24. Sloan PJ, O'Neil TC, Smith CJ, Holdsworth CD. Multi-system sarcoid presenting with gingival hyperplasia. *Br J Oral Surg.* 1983;21:31-35.
25. Antunes KB, Miranda MMA, Carvalho SRS, Azevedo ALR, Tatakis DN, Pires FR. Sarcoidosis presenting as gingival erosion in a patient under long-term clinical control. *J Periodontol.* 2008;79:556-561.
26. Bouaziz A, Le Scanff JL, Chapelon-Abric C, et al. Oral involvement in sarcoidosis: report of 12 cases. *Quart J Med.* 2012;105:755-767.
27. Tilman HH. Sarcoidosis with unsuspected oral manifestations: report of a case. *Oral Surg Oral Med Oral Pathol.* 1964;18:130-135.
28. Watts KD. Sarcoid of the gingiva: a case report. *Br J Oral Surg.* 1968;6:108-113.
29. Hogan JJ. Sarcoid gingivitis. *Br Dent J.* 1983;154:109-110.
30. Altman K, Robinson PD. Sarcoidosis with oral involvement. *Br Dent J.* 1984;157:310-311.
31. Zakrzewska J, Nally FF. Sarcoid with oral involvement. *Br Dent J.* 1985;158:3-4.
32. Hayter JP, Robertson JM. Sarcoidosis presenting as gingivitis. *Br Med J.* 1988;296:504.
33. Caudill R. Sarcoidosis of the gingiva: an elusive diagnosis. *J Periodontal Res Dent.* 1988;2:67-74.
34. Aslangul E, Gadhoum H, Badoul C, Szwebel T, Perrot S, Le Jeunne C. A chronic gingival hypertrophy. *Rev Med Interne.* 2009;30:260-261 [in French].
35. Poate TW, Sharma R, Moutasim KA, Escudier MP, Warnakulasuriya S. Orofacial presentation of sarcoidosis—a case series and review of the literature. *Br Dent J.* 2008;205:437-442.
36. Saylor C, Beaini N, Rokos J, Satheesh K, Cobb C. Primary manifestation of sarcoidosis involving the gingivae. *Int J Experiment Dent Sci.* 2012;1:102-105.
37. Tripathy P, Aggarwal J, Chopra D, Bagga S, Sethi K. Sarcoidosis presenting as isolated gingival enlargement: a rare case entity. *J Clin Diagn Res.* 2014;8: ZD25-ZD26.
38. Fernández EF. Epidemiology of sarcoidosis. *Arch Bronconeumol.* 2007;43:92-100.
39. English JC, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol.* 2001;44:725-743.
40. Moller DR, Chen ES. What causes sarcoidosis? *Curr Opin Pulm Med.* 2002;8:429-434.
41. Drake WP, Newman LS. Mycobacterial antigens may be important in sarcoidosis pathogenesis. *Curr Opin Pulm Med.* 2006;12:359-363.
42. Ueda E, Kawabe T, Tachibana T, Kokubu T. Serum angiotensin-converting enzyme activity as an indicator of prognosis in sarcoidosis. *Am Rev Respir Dis.* 1980;121:667-671.
43. Samtsov AV. Cutaneous sarcoidosis. *Int J Dermatol.* 1992;117:203-207.
44. Makris GP, Stoller NH. Rapidly advancing periodontitis in a patient with sarcoidosis. A case report. *J Periodontol.* 1983;54:690-693.
45. Van Swol RL. Periodontosis in a patient with previously diagnosed sarcoidosis. *J Periodontol.* 1973;44:697-704.
46. Jackowski J, Dragisic D, Arnold G, Dirschka T. Primary oral sarcoidosis preceding Lofgren's syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;100:183-185.
47. Alawi F. Granulomatous diseases of the oral tissues: differential diagnosis and update. *Dent Clin North Am.* 2005;49:203-221.
48. Suresh L, Aguirre A, Buhite RJ, Radfar L. Intraosseous sarcoidosis of the jaws mimicking aggressive periodontitis: a case report and literature review. *J Periodontol.* 2003;75:478-482.
49. Sciubba JJ, Said-Al-Naief N. Orofacial granulomatosis: presentation, pathology and management of 13 cases. *J Oral Pathol Med.* 2003;32:576-585.

CLINICAL PATHOLOGIC CONFERENCE CASE 3: A SLOW-GROWING EXPANSILE POSTERIOR MANDIBULAR SWELLING

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Clinical Presentation: A 54-year-old female patient presented with an asymptomatic swelling of 3 months' duration after dental extractions (Figure 1). The patient remembered having facial asymmetry 2 years before the dental extractions. The patient showed a cooperative attitude and consented to having laboratory tests and imaging performed. Clinically, there was an intraoral blue, solid, and diffuse swelling, with intact overlying mucosa (Figure 2).

The panoramic radiograph showed a relatively well-defined multilocular radiolucency extending form the area of the missing mandibular permanent right first molar anteriorly, toward the posterior part of the mandibular ramus posteriorly, past the normal location of the inferior dental canal, which was not seen in the radiograph (Figure 3). The radiolucency was clearly demarcated toward the anterior part of the right-hand side of the mandible but less so in the posterior and superior margins of the radiolucency. Inferiorly, the radiolucency extended toward the lower border of the body of the mandible. The inferior cortex appeared sound, and no periosteal reaction was detected. In addition, the area of the missing mandibular permanent right first molar appeared punched out, and there was loss of trabeculation anterior to the main radiolucent area and posterior to the right mental foramen. Close to the ascending ramus of the mandible, a soft tissue shadow accompanied by irregular radiolucent specks and trabeculae was seen.

On the panoramic radiograph taken 2 years before the dental extractions, root canal fillings were evident. There was no visible radiolucency, but there were signs of condensing osteitis (Figure 4).

Aspiration of the swelling yielded blood, and an incisional biopsy specimen (Figure 5) showed significant bleeding.

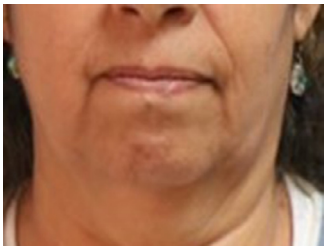

Fig. 1. Photograph of patient at presentation.

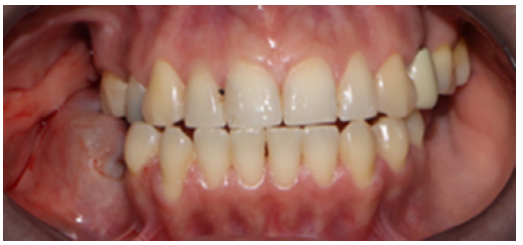

Fig. 2. Clinical photograph showing the intraoral appearance of the lesion. The swelling has a bluish color with intact oral mucosa.

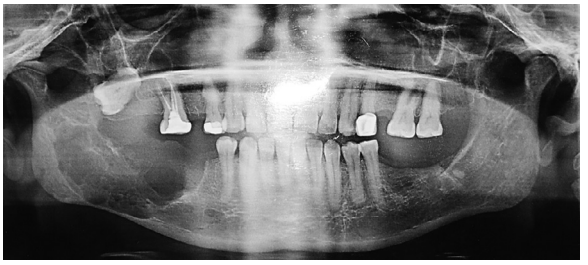

Fig. 3. Panoramic radiograph showing a multilocular radiolucency on the right-hand side of the mandible.

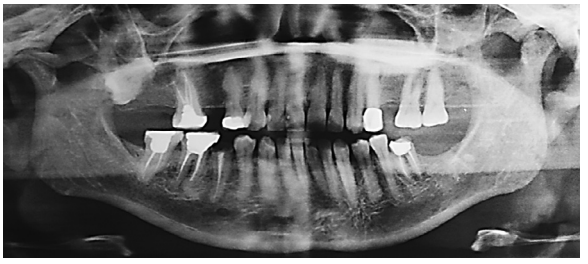

Fig. 4. Panoramic radiograph 2 years before dental extractions showing no signs of radiolucency on the right-hand side of the mandible.

Differential Diagnosis: The differential diagnosis of an expansile mandibular radiolucency with swelling includes odontogenic and nonodontogenic lesions. Among odontogenic lesions, ameloblastoma, odontogenic keratocyst (OKC), and odontogenic myxoma were considered. Other less likely differential diagnoses included giant cell lesions and bone cysts, as well as connective tissue neoplasms.

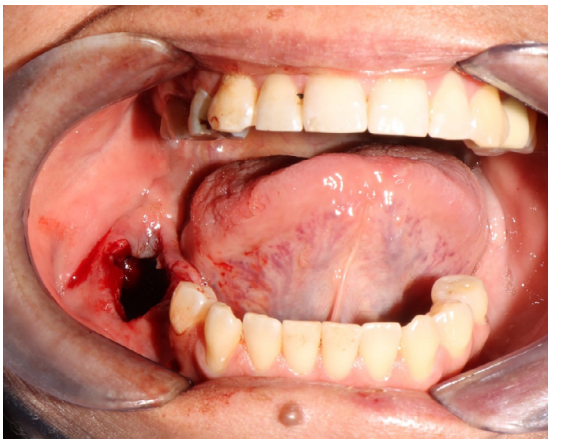

Fig. 5. Clinical photograph of the intraoral view of the lesion after performing incisional biopsy.

Ameloblastoma is a benign odontogenic epithelial neoplasm and should be the first lesion to be considered in the differential diagnosis of expansile posterior mandibular radiolucencies.[1,2] Excluding odontomas, ameloblastomas account for approximately half of central odontogenic tumors. Eighty percent of ameloblastomas arise in the mandible, and nearly half of them arise in the posterior mandible. This lesion occurs over a wide age range but most commonly in patients in their fifth to sixth decades of life.[3]

Odontogenic myxomas are benign mesenchymal odontogenic tumors, which are also known to cause bony expansion, to arise in the posterior mandible, and to occur in patients in their third decade of life.[4]

OKCs are developmental odontogenic cysts that most commonly arise in the mandible, and almost half of those arise in the posterior region of the mandible. OKCs most commonly occur in the second to third decades of life, although a second peak in the sixth to seventh decades is also reported. However, they do not usually cause bony expansion.[5]

Central giant cell granulomas usually arise from the anterior part of the mandible, and bone cysts, such as solitary and aneurysmal bone cysts, tend to occur in a younger age group. Connective tissue neoplasms, such as haemangiomas and, rarely, schwannomas, can arise in the posterior mandible.[6,7]

Diagnosis: Microscopically, basophilic cells with a cribriform pattern and cystic spaces were noted (Figure 6). Evidence of recent hemorrhage was also seen. In other regions, we could see a further population of epithelial basaloid cells and myoepithelial cells with a classic cribriform pattern in a dense fibrous

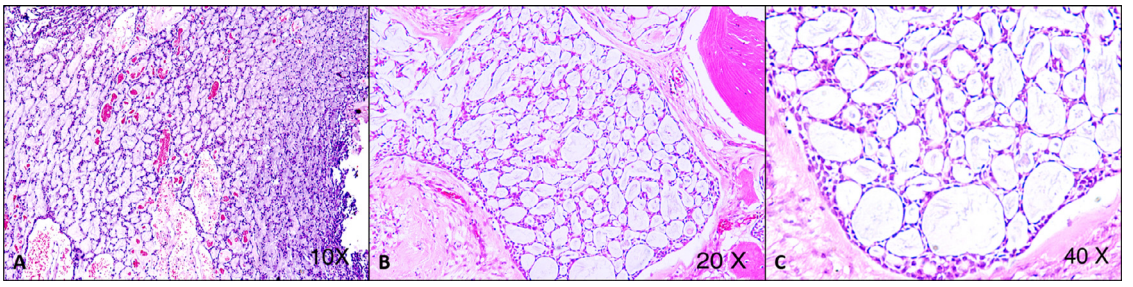

Fig. 6. Photomicrographs of the lesion at × 100 **(A)**, × 200 **(B)**, and × 400 **(C)** magnification, showing hyperchromatic epithelial and myoepithelial cells with angular nuclei and scant cytoplasm.

dense connective tissue with blood vessels, recent hemorrhage and bone. The epithelial cells were either hyperchromatic basaloid cells with scant cytoplasm or cells with clear cytoplasm.

An immunohistochemical panel was performed to arrive at a more definitive diagnosis. Cytoplasmic positivity for cytokeratin 7, intense cytoplasmic calponin positivity in the myoepithelial cells, cytoplasmic positivity for S-100, and cytoplasmic and membranous CD-117 reactivity was seen. Nuclear p63 and p40 expression was also noted (Figure 7).

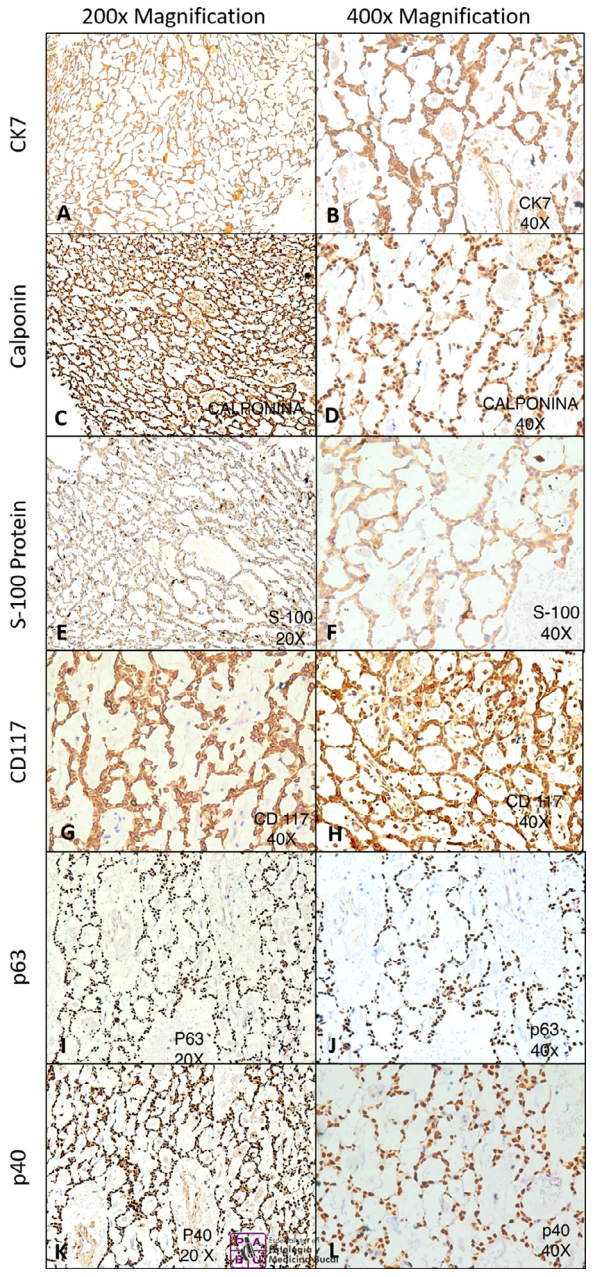

Fig. 7. Photomicrographs of the immunohistochemistry panel at × 200 and × 400 magnification. Cytoplasmic positivity for cytokeratin (CK) 7 **(A, B)**, intense cytoplasmic calponin positivity in the myoepithelial cells **(C, D)**, cytoplasmic positivity for S-100 **(E, F)**, and cytoplasmic and membranous CD-117 reactivity can be seen **(G, H)**. Nuclear p63 **(I, J)** and p40 **(K, L)** expression can also be noted.

The clinical and radiographic features, including the absence of extraosseous neoplastic salivary tissue, intact overlying mucosa, and cortical plate, indicated an intraosseous neoplasm. On the basis of histology and immunohistochemistry (IHC) results, our final diagnosis was an intraosseous biphasic malignant salivary gland tumor, consistent with adenoid cystic carcinoma.

Management: The treatment consisted of hemimandibulectomy with neck dissection (Figure 8). Fifteen lymph nodes were found to be negative for neoplasia, and the submandibular salivary gland was free of neoplastic tissue.

After the surgery, the patient was followed up for 6 months (Figure 9). The only complication was an infection, which resolved with antimicrobial therapy. No metastases were found when tumor metastasis tracking was performed.

Discussion: Intraosseous carcinomas involve bone and bone marrow space and are not derived from surface epithelium invading bone.[8] Primary intraosseous squamous cell carcinomas represent the majority of intraosseous carcinomas and most commonly arise from odontogenic cysts.[8]

The most common primary intraosseous salivary gland carcinomas (PIOSGCs) are primary intraosseous mucoepidermoid carcinoma, accounting for more than two-thirds of PIOSGCs, followed by primary intraosseous adenoid cystic carcinoma (PIACC), which accounts for nearly one-third of PIOSGCs, and adenocarcinomas not otherwise specified and others.[9] The origin of intraosseous salivary gland tissue remains a matter of debate.

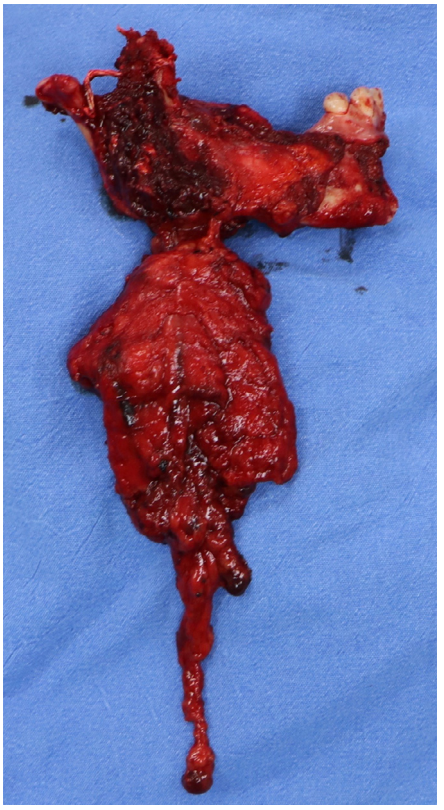

Fig. 8. Hemimandibulectomy and neck dissection specimen.

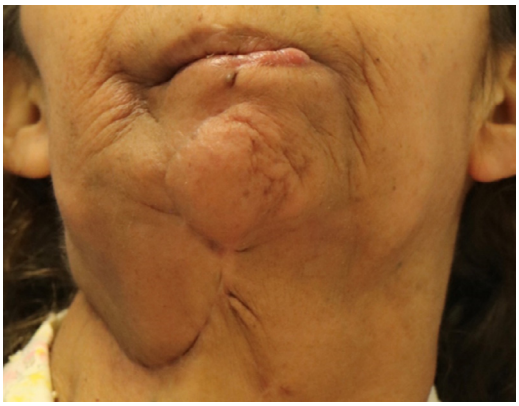

Fig. 9. Postoperative photograph of the patient.

It is not known whether such tissue originates from ectopic salivary gland tissue or metaplastic odontogenic epithelium.[9] However, Li et al.[10] showed that PIACC and adenoid cystic carcinoma (ACC) have similar *MYB* gene abnormalities, suggesting that PIACCs may originate from ectopic intraosseous salivary gland tissue.[10]

There are several reports, including a few case series with literature reviews, of PIACC.[9-11] PIACC has a predilection for the mandible—particularly the body and the ramus—rather than the maxilla, and most patients present with pain, swelling, and trismus, but some may also present with numbness and tooth mobility.[9-11] PIACC occurs over a wide age range from the third through the ninth decades of life.[9,11] PIACC may present as multilocular radiolucencies with ill-defined borders[9]; however, in the current case, most areas had well-defined borders.

The histopathologic picture of PIACC is similar to that of ACC, showing hyperchromatic basophilic cells arranged in cribriform, tubular, or solid patterns.[12] In the present case, the cribriform pattern was the predominant pattern, with areas of clear cell change.

The histologic differential diagnosis of ACC may include polymorphous adenocarcinoma, pleomorphic adenoma, and basal cell neoplasms.[13] However, with the characteristic cribriform histology and with the aid of IHC, a diagnosis of PIACC was made in the present case.

The immunohistochemical profile of PIACC is similar to that of ACC. Although most of the IHC markers are not specific and have variable expression patterns, they are essential for arriving at a diagnosis. ACC shows strong cytokeratin 7 positivity. In addition, most ACCs show membranous and cytoplasmic CD-117 reactivity, which may point to a diagnosis of ACC and rule out other neoplasms with myoepithelial components.[13,14] The myoepithelial components of ACC, however, show reactivity to p63, calponin, and S-100 protein, although the latter may be weak and patchy.[13] Recent studies have shown that the p63/p40 profile is particularly useful in differentiating ACC from polymorphous adenocarcinoma and pleomorphic adenoma.[15,16] Although p63 antibody recognizes both isoforms, p40 is used to detect changes in p63 and is a better indicator of myoepithelial differentiation.[15,16] Approximately 90% of ACCs show reactivity to both p63 and p40, whereas almost all polymorphous adenocarcinomas show only p63 reactivity and are negative for p40.[15,16] MYB protein reactivity on IHC has also been shown to be an accurate and specific diagnostic marker for ACC.[10,15,16] In addition to IHC for MYB protein, *MYB* gene rearrangements, including fusion with *NFIB* gene, can be demonstrated by fluorescent in situ−hybridization (FISH). In their recent report, Li et al. showed a high extent of MYB protein expression on IHC, in addition to *MYB* gene abnormalities, by using FISH in all 4 of their PIACC.[10]

The reported 5-year survival rate of patients with ACC is 80%, but the 10-year survival rate can be as low as 50%.[12,17] Negative prognostic factors include age, perineural invasion in large nerves, surgical margins, tumor stage, and lymph node metastasis.[12] Patients with ACC treated with radical surgery and adjuvant therapy have shown better outcomes.[12,17]

Data regarding the prognosis of patients with PIACC are limited. There is no follow-up information in many cases. According to the more recent reviews and including the present case, the follow-up periods range from 5 months to 14 years with nearly one-fourth of patients being disease-free at follow-up, and greater than 20% having metastasis, mainly to the lung.[10,11]

In conclusion, PIACC is rare. The patients frequently present with swelling, lower lip numbness, and pain. Radiographically, the lesions appear predominantly as ill-defined multilocular radiolucencies but can also have well-defined borders. Diagnosis can be made by using histopathologic examination, which can be aided by IHC showing a high extent of MYB protein expression, positive p63/p40 profile, and CD-117 reactivity. Additionally, *MYB* gene abnormalities can be detected by using FISH. Because of the poor long-term survival rates, multimodal treatment and long-term follow-up are recommended by most authors.

Acknowledgments

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References

1. Reichart PA, Philipsen HP, Sonner S. Ameloblastoma: biological profile of 3677 cases. *Eur J Cancer Part B Oral Oncol.* 1995;31:86-99.
2. Odell E. *Cawson's Essentials of Oral Pathology and Oral Medicine*. ed 9. London, UK: Elsevier; 2017.
3. Buchner A, Merrell PW, Carpenter WM. Relative frequency of central odontogenic tumors: a study of 1,088 cases from Northern California and comparison to studies from other parts of the world. *J Oral Maxillofac Surg.* 2006;64:1343-1352.
4. Chrcanovic BR, Gomez RS. Odontogenic myxoma: an updated analysis of 1,692 cases reported in the literature. *Oral Dis.* 2018 Apr 23. doi: 10.1111/odi.12875. [Epub ahead of print].
5. Jones AV, Craig GT, Franklin CD. Range and demographics of odontogenic cysts diagnosed in a UK population over a 30-year period. *J Oral Pathol Med.* 2006;35:500-507.
6. Huang IY, Shih Y-L, Shu C-W, Chen Y-K. Multilocular radiolucency of the mandibular condyle in a 19-year-old woman. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011;112:6-10.
7. Zhang L, Xia BQ, Sun H, et al. Intraosseous schwannomas of the jaws: 2 case reports and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012;114:e13-e17.
8. Woolgar JA, Triantafyllou A, Ferlito A, et al. Intraosseous carcinoma of the jaws—a clinicopathologic review. Part I:

Metastatic and salivary-type carcinomas. *Head Neck*. 2013;35:895-901.
9. Li Y, Li LJ, Huang J, Han B, Pan J. Central malignant salivary gland tumors of the jaw: retrospective clinical analysis of 22 cases. *J Oral Maxillofac Surg*. 2008;66:2247-2253.
10. Han J, Gu T, Yang X, et al. Primary intraosseous adenoid cystic carcinoma of the mandible: a comprehensive review and analysis of four new cases with emphasis on morphologic, immunophenotypic, and molecular characteristics. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;123:365-373.
11. Bouaichi A, Aimad-Eddine S, Mommers XA, Ella B, Zwetyenga N. Intra-mandibular adenoid cystic carcinoma. *Rev Stomatol Chir Maxillo-Fac Chir Orale*. 2014;115:100-104.
12. Stenman G, Licitra L, Said-Al-Naief N, van Zante A, Yarbrough W. WHO classification of head and neck tumours. In: El-Naggar AK, Chan JKC, Grandis J, Takata T, Slootweg PJ, eds. *World Health Organization Classification of Tumours*. ed 4. Lyon, France: International Agency for Research on Cancer; 2017:164-165.
13. Hellquist H, Skalova A. Adenoid cystic carcinoma. In: Skalova A, ed. *Histopathology of the Salivary Glands*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014:221-253.
14. Simpson RH, Skalova A, Di Palma S, Leivo I. Recent advances in the diagnostic pathology of salivary carcinomas. *Virchows Arch*. 2014;465:371-384.
15. Argyris PP, Wetzel SL, Greipp P, et al. Clinical utility of myb rearrangement detection and p63/p40 immunophenotyping in the diagnosis of adenoid cystic carcinoma of minor salivary glands: a pilot study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;121:282-289.
16. Rooper L, Sharma R, Bishop JA. Polymorphous low grade adenocarcinoma has a consistent p63+/p40- immunophenotype that helps distinguish it from adenoid cystic carcinoma and cellular pleomorphic adenoma. *Head Neck Pathol*. 2015;9:79-84.
17. Rettig EM, Tan M, Ling S, et al. MYB rearrangement and clinicopathologic characteristics in head and neck adenoid cystic carcinoma. *Laryngoscope*. 2015;125:E292-E299.

CLINICAL PATHOLOGIC CONFERENCE CASE 4: RECURRENT GINGIVAL GROWTH IN THE ANTERIOR MAXILLA

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Clinical Presentation: A 57-year-old female presented to an oral surgeon with recurrence of an asymptomatic, slowly enlarging, firm swelling involving the anterior maxillary gingiva. Six excisional biopsies had previously been performed by several different clinicians over the preceding decade. The histologic diagnoses included multiple diagnoses of fibrous epulis and peripheral ossifying fibroma. The patient had no contributory medical history. Extraoral examination was unremarkable. Intraoral examination showed a 2.0 × 1.5 × 1.5 cm sessile nodular mass involving the buccal and palatal attached gingiva and extending from the extraction site of right maxillary central incisor to the interdental papilla between the left maxillary central and lateral incisor (Figure 1). The affected area showed normal mucosal coloration with a stippled surface texture. There was no apparent ulceration, hemorrhage, or exudate associated with the lesion. The left maxillary lateral incisor was noted to be displaced coronally and buccally compared with the contralateral lateral incisor. All remaining maxillary teeth were confirmed to be vital. Periapical radiographs showed generalized alveolar bone loss. In the area of the lesion, the alveolar crest mesial to the left maxillary central incisor approximated the level of the central incisor's cementoenamel junction, which was considerably higher than the overall alveolar crest height of the adjacent maxillary teeth. At the superior aspect of the bony crest, faint spicules were identified. A diagonal, linear radiolucency was present just inferior to the crest of bone (Figure 2). There was no obvious cortical erosion or thickening of the soft tissue shadow in the area of the lesion. No widening of the periodontal ligament (PDL) spaces or loss of lamina dura was identified. There was no displacement or resorption of tooth roots; however, the left maxillary lateral incisor appeared to be displaced coronally. Several teeth showed evidence of previous endodontic treatment and restoration with porcelain crowns.

Differential Diagnosis: The clinical presentation of a sessile, smooth-surfaced, normocolored nodule involving the gingiva suggested that the lesion was composed of tissue(s) located below the epithelial surface. Therefore, the differential diagnosis included reactive and neoplastic proliferations of mesenchymal tissues typically located below the surface epithelium in the gingiva. The differential diagnosis list included common gingival reactive connective tissue lesions: peripheral fibroma, pyogenic granuloma, peripheral ossifying fibroma (POF), and peripheral giant cell granuloma (PGCG), as well as uncommon benign mesenchymal neoplasms or tumor-like conditions, such as neurofibroma, schwannoma, and vascular malformation. Moreover, given the location, a peripheral odontogenic tumor was also included in the differential diagnosis list.

Fibroma is the most common reactive proliferation or "tumor" of the oral cavity and represents a focal hyperplasia of fibrous connective tissue in response to chronic irritation or trauma.[1,2] This lesion most commonly occurs at the level of the occlusal plane in the buccal mucosa; however, the gingiva is also a possible location. A typical fibroma presents as a well-defined, pink, smooth-surfaced, sessile nodule of fibrous consistenty.[3] Pyogenic granuloma represents an exuberant, hypervascular proliferation of granulation tissue in response to low-grade irritation or trauma.[4] Clinically, it appears as a rapidly growing smooth or lobulated erythematous mass that is usually painless, bleeds easily, and most commonly involves the gingiva.[2] PGCG is another common reactive lesion of the oral cavity that occurs exclusively in the gingiva or the edentulous alveolar ridge. This lesion usually appears as a red-blue or purple nodule that might be sessile or pedunculated. The average age at onset for PGCG is 46 years, and a recurrence rate of 17.5% has been reported.[5] Finally, POF completes the list of the 4 most common reactive localized overgrowths of the gingiva. POF is believed to originate from the periodontal ligament; consequently, it occurs exclusively on the gingiva. It shows a predilection for females in the second decade of life and tends to occur in the maxilla, particularly the incisor−cuspid region.[6] The POF usually appears as a sessile or pedunculated nodule that varies in color from pink to red and usually exhibits an ulcerated surface.[7] Although these lesions are usually less than 2 cm in diameter, rare "giant" POFs measuring greater than 2.5 cm and causing displacement of teeth have been described.[8] Furthermore, recurrences have been reported for POFs, and the recurrence rate has been estimated to be around