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LETTER TO THE EDITOR

What Is the Non-calcifying Langerhans Cell-Rich Variant of Calcifying Epithelial Odontogenic Tumor?

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To the Editors,

There have been rare reports of the non-calcifying Langerhans cell-rich (NCLC) variant of calcifying epithelial odontogenic tumor (CEOT) [1, 2]. Previously known as NC-CEOT with LC, the term "NCLC variant of CEOT" was introduced in 2011 by Chi and Neville [3], and has since become familiar. Santosh et al. [1], like other authors [2, 4], listed seven intraosseous cases, but failed to include three other documented examples [5, 6]. Because of its rarity, the NCLC variant remains an area of debate and confusion [4]. Here we offer some alternative viewpoints regarding its true nature.

On the basis of existing knowledge [1, 2, 4–6], the NCLC variant can be said to show the following characteristics: (1) predilection for individuals of Asian ethnicity; (2) usual onset at middle age; (3) almost 2:1 female predominance; (4) predilection for the anterior maxilla; (5) typically a unilocular radiolucency around the roots of teeth; (6) no detectable radiopaque foci; (7) characteristic depression of the palatal bone/mucosa; (8) extensive root resorption; (9) widely scattered and very small epithelial islands in a hypocellular fibromyxoid background; (10) numerous LCs within the epithelium; (11) juxtaepithelial deposition of amyloid globules without calcification; and (12) only one case of recurrence [5]. Although Santosh et al. [1] concluded that all reported tumors had been found in patients of Asian descent and that their own case was the first Caucasian example, this was erroneous. In 2013, Ganatra et al. [5] documented a NCLC variant in a white female patient. Furthermore, there have been a number of cases of a histologically similar tumor from Western authors reported as "NC-CEOT" [7, 8] and "atypical CEOT" [9, 10], or other more well-known tumors such as central odontogenic fibroma (COdF) [11–17] and odontogenic myxoma [18].

We concur with the suggestion by Eversole [15] in 2011 that the NCLC variant be placed under the umbrella of COdF. This behaves more like COdF (non-aggressive [4, 13, 15, 19]) than CEOT (locally aggressive [2, 4, 19–21]). COdF frequently involves the anterior-premolar region (77% of all cases and 91% of maxillary cases [4, 13, 22–25]) [3, 14, 21, 26]. This is in contrast to CEOT, which arises most often in the mandible (59% [2]–74% [27]), particularly the posterior area (82% [19, 20, 26]) [1]. A notable predilection for the anterior maxilla has been noted for the NCLC variant [1, 2, 4–6]. COdF is more than twice as common in females [3, 13, 19, 21, 22, 24–26], while there is almost equal distribution of CEOT between males and females [2, 19, 20, 26, 27]. As stated above, the NCLC variant shows a strong female predilection. Almost 60% of CEOTs show a dentigerous relationship to an impacted tooth [1, 20, 27]; more than half of such cases involve mandibular molars [1, 19, 20, 26], whereas only 11% [22] to 27% [25] of COdFs are associated with the tooth crown. Most COdFs reside in a peri- or interradicular location [3, 4, 13–15, 22–26, 28], and the NCLC variant has been defined as "root-associated" [1, 2, 4–6]. Root resorption is common in COdF (29% [13, 25] to 76% [4]) [15, 21, 23, 26], but uncommon in CEOT (4% [19, 27] to 13% [2]). About 70% of cases of the NCLC variant have exhibited this radiographic characteristic [4]. The presence of a palatal perforation of maxillary lesions anterior to the first molar (25% [24] to 80% [28]) is highly suggestive of COdF [4, 15, 22, 23, 26]. This unique COdF-associated clinical sign has been recorded in more than half of cases of the NCLC variant [4, 6]. CEOT recurs at a significantly higher rate (up to 20%) [2, 3, 19, 20, 26, 29] when compared with COdF (4%) [29]. There is no well-documented tendency for the NCLC

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variant to recur [1, 2, 4, 6], and only a rare recurrence is to be expected [5].

The first author to have publicly suggested the concept of NC-CEOT-like COdF was Dunlap [13] in 1999, but almost 2 decades previously Gardner [11] had called attention to COdF containing eosinophilic globules, creating confusion with CEOT. As with Smith et al. [10], Odell and Morgan [30] illustrated NC-CEOT with microscopic features of COdF in their 1998 textbook. This diagnostic problem was further discussed in 2009 [19] and 2011 [3, 15], respectively. Neville et al. [26] expressed similar frustration in the 4th edition of their widely used textbook. In 2011, Eversole [15] suggested consideration of the term "amyloid/dendritic cell-associated, amyloid/CD1a-associated or amyloid variant" to describe NCLC-CEOT-like COdF. Four years later, Carolina et al. [17] chose to use the term "amyloid/dendritic cell-associated variant" in the title of their abstract. Very recently, Zhou and Li [4] provided additional support for Eversole's suggestion by using the term "amyloid variant" in their series of four new cases. This variant accounts for 16% [15] to 35% [4] of COdFs.

Since the first description by Smith et al. [7] in 1977, NC-CEOT has been well documented [8, 10, 21, 30–36], and the 1992 World Health Organization blue book recognized it specifically [37]. Because of the contradictory prefix "NC (non-calcifying)-C (calcifying)," a number of authors favored the modified term "NC-EOT" [5, 7, 31, 36]. To our knowledge, only two reports of NC-CEOT have briefly mentioned that LCs were absent [33, 34]. Although LC markers were not examined in most cases, several articles of conventional CEOT with small amounts of LCs have been published [4, 6, 38–40]. Taken together, the presence or absence of LCs may not be primarily related to calcification in CEOT [39], and too much emphasis is probably placed on their participation in lesion formation. Prætorius [19] concluded that progressive calcification is usually seen in large tumors of long duration.

In summary, the profile of the NCLC variant is quite different from that of classic CEOT [1, 4]. It seems advantageous to reconsider the categorization of this intriguing tumor as COdF [4, 15], in terms of both clinical presentation and pathological features. A supporting observation is that the COdF epithelium frequently contains substantial numbers of LCs (50% [41] to 100% [4, 42] of tested cases) [16]. Additional support comes from Eversole's work that COdF-amyloid is odontogenic ameloblast-associated protein [15], which has been detected in CEOT-amyloid [3, 4, 19, 26]. Of particular interest is that epithelial/fibroblastic cells and globular deposits positive for amelogenin are reportedly scattered in COdF [43]. Multi-institutional cooperation and/or international collaboration is needed for comparative study of the NCLC variant of CEOT and the amyloid variant of COdF.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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