The significance of the variable p16 expression in AME (p16+) and AMECA (p16–) is unclear and somewhat counterintuitive. The p16 staining did, however, serve alongside BCL-2 and Ki-67 as a consistent internal control, highlighting areas of transformation.[8] Although p53 staining (not shown) can be useful in distinguishing between AME and AMECA, our case yielded only nonspecific blush staining in both the AME and AMECA components.[12]

Achieving negative surgical margins through radical excision is the mainstay of treatment. Beyond radical surgical intervention, an ideal therapeutic algorithm has not been established.[13] Although *BRAF* mutation was not identified in our case, *BRAF* and other potential molecular targets have been identified in AME and to a lesser extent AMECA.[14,15]

A more comprehensive multidisciplinary review of this case is planned for after a meaningful postoperative period of treatment and evaluation.

Disclaimer: The opinions or assertions expressed herein are those of the authors and do not reflect the views of the Department of the Air Force or the Department of Defense.

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CLINICAL PATHOLOGIC CONFERENCE CASE 3: ANTERIOR MANDIBLE RADIOLUCENCY IN A 12-YEAR-OLD

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Clinical Presentation: A 12-year-old female presented with a unilocular, non-expansile radiolucency between the roots of teeth #25 and #26 (Figure 1). The lesion was causing divergence of these tooth roots and overlapping of the clinical crowns (Figure 2). The patient was asymptomatic. Past surgical history included tonsillectomy and adenoidectomy; however, the patient was otherwise healthy and taking no medications.

Differential Diagnosis: Panoramic radiography demonstrated a full complement of erupted and developing permanent teeth, consistent with the age of the patient. The radiograph featured a radiolucent lesion located in the alveolar bone between teeth #25 and #26; the lesion was well defined, was noncorticated, and caused the roots to diverge. All bony landmarks were present and intact. Computed tomography further identified the radiographic features of the lesion. It appeared as a unilocular radiolucency with incomplete septations. There was thinning of the buccal and lingual cortices, without dehiscence, perforation, noticeable bony expansion, or a soft tissue component. The lesion was totally radiolucent and appears to be lacking calcifications.

The clinical image showed overlap of the crowns of the right central and lateral incisors (#25 and #26), and this was consistent with a process causing divergence of the roots. The teeth were neg-

Fig. 1. **A,** Radiographic presentation of lesion (cropped image from panoramic radiograph). **B,** Axial CBCT image of lesion. **C,** Sagittal CBCT image of lesion.

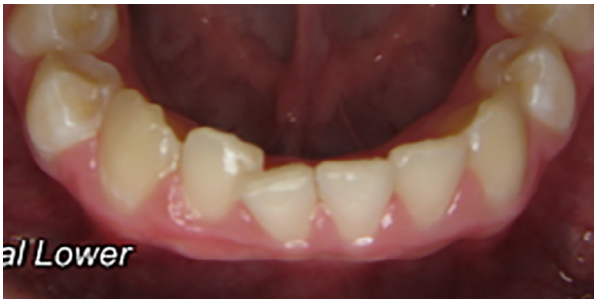

Fig. 2. Clinical photograph showing overlapping crowns of teeth #25 and #26.

ative for caries or restorations that may cause periodontal pathology. There did not appear to be any buccal–lingual expansion. The overlying gingival mucosa appeared healthy and intact.

These radiographic and clinical findings were suggestive of a benign process. The differential diagnosis was expansive, and we had to consider benign odontogenic cysts and tumors, non-odontogenic neoplasms, and reactive lesions.

The diagnosis of an odontogenic cyst, such as a lateral periodontal cyst or an inflammatory cyst in the lateral periodontal position, was a distinct possibility for this lesion because of its location adjacent to the roots of teeth #25 and #26. Both those possibilities present radiographically as a well-defined radiolucency that may cause divergence of the roots. The inflammatory cyst in the lateral periodontal position was less likely because of the absence of caries, restorations, or other signs suggesting necrotic pulp tissue. Odontogenic keratocyst may present identically to a lateral periodontal cyst.[1] Calcifying odontogenic cyst typically presents as a unilocular radiolucency, with or without calcifications. It may cause root divergence and has a predilection for the anterior jaws.[1]

Ameloblastoma must be considered in the differential diagnosis because it is a common odontogenic tumor. Although the typical radiographic presentation is a multilocular radiolucency, early lesions and the less common unicystic variant can present as a small, circumscribed radiolucency that may be radiographically identical to a cyst.[1] Adenomatoid odontogenic tumor (AOT) is mostly seen in younger patients, and although in the majority of cases, it encircles the crown of an unerupted tooth, 25% present as the "extrafollicular" type or as a well-defined radiolucency adjacent to the roots of erupted teeth.[1] "Snowflake" calcifications may be appreciated in AOT, although it is not a requirement for diagnosis. Central odontogenic fibroma (COF) has a wide age distribution and typically presents as a well-defined unilocular radiolucency. Although the periradicular region is often involved, lesions developing between teeth usually cause divergence of roots.[1] The rare squamous odontogenic tumor has a wide age distribution, and the most common presentation is a small unilocular radiolucent lesion causing divergence of roots of adjacent teeth.[2] The shape of the radiolucency has been described as triangular, and it may be well circumscribed or ill defined.[1,2]

Reactive lesions, including central giant cell granuloma (CGCG), and non-odontogenic tumors, such as central hemangioma and central ossifying fibroma, may present in pediatric populations as well-defined radiolucent lesions causing root divergence. CGCGs have a variable radiographic appearance, ranging from small, asymptomatic, incidental radiolucencies to large, expansile, multilocular lesions. They tend to be located in the anterior mandible and may cross the midline.[1] Hemangiomas are uncommon in the jaws and can have a wide range of radiographic profiles. Classically, central vascular lesions are multilocular and expansile; however, they may present as a circumscribed radiolucency resembling a cyst.[1] Drage et al. reported a case of a central hemangioma that was a corticated radiolucency located between the roots of teeth.[3] Central ossifying fibroma has a broad age distribution and a wide range of radiographic presentations. In a study of 43 ossifying fibromas, Eversole et al. reported that 5% of them were unilocular radiolucencies located between the roots of adjacent teeth.[4] Central ossifying fibroma is a true neoplasm, and its expansile nature is evident in its ability to cause root resorption and divergence.

Diagnosis and Management: Excisional biopsy was performed. The specimen consisted of a fibrous connective tissue proliferation containing abundant small islands of odontogenic epithelium (Figure 3A). The specimen also exhibited multiple zones composed of a hypercellular mesenchymal proliferation infiltrated by multinucleated giant cells and extravasated erythrocytes (Figure 3B). Scattered spicules of reactive viable bone and osteoid were contained within the proliferation (Figure 3C). The odontogenic epithelial cells were intensely positive with pancytokeratin (AE1/AE3) immunohistochemical staining (Figure 3D). The diagnosis was hybrid COF and CGCG. A follow-up radiograph taken 5 months after surgery showed normal-appearing bone filling in the area where the lesion had been present (Figure 4).

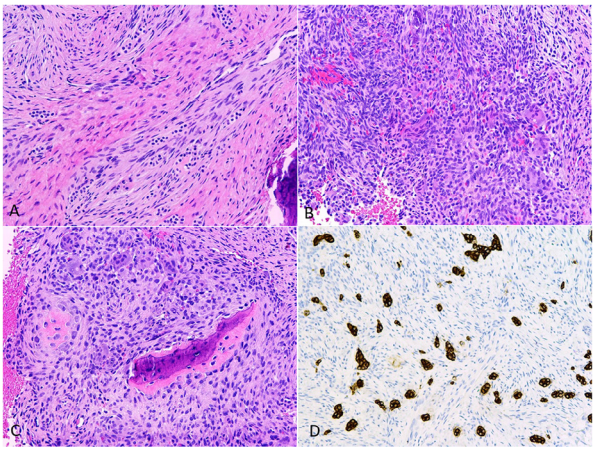

Fig. 3. **A,** Islands and strands of odontogenic epithelium within a cellular fibrous stroma (hematoxylin and eosin [H&E], original magnification ×20). **B,** Multinucleated giant cells set within a spindled mesenchymal cell proliferation with areas of hemorrhage (H&E, original magnification ×20). **C,** Production of osteoid and woven bone within CGCG-like areas (H&E, original magnification ×20). **D,** Islands of odontogenic epithelium exhibiting intense immunoreactivity with AE1/AE3 (immunohistochemistry [IHC], original magnification ×20).

Discussion: The histopathologic finding of both COF and CGCG occurring within the same lesion was first described in 1992 by Allen et al. as "central odontogenic fibroma, WHO type, with an unusual associated giant cell reaction."[5] Since that initial report, many additional cases have been published, with "hybrid COF and CGCG" being the most widely adopted current terminology. A literature search identified 30 published cases of this entity.[5-15] Eleven additional cases have been presented as essays or abstracts at the annual meetings of the American Academy of Oral and Maxillofacial Pathology.[16-18] With the addition of our case, this brings the total to 42. Table I lists the 39 cases for which some demographic or clinical data are known.

Hybrid COF and CGCG appears to be slightly more common in females than in males (female/male ratio 1.44:1). The condition occurs within a wide age range (5-75 years), with an average age of 28.13 years. These age demographic characteristics were calculated from 32 of the 39 cases where age was known.

Hybrid COF and CGCG exhibits a strong predilection for the mandible (95% of cases). Only 2 cases have been reported in the maxilla. In 10 of the 39 cases, a precise anatomic location was not specified. For the 29 cases in which a specific location was reported, the posterior regions were predominantly affected in both jaws (25 of 29 [86%]). Only 3 cases, including ours, were described as limited to the anterior mandible.[13,15] In a case reported by de Lima, the lesion was extensive, spanning from the right to the left first molars.[10] Hybrid COF and CGCG may appear as either