrolipoma, odontogenic keratocyst with giant cell granuloma, juvenile ossifying fibroma with central giant cell granuloma and tumor-induced osteomalacia were the most common diagnoses where the tissue specimens resembled malignancies on routine clinicoradiological evaluation and light microscopy of tissue specimens. Their differential diagnosis and the pathological diagnostic dilemmas are explained. We have also highlighted the importance of correlating clinical, radiological and microscopic details with the findings deduced from advanced pathological aids to establish the final diagnosis.

**Conclusions:** Pathologists should be aware of the conditions where the diagnosis of malignancy needs stricter evaluation to rule out malignant mimics. In such scenarios, correlation of light microscopy findings with clinical and radiological details cannot be overemphasized. Advanced pathological aids such as IHC, where necessary are often indispensable for reaching the accurate diagnosis in these cases.

**Keywords:** Immunohistochemistry, oral and maxillofacial region, pseudotumors, radiology

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## INTRODUCTION

Histopathology is still considered as gold standard for accurate diagnosis of lesions despite advancement in

clinical and imaging modalities. The clinician's dilemma when faced with clinically malignant looking lesions is dispelled by microscopic examination; however,

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histopathologically malignancy mimics pose a diagnostic challenge for the pathologists too. Table 1 summarizes the pseudotumors reported in literature.<sup>[1-6]</sup>

These (pseudotumors) lesions are actually benign or reactive in nature but microscopically show overlapping features with malignant neoplasms such as increased cellularity, cellular nuclear pleomorphism, spindle or infiltrative growth.<sup>[7]</sup> Erroneous diagnosis of malignancy in these lesions may result in considerable distress for the patient, repeat biopsies and unnecessary treatment. Litigation and souring of the clinician–patient relationship in these situations is not unexpected. Thus, adequate knowledge of these entities is essential, and they should be considered as a part of the differential diagnosis in our pathology practice. Recent advances in radiology, serology and histopathology (immunohistochemistry [IHC]) have greatly facilitated the exclusion of malignancy in such lesions.

Thus, this retrospective study was planned with the aim of identifying those benign aggressive rare lesions of the oral and maxillofacial region which imitated malignancies on clinical-radiological and light microscopic appearance and presented a diagnostic challenge for oral pathologists. Further, we emphasize the role of multidisciplinary approach combining clinical, histology and radiology with IHC to avoid erroneous diagnosis.

**Table 1: Various pseudomalignant lesions reported in literature and Benign lesions mimicking malignancy in our series**

Various pseudomalignant lesions reported in literature	
1. Inflammatory myofibroblastic tumor: Considered under spectrum of IgG-related disease which includes salivary glands, lacrimal glands (Mikulicz disease, Küttner's tumor)	
2. Amalgam tattoo: Resembles melanoma	
3. Aggressive mesenchymal tumors	
Juvenile OF, osteoblastoma, nodular fasciitis, intramuscular lipoma appears infiltrative, fibrolipoma, spindle cell lipoma and pleomorphic lipoma: Resembles sarcomas	
4. Necrotizing sialometaplasia	
5. Adenomatoid hyperplasia of minor salivary glands	
6. Sclerotic polycystic adenosis	
7. Traumatic granuloma with stromal eosinophilia	
Benign lesions mimicking malignancy in our series	
1. Inflammatory lesions	
IgG4-related disease	
2. Mesenchymal tumors	
Nodular fasciitis	
Fibrolipoma	
3. Hybrid lesions	
Odontogenic keratocyst with giant cell granuloma	
Juvenile ossifying fibroma with central giant cell granuloma	
4. Miscellaneous/paraneoplastic syndrome	
Tumor-induced osteomalacia	

IgG: Immunoglobulin G

## METHODS

We retrospectively queried the database of cases reported in the Department of Oral Pathology and Microbiology between January 2018 and September 2019. Lesions which were ultimately diagnosed as benign but displayed pseudotumors characteristics initially were retrieved from the archives.

In all these cases, there was substantial disagreement initially, with regard to the diagnosis, among the five experienced pathologists who independently examined the stained slides and correlated them with the clinicoradiological findings. After special staining (including IHC) and employment of ancillary and newer pathological techniques, the final diagnosis was declared to be the one mutually agreed upon by the three most experienced members of the pathology team. A working classification was formulated on the basis of their presenting features [Table 1].

## RESULTS

Out of total biopsies of 1500 cases, 6 benign lesions were found to be pseudotumors in nature. These included immunoglobulin G4 (IgG4)-related disease, nodular fasciitis, fibrolipoma, odontogenic keratocyst with giant cell granuloma, juvenile ossifying fibroma with central giant cell granuloma (CGCG) and tumor-induced osteomalacia. These cases are summarized in Table 2.

### Cases

#### *Inflammatory lesions*

##### Case 1

A 48-year-old male presented with diffuse firm swelling on the left posterior maxilla of 2.5-month duration. Computed tomography (CT) scan showed a soft-tissue mass lesion within the left retromolar trigone, involving the posterolateral and posterior parts of the medial wall of the left maxillary sinus with extension into the infratemporal fossa. Differentials of malignancy and aspergillosis were considered. Microscopy revealed loose collagen fiber bundles with interspersed fibroblasts, dense plasma lymphocytic infiltrate chiefly composed of plasma cells and lymphocytes surrounded by storiform fibrosis. IgG4 staining revealed more than 10 IgG4-positive plasma cells per high-power field. Verhoeff–Van Gieson stain did not reveal prominent obliterative phlebitis. Serum IgG levels were increased to 1.82g/dl. Final diagnosis of IgG4-related disease (IgG4-RD) was given [Figure 1].

#### *Mesenchymal tumors*

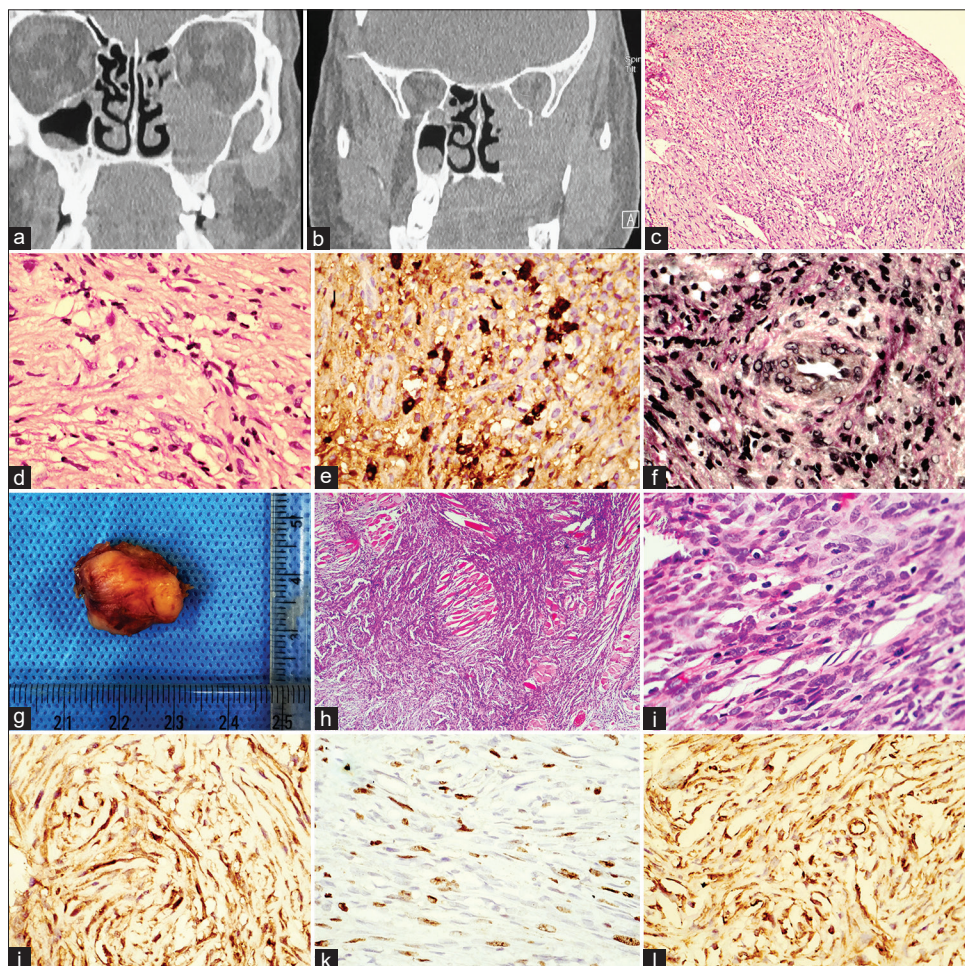
##### Case 2

A 71-year-old male presented with fibrous growth on the right maxilla noticed over a year. Gross examination

**Table 2: Summary of the cases described in the study**

Case number	Age (years)/sex	Site	Clinical presentation	Suspected malignancy (differential diagnoses)	Final diagnosis
1	48/male	Maxilla	Clinically presented as mild swelling in the maxilla. CT scan shows diffuse soft-tissue mass lesion extending from RMT to lateral pterygoid muscle	Lymphoma	IgG4-related disease
2	71/male	Maxilla	Clinically presented as firm pink growth	Fibrosarcoma Spindle cell squamous cell carcinoma Leiomyosarcoma	Nodular fasciitis
3	4/male	Buccal mucosa	Clinically presented as soft growth	Liposarcoma	Fibrolipoma
4	51/male	Mandible	Presented as mild swelling in the posterior mandible	Squamous cell carcinoma Histiocytic sarcoma	Odontogenic keratocyst with giant cell granuloma
5	6/male	Mandible	Presented as hard swelling in the mandible which radiographically showed unilocular radiolucency ballooning out from the lower border of the mandible	Osteosarcoma	Juvenile ossifying fibroma
6	33/male	Mandible	Bone pain and multiple fractures in skeleton with radiology showing mixed radiolucent radio-opaque lesion	Vitamin D deficiency osteomalacia Multiple myeloma Hyperparathyroidism	Tumor-induced osteomalacia (ameloblastic fibro-odontoma)

CT: Computerized tomography, RMT: Retromolar trigone



**Figure 1:** Case 1 – Immunoglobulin G4-related disease (a-f): NCCT face (coronal multiplanar reconstructed bone window) shows opacification of the left maxillary sinus with erosion of walls of the maxillary sinus and upper alveolus with soft-tissue extension into masticator space (a and b). Histopathology reveals storiform fibrosis, dense plasma lymphocytic infiltrate (c and d) and > 10 immunoglobulin G4 + plasma cells/high-power field (e). However, Verhoeff–Van Gieson Stain did not reveal prominent obliterative phlebitis (f) Case 2 – Nodular fasciitis (g-l): Photograph shows gross excisional specimen (g) which on histopathology reveals hypercellular stroma with fascicular and storiform arrangement with skeletal muscle invasion (h), few mitotic figures (i) and positivity for S100 (j), low Ki-67 proliferation index (k) and vimentin positivity (l)

showed well-circumscribed multinodular brownish firm tissue which on microscopy revealed discontinuous epithelium overlying hypercellular dense fibrous stroma with diffuse fascicular and storiform arrangement of collagen bundles along with a few areas of mature skeletal muscle invasion. High power revealed numerous spindle cells displaying few mitotic figures, numerous wavy fibers and some neural bundles. Differential diagnoses comprising spindle cell malignancies such as fibrosarcoma, spindle cell squamous cell carcinoma, leiomyosarcoma and synovial sarcoma were contemplated and aggressive, but benign spindle cell lesions such as nodular fasciitis, inflammatory myofibroblastic tumor and solitary fibrous tumor were considered as other possibilities.

IHC revealed immunopositivity for S100 and vimentin, patchy positivity for BCL2 and CD34 and immunonegativity for smooth muscle actin (SMA), desmin, PanCK, anaplastic lymphoma kinase (ALK),  $\beta$ -catenin and approximately 16% of Ki-67 proliferative index. No dysplasia in the overlying epithelium and negativity to PanCK excluded spindle cell squamous cell carcinoma.

Lack of cellular and nuclear atypia and immunopositivity to S100 excluded fibrosarcoma and immunonegativity to SMA and desmin ruled out leiomyosarcoma. Synovial sarcoma usually exhibits immunopositivity for PanCK and diffuse immunopositivity for BCL-2,<sup>[8]</sup> thus it was excluded. Majority of inflammatory myofibroblastic tumors show positivity to ALK and negativity to S100 and CD34, contrary to the findings in the present case. Thus, it was excluded.<sup>[9]</sup> Solitary fibrous tumor is diffusely positive for CD34 in 95% of cases, as well as for bcl-2 and beta-catenin and hence was ruled out. Although the present case was immunonegative for SMA, overall morphological features along with clinical features were suggestive of nodular fasciitis [Figure 1].

### Case 3

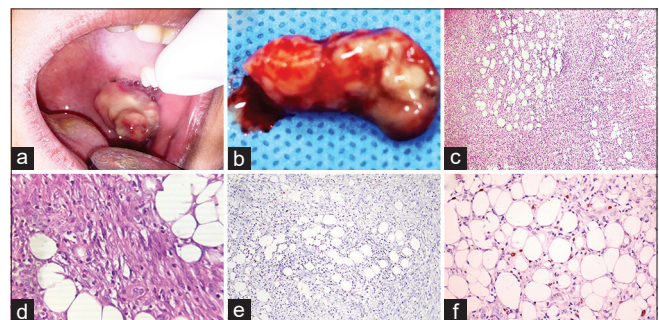
A 4-year-old child presented with a soft-to-firm swelling in the right buccal mucosa extending intraocclusally which was noticed 8 days back after an incident of trauma. Provisional diagnosis of fibroma and differential diagnosis of lipoma were considered. Histopathology reveals numerous lobules composed of adipocytes, separated by fibrous septa and surrounded by densely cellular stroma. High power shows the presence of mature adipocytes admixed with numerous spindle cells and multi-vacuolated cells. These cells displayed an abnormal increase in mitosis which raised the suspicion of well-differentiated liposarcoma. IHC revealed negativity for CDK4 and MDM2 with low Ki-67 proliferation index. Liposarcoma was excluded as

it is common in adults and accounts for less than 3% of pediatric soft-tissue sarcomas. Furthermore, it exhibits cytological and nuclear atypia, atypical mitosis, presence of bizarre cells, lipoblasts and immunopositivity to CDK4 and MDM2. As the present case lacks these features and considering increased mitosis can be seen in pediatric age, final diagnosis of lipoma was given [Figure 2].

### Hybrid lesions

#### Case 4

A 51-year-old male presented with diffuse swelling on the right side of the mandible. There is a history of cyst enucleation twice with extraction of the right mandibular third molar (2005) and right mandibular second molar (2012). On examination, there was diffuse swelling on the mandible angle, body and ramus region causing obliteration of the lower buccal vestibule intraorally. Orthopantomogram (OPG) showed well-defined multilocular radiolucency in the right body and ramus region of the mandible with thinning of the posterior and inferior borders and resorption of the right mandibular first molar. Contrast-enhanced CT scan showed an expansile lytic lesion with cortical breach without buccal or lingual cortical expansion [Figure 3]. Provisional diagnosis of odontogenic keratocyst was considered. Enucleation of cystic lining with extraction of the mandibular first molar was done. Histopathology revealed sporadic presence of hyperplastic stratified squamous epithelium of variable thickness showing multiple areas of separation from underlying capsule which was moderately collagenous. Few areas showed basilar budding as well as focal basal palisading within the epithelium. One separate tissue showed dense presence of histiocytes, multinucleated giant cells and endothelial cells proliferating into the underlying stroma. High power revealed histiocytes displaying nuclear hyperchromatism and pleomorphism in few areas. These cells were immunopositive for CD68 and immunonegative for p40, PanCK and p53. Ki-67 proliferation index was

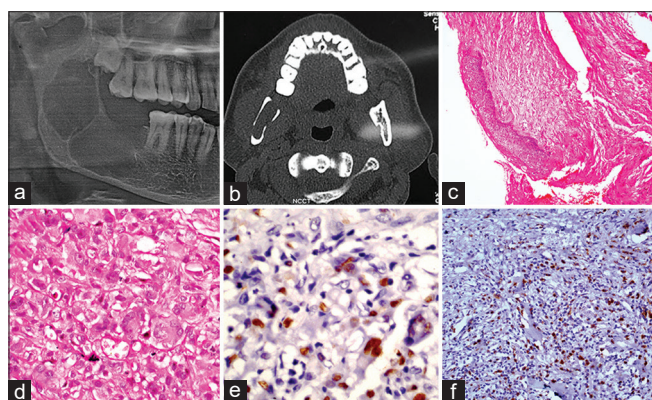


**Figure 2:** Case 3 – Fibrolipoma (a-f): Solitary growth on the left buccal mucosa and the gross excisional specimen (a and b), histopathology depicting adipocytes in cellular stroma (c and d) and immunonegativity for MDM2 (e) with low Ki-67proliferation index (f)

found to be low. As the lesion was highly cellular, so squamous cell carcinoma and histiocytic sarcoma were considered as differentials. Low Ki-67 index was indicative of benign behavior, and CD68 positivity suggested histiocytic cells. Our final diagnosis was odontogenic keratocyst with giant cell granuloma [Figure 3].

### Case 5

A 6-year-old male presented with bony hard swelling on the left side of the jaw for 6 months. On examination, there was an obvious expansion of the buccal cortical plates. OPG revealed well-defined unilocular radiolucency in the left body of the mandible ballooning out from the lower border of the mandible. No history consistent with systemic illness, café au lait spots, multiple bone involvement or endocrinal disturbance could be elicited, thus excluding polyostotic fibrous dysplasia (FD) and McCune–Albright syndrome.



**Figure 3:** Case 4 – Odontogenic keratocyst with GCL (a-f) – Orthopantomogram showing multilocular radiolucency in the right body and ramus of the mandible (a). Contrast-enhanced computed tomography face revealing osteolytic lesion with thinning and breach in cortical plates but no buccolingual cortical plate expansion (b). Parakeratotic lining overlying a connective tissue capsule and one area showing highly cellular stroma (c and d) with CD68 positive histiocytes (e) and low Ki-67 proliferation index (f)

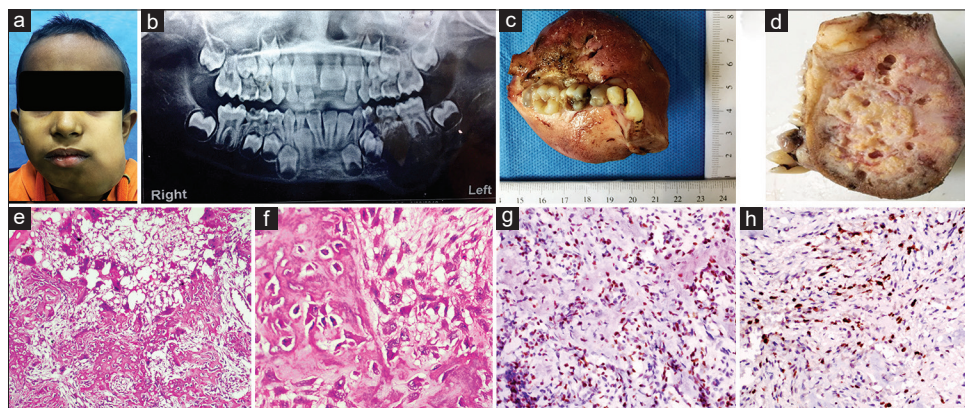
Clinical differentials as per age and clinical presentation were low-grade osteosarcoma, ossifying fibroma (juvenile type) and FD. However, the well-defined borders of the expansile osteolytic lesion and absence of ground-glass appearance or indistinct borders with adjacent uninvolved bone ruled out FD. Grossly, the tumor completely involved the body of the mandible with buccal and lingual cortical expansion. Histopathology revealed hypercellular connective tissue comprising loose collagen fibers interspersed with plump fibroblasts. Irregular strands of osteoid in varying degrees of calcification encasing plump and irregular osteocytes are seen with osteoblastic rimming in few areas. One tissue showed clusters of many multinucleated giant cells interspersed with abundant areas of hemorrhage. Histological differentials were juvenile ossifying fibroma, monostotic FD, osteosarcoma and giant cell lesion. Hypercellular stroma and osteoblastic rimming excluded FD. Tumor cells were immunopositive for SATB2 and immunonegative for MDM2 and CDK4 with approximately 15% of Ki-67 proliferative index. Literature reveals that low-grade osteosarcoma shows positivity for MDM2 and CDK4 and high-grade osteosarcoma shows high Ki-67 proliferative index and sometimes negativity for MDM2, CDK4.<sup>[10]</sup>

Thus, we narrowed the final diagnosis to juvenile trabecular ossifying fibroma with CGCG [Figure 4].

### Miscellaneous/paraneoplastic syndromes

#### Case 6

A 33-year-old male presented on wheelchair with bone pain and a history of multiple fractures. Routine blood and serological examination revealed hypophosphatemia. Thus, correlating with age and clinical history of fractures, provisional diagnosis of Vitamin D deficiency osteomalacia and differential diagnosis of primary hyperparathyroidism,



**Figure 4:** Case 5 – JOF with central giant cell granulomas (a-h) – Bony hard swelling on the left side of the jaw (a), Large, well defined, expansile, unilocular lytic lesion in the body of the left hemimandible (b), Photograph showing gross resected mandible specimen (c) and the cut surface with hemorrhagic strands (d). Histopathology reveals osteoid in varying degrees of maturation with multinucleate giant cells and adjacent area showing osteoid encasing plump and irregular osteocytes (e and f) which were immunopositive for SATB2 (g). Ki-67 proliferative index was low (h)

tumor-induced osteomalacia and multiple myeloma were contemplated. Serological investigations revealed normal Vitamin D, calcium and *parathyroid* hormone levels, thereby excluding Vitamin D deficiency osteomalacia and primary hyperparathyroidism. Special investigations showed increased serum fibroblast growth factor 23 (FGF-23) levels which created suspicion of some tumors releasing the same. Skeletal survey revealed localization of tumor in the left mandible involving body and ramus as mixed radiolucent radio-opaque lesion and multiple lytic lesions in other parts of skeleton. After surgical removal of the mandible, there was a gradual normalization in serum phosphate levels.

Histopathology showed dense hypercellular stroma consisting of numerous odontogenic epithelial nests, cords and islands dispersed within primitive ectomesenchyme. Stroma showed abundant dentinoid deposition, cementoid and lamellated calcification with interspersed developing tooth germs in different stages, few showing enamel matrix and dentinoid deposition. Odontogenic islands displayed peripheral tall columnar cells with reversely polarized hyperchromatic nuclei, subnuclear vacuolization and centrally placed stellate reticulum-like cells. Morphological features were suggestive of ameloblastic fibro-odontoma (developing stage of odontome). Considering the clinical and radiological details, final diagnosis of tumor-induced osteomalacia associated with ameloblastic fibro-odontoma was rendered [Figure 5].

## DISCUSSION

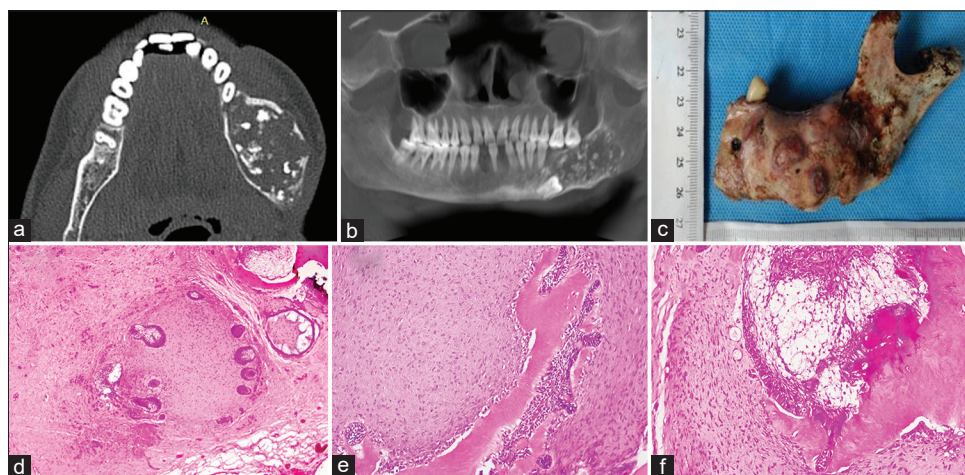
Diagnostic dilemmas caused by pseudotumors may have serious consequences in terms of unnecessary treatment,

unwarranted anxiety for the patient and sometimes a litigious nightmare for the clinical and the pathologist.

It is well known that some structures like juxtaoral organ of Chievitz frequently found at an angle of the mandible near insertion of the pterygomandibular raphe may be mistaken for squamous cell carcinoma as it contains squamous islands.<sup>[11]</sup> The rarity of malignancy mimickers in the head-and-neck region further increases diagnostic complexity in suspicious cases and can encumber the pathologist unfamiliar with these possibilities.

Literature has described various pseudotumors comprising inflammatory conditions such as cutaneous pseudolymphoma, liver pseudotumors, pulmonary pseudotumors, orbital pseudotumors and Küttner's tumor. Recently, all these disease entities have been collected under the spectrum of IgG4-RD. IgG4-RD (case 1) represents an immune-mediated fibro-inflammatory condition with a characteristic histopathological appearance that can affect various organs with the pancreas and salivary glands affected more commonly.

In the head-and-neck region, spectrum of IgG4-RD involves salivary glands (Mikulicz disease and chronic sialadenitis – Küttner tumor), orbits (lacrimal glands – Mikulicz disease and chronic dacryoadenitis, idiopathic orbital inflammation [pseudotumor], lymphoid hyperplasia and perineural spread [trigeminal nerve branches]), sinonasal cavities, thyroid gland (Hashimoto thyroiditis and Riedel thyroiditis), pituitary gland (hypophysitis), larynx (submucosal lesion) and lymph nodes.<sup>[12]</sup> International Consensus Guidance Statement on IgG4-RD suggests that there are no laboratory, serological or imaging characteristics that are exclusive for this



**Figure 5:** Case 6 – (a-f) NCCT face and orthopantomogram shows lytic lesion with narrow zone of transition involving the body and ramus of the left hemimandible with cortical erosions and buccolingual expansion and multiple calcific foci within (a and b), Photograph showing gross resected specimen which on histology revealed haphazard arrangement of dentinoid, enamel matrix and odontogenic epithelium (c-f)

disease.<sup>[13,14]</sup> Serum IgG4 levels were originally considered to be highly significant in terms of diagnosis but now have lost importance as it can be elevated in other conditions (like malignancies) as well. According to the Boston consensus, histopathology is still regarded a gold standard and should be obtained wherever possible.<sup>[13]</sup> Further, they have laid down the diagnostic criteria for IgG4 disease [Table S1].<sup>[13,14]</sup> Further, differential diagnoses, especially malignancies, should be excluded before the treatment. Measurement of plasmablast counts in flow cytometry has been recently suggested as an indicator of disease activity but requires further research.<sup>[13]</sup> When untreated, IgG4-RD can cause irreversible organ damage, thus it requires an early and aggressive treatment.

When aggressive mesenchymal lesions are suspected, benign entities such as nodular fasciitis, fibromatosis, ectomesenchymal chondromyxoid tumor of the tongue, peripheral myxoma, solitary fibrous tumor and lipoma can sometimes mimic malignancies histologically.<sup>[15]</sup> Nodular fasciitis or infiltrative or pseudosarcomatous fasciitis is a benign soft-tissue tumor of fibroblastic/myofibroblastic differentiation. In 7%–20% of the reported cases, the lesion is located at the head-and-neck region. Intraoral location of the lesion is very unusual and is often confused with sarcomas because of rapid growth, rich cellularity, high mitotic activity and poorly circumscribed nature.<sup>[16]</sup> The clinical and imaging features (*magnetic resonance imaging*) of nodular fasciitis are only supportive but not pathognomonic. Spindle cells in nodular fasciitis stain positive for vimentin, variably for actin, S100 and negative for desmin (positive in soft-tissue sarcomas).<sup>[17]</sup> Our case (case 2) stained positive for vimentin and S100 and negative for desmin, ALK (positive in myofibroblastic tumor), PanCK (positive in spindle cell squamous cell carcinoma), beta-catenin (positive in solitary fibrous tumor) and focally positive for BCL-2 and CD34 (diffuse in synovial sarcoma). This led us to the final diagnosis of nodular fasciitis. Although literature suggests the positive staining with alpha-SMA is a feature of nodular fasciitis suggesting a myofibroblastic differentiation, the present case was negative for SMA.

Other diagnostic groups, which are frequently a source of confusion, are the hybrid lesions. The concept of hybrid lesions comes from the hybrid odontogenic tumors which represent a single lesion presenting with characteristics of more than one lesion. Four cases of hybrid lesion of odontogenic keratocyst with giant cell granuloma similar to our case (case 4) have been reported in literature till now.<sup>[18-20]</sup> Whether the giant cells form a part of reactive process in primary lesion or a collision lesion remains

unclear.<sup>[19,21]</sup> Although our case was puzzling because of increase in cellularity, IHC finally resolved the dilemma.

Similarly, hybrid lesions of CGCG are also reported with of Rai *et al.* and Geetha *et al.*<sup>[21,22]</sup> Moreover, juvenile ossifying fibroma which presents with high cellularity also appears superficially similar to low-grade osteosarcoma. Literature reports that diffuse MDM2 and CDK4 staining reliably distinguish low-grade osteosarcoma from its benign mimics.<sup>[23]</sup> Our case (case 5) stained negative for MDM2 and CDK4 expression, had a low Ki-67 proliferative index, no cytological atypia and no abnormal mitosis. We excluded osteosarcoma leading to a final diagnosis of juvenile ossifying fibroma with CGCG.

Sometimes, seemingly aggressive clinical and radiological characteristics can also create uncertainty among histopathologists. One of these lesions is the tumor-inducing osteomalacia (case 6) which is a rare paraneoplastic syndrome of abnormal phosphate and vitamin metabolism. It is caused by some typically small endocrine tumors (usually benign) that secrete the phosphaturic hormone, FGF23.<sup>[24]</sup> These tumors are collectively called as phosphaturic mesenchymal tumors. Lack of familiarity with this entity among the oral pathologists and rarity of its occurrence often causes a delay in diagnosis. The tumors may appear in almost any location with 27% prevalence in the head-and-neck region.<sup>[25]</sup> Various head-and-neck tumors such as ossifying fibroma, hemangiopericytoma, CGCG and odontogenic fibroma are reported in literature to be the cause of tumor-induced osteomalacia.<sup>[25-27]</sup> The stepwise approach to locate the tumor is initiated by functional imaging and followed by anatomical imaging and venous sampling to measure the FGF-23 levels. The tumors which cannot be located are managed by medical treatment such as phosphate supplements with active Vitamin D.<sup>[24]</sup> Our case (case 6) represents the second report of an odontogenic tumor being the cause of osteomalacia.<sup>[27]</sup>

## CONCLUSIONS

Familiarity with the described entities is expected to help the pathologists navigate through the treacherous territory of pseudotumorous lesions occurring in the oral and maxillofacial region. Although advanced diagnostic modalities have a considerable role in resolving the interpretative confusion around these lesions, no single investigation is confirmatory. Clinical, radiological, histological correlation and IHC are mandatory for avoiding the diagnostic pitfalls and overtreatment of a patient. A thorough knowledge of the differentials in these heterogeneous groups of lesions is helpful. This study

attempts toward simplifying the diagnostic strategy and is expected to be practically useful for the oral pathologist encountering such rare entities.

### Ethical approval

Ethics committee approval and informed consent were obtained (IEC-720/04.10.2019, RP-31/2019).

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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**Table S1: Comprehensive diagnostic criteria for immunoglobulin G4-related disease**

<b>Criteria</b>	<b>Diagnosis</b>
Clinical examination (clinical history, physical examination, imaging)	1+2=possible IgG4-RD
Immunological examination: IgG4 in serum. 135 mg/dL or elevated IgG4/IgG ratio; optionally accompanied by other laboratory alterations like in immunoglobulin E, $\gamma$ -globulin or complement	1+3=probable IgG4-RD
Histopathologic examination: Lymphoplasmacytic infiltration with storiform fibrosis and obliterative phlebitis, infiltration by IgG4 + plasma cells (>>10–50 IgG4 (+) plasma cells per HPF or IgG4+/IgG+0.40%)	1+2+3=definite IgG4-RD

IgG: Immunoglobulin G, HPF: High-power field, RD: Related disease