Pigmented odontogenic tumors: Adding color to diagnosis?

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ABSTRACT
Melanocytes are neural crest derivatives that exhibit a ubiquitous presence in the epidermis. They determine the complexion of an individual and most importantly, provide a barrier against ultraviolet radiations from the sun. Their presence in the oral cavity is a consistent finding, especially in the gingiva and buccal mucosa of the dark complexioned. Melanocytes occasionally form a part of the histology of a variety of odontogenic cysts and tumors. How these cells make their way into the lesional tissue and the diagnostic relevance of their presence remains elusive. This write up attempts to trace the path melanocytes take to find themselves within odontogenic tumors and also offer possible explanations for the same.

Key words: Melanocytes, neural crest cells, odontogenic tumors

INTRODUCTION
Melanocytes are dendritic cells of neural crest origin, usually found in the epidermis. It is attributed to the production of melanin, a pigment that renders color to the skin and is also an integral part of a protective barrier against ultraviolet radiations from the sun. Their presence in the oral cavity, especially in the gingiva and buccal mucosa is a fairly consistent and well-documented finding, especially in the dark complexioned individuals.

Histologically, the melanocyte is a highly differentiated entity, with a well-endowed cellular synthetic and secretory apparatus. They are characterized by the presence of intracellular granules, also called melanosomes, which actually are a product of the cell’s Golgi apparatus. It is these granules, which on maturation release melanin, an endogenous pigment into the surrounding epithelial cells through a unique “cytocrine” mechanism. The pigmentation is discerned clinically when melanocytes aggregate in clusters of about 1–3μm in size. The absence of obvious pigmentation in Caucasians/fair-skinned people has been associated with the presence of premelanin within the cells.

Melanocytes and odontogenic tumors
Melanocytes are quite rare in odontogenic tumors, but all the same, it is not unheard of. The melanotic neuroectodermal tumor of infancy was initially considered to be the only pigmented jaw tumor in existence. This was until 1964, when the first case of odontogenic origin, that of a pigmented gingival cyst was reported by Grand and Marcoah.

Odontogenic tumors that have exhibited a pigmented variant in their ranks include: Adenomatoid odontogenic tumor (AOT), odontoma, ameloblastic fibroodontoma, ameloblastic odontoma and calcifying odontogenic cyst. The presence of melanocytes in these tumors have not been found to relate to the location of occurrence, gender predilection or biological behavior of these lesions. But how exactly do these cells make their way into the lesion is intriguing and certainly a worthy query.

Thirty-seven cases of odontogenic tumors showing the presence of predominantly extracellular pigmentation have been reported till date which includes 20 calcifying cystic odontogenic tumors (CCOTs) [Figures 1 and 2], four AOTs, three ameloblastic fibroodontomas, three odontomas [Figure 3], two odontoameloblastomas, two ameloblastomas and one each of ameloblastic fibrodentitionoma (AFD), calcifying epithelial odontogenic tumor (CEOT), odontogenic fibroma and ameloblastic fibroma each as summarized in Table 1. The tumors show an increased predisposition to occur in the maxilla in females (75%) and the mandible in males (64.3%) [Figure 4]. Ethnicity also seems to play a role in occurrence with 44.44% males and 46.15% females presenting with the tumor, being of Japanese origin [Figure 5].
One of the earlier theories, pertaining to pigmented tumors of the jaw, was the retinal anlage theory, put forth by Halpert and Petzer in 1947. This theory linked the pigmented jaw tumor to a retinal and choroidal cell lineage. This theory was opposed by Willis in 1958, sighting a stark lack of anatomical relativity to the lesion and the unreasonable exclusion of a very much possible “odontogenic” explanation for the pigmentation.\[2,3\] The neural crest theory, on the contrary, finds greater acceptance.\[20,21\]

The “neural crest” tag prefixes the origin of a diverse group of cells, which include ganglion cells, parts of autonomic nervous system, chromaffin cells, melanocytes, neurilemma, odontoblasts and choroidal cells.\[22\] Neural crests, as described by Avery, function in the primary induction and formation of the tooth anlage. Moreover, formative melanocytes have been found to be associated with odontoblasts on the surface of the dental papilla and have also been consistently isolated from the dental primordium.\[20,23,24\]

The fly paper model—Tracing footstep

The movement of the neural crest cells has been illustrated most elegantly by Thorogood (1988) through the fly paper model that explains their differential, yet accurate migration as an intricate balance of active movement and passive displacement.\[20\] It is their subsequent response to guiding stimuli that dictates their course of differentiation.

The synchronized migration of an otherwise close knit group of cells is attributed to the “push or pull” effect elicited by various molecules. This involves initial loss of intercellular adhesion, brought about by the Slug proteins and the loss of N-cadherin, the glue that binds these cells together.\[20,23\] This is followed by the action of RhoB that induces changes which promote cell migration, further compounded by fibronectin, tenasin, laminin and other collagen molecules. The extent of cellular migration is curtailed by the action of Eph proteins that ensure the precise localization of these cells. What the neural crest cells then differentiate into, is a product of the synchrony between molecular activity and interactions with the surrounding cells and the environment. Molecules like the endothelin-3 and stem cell factor (SCF) have been implicated in the formation and proliferation of melanocytes, respectively.\[20\]

What causes melanocytes to be seen in odontogenic tumors

Though largely ambiguous, the reports of melanocytes forming part of the regular histology of odontogenic neoplasms could be associated with the following causes:

Firstly, the neural crest cells of different origins can intermingle at the same site, thus differentiating into their respective lineage cells on being stimulated.\[20\] Secondly, melanocytes are seen on
the surface of the dental papilla and as the dentin laid down, the odontoblasts and melanocytes retract, but the pigment still remains in the processes that are entrapped between the newly formed dentin. This could be a probable explanation to the compelling finding of extracellular pigmentation occurring in tumors that present with “dentinoid”-like material as an integral part of their histology. Thirdly, the dental lamina is a derivative of the oral ectoderm just like the neural crest cells, which could explain the strong tendency for melanocytes to aggregate around the dental lamina. All these factors compounded by the incomplete migration or aberrant differentiation of the neural crest cells offer a plausible explanation as to how melanocytes gain access to the odontogenic environment.

The remnants of cells that contribute to the odontogenic apparatus, proliferate in most tumors, thus increasing the expressions of

| Author and year of reporting | Tumor | Age (years) | Sex | Site | Race |
|------------------------------|-------|-------------|-----|------|------|
| Lurie (1961)[4,5]            | CCOT with compound odontome | 23 | F | Maxilla | Bantu |
| Gordon et al. (1965)[4,5]    | CCOT | 16 | M | Maxilla | Unknown |
| Duckworth and Seward (1965)[4,5] | CCOT | 24 | F | Maxilla | Negro |
| Abrams and Howell (1968)[4,5] | CCOT | 21 | F | Maxilla | Caucasian |
| Chandi and Simon (1970)[4,5] | CCOT | 27 | M | Mandible | Indian |
| Sauk (1972)[4,5]             | CCOT | 64 | M | Mandible | Unknown |
| Petri and Stump (1976)[4,5]  | CCOT | 11 | F | Maxilla | Negro |
| Saito et al. (1982)[4,5]     | CCOT | 13 | M | Mandible | Japanese |
| Saito et al. (1982)[4,5]     | CCOT with compound odontome | 9 | F | Mandible | Japanese |
| Saito et al. (1982)[4,5]     | CCOT | 35 | F | Maxilla | Japanese |
| Nagao et al. (1982)[4,5]     | CCOT with complex odontome | 13 | F | Mandible | Japanese |
| Soames (1982)[4,5]           | CCOT | 15 | F | Mandible | West Indian |
| Schwimmer et al. (1983)[4,5] | CCOT | 13 | M | Mandible | Hispanic |
| Takeda et al. (1985)[4,5]    | CCOT | 21 | M | Maxilla | Japanese |
| Keszler and Guggielmotti (1987)[4,5] | CCOT with composite odontome | 15 | F | Maxilla | Unknown |
| Sia and Ng (1987)[4,5]       | CCOT with compound odontome | 16 | F | Maxilla | Chinese |
| Sia and Ng (1987)[4,5]       | CCOT | 31 | M | Maxilla | Indian |
| Sia and Ng (1987)[4,5]       | CCOT | 68 | F | Mandible | Malay |
| Takeda et al., (1990)[4,5]   | CCOT | 17 | M | Mandible | Japanese |
| Takeda et al., (1990)[4,5]   | CCOT | 11 | F | Mandible | Japanese |
| Takeda (1989)[4,5]           | AOT | 12 | F | Japanese |
| Warter et al., (1990)[7]     | AOT with DC | 8 | M | Right mandibular cuspid area | Nigerian |
| Aldred and Gray (1990)[8]    | AOT | 15 | F | Maxillary left canine region | Indian |
| Kitano (1994)[5,9]           | Fibroodontoma | 9 | F | Japanese |
| Takeda (1988)[5,10]          | Fibroodontoma | 11 | F | Japanese |
| Eda (1977)[9]                | Fibroodontoma | 27 | F | Japanese |
| Gurkiran et al.[11]          | Odontoma | 23 | M | Lower right posterior region | Indian |
| Takeda and Yamamoto 1987[5,12] | Odontoma | 53 | F | Japanese |
| Takeda et al., 1987[5,13]    | Odontoma | 19 | M | Japanese |
| Takeda (1989)[14]            | Odontoameloblastoma | 11 | F | Maxilla | Japanese |
| Martin Granizo Lopez (2004)[15] | Odontoameloblastoma | 12 | F | Right anterior mandible | Caucasian |
| Edwards and Gouban (1980)[1,5] | Ameloblastic fibroma | 18 | M | Right mandible from canine to premolar | African |
| Handlers et al., (1991)[16]  | Odontogenic Fibroma | Review of 19 cases | | |
| Takeda (2000)[17]            | AFD | 21 | M | Right retromolar area | Japanese |
| Richardson (1974)[18]        | CEOT (previously unidentified) | 12 | F | Right mandibular second molar region | Negro |
| Bernier (1956)[19]           | Melanotic ameloblastoma | | | |
| Raubenheimer (1995)[5]       | Ameloblastoma | | | |
wingless neurotropin (WNT) signaling pathway and stem cell factor (SCF). These molecules in turn, are known to directly affect proliferation and differentiation of melanocytes, thus rendering a pigmented component to the tumoral histology. Also, odontogenic lesions are believed to contain inactive melanocytes that may escape routine histopathological examination, but under certain conditions, they are activated to produce the pigmented variant of their respective lesions.[24-26]
CONCLUSION

Pigmented variants are rare in odontogenic tumors, and questions pertinent to their appearance and diagnostic relevance remain largely unanswered. Astute observations of the histology, the presence of melanocytes and biological behavior of pigmented odontogenic lesions need to be made and documented, to facilitate an enhanced understanding of this feature and its possible prognostic implications if any.

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How to cite this article: Bhanu U, Kulkarni R, Boaz K, Srikan N. Pigmented odontogenic tumors: Adding color to diagnosis?. J Oral Maxillofacial Pathol 2014;18:398-402.

Source of Support: Nil. Conflict of Interest: None declared.