REVIEW ARTICLE

Pigmented odontogenic tumors: Adding color to diagnosis?

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Received: 22-11-2013
Accepted: 05-01-2015

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.[1,2] They are characterized by the presence of intracellular granules, also called melanosomes, which actually are a product of the cell's Golgi apparatus.[3] 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.[2,3]

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.151325

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],[10] four AOTs, three ameloblastic fibroodontomas, three odontomas [Figure 3],[16] two odontoameloblastomas, two ameloblastomas and one each of ameloblastic fibrodentionoma (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].

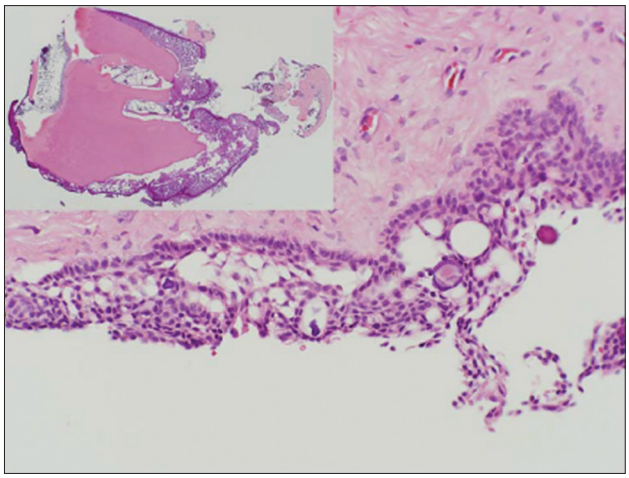

Figure 1: The epithelial lining of a cystic odontogenic tumors (CCOT) showed basal palisaded cuboidal cells and suprabasal stellate cells. Small focal calcifications within the epithelium can also be observed (H&E stain, ×100). Inset: Small organoid denticles may also be seen. (H&E stain, ×40) (as shown in the inset).

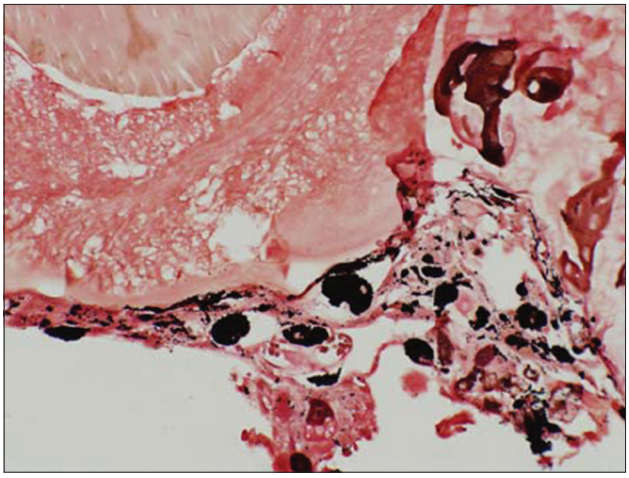

Figure 2: Odontogenic epithelium and ghost cells stained with Masson Fontana for melanin pigmentation. Melanin pigments are detected within the epithelial cells, in the ghost cells and also lie freely within the extracellular connective tissue. (Masson Fontana stain, ×400)

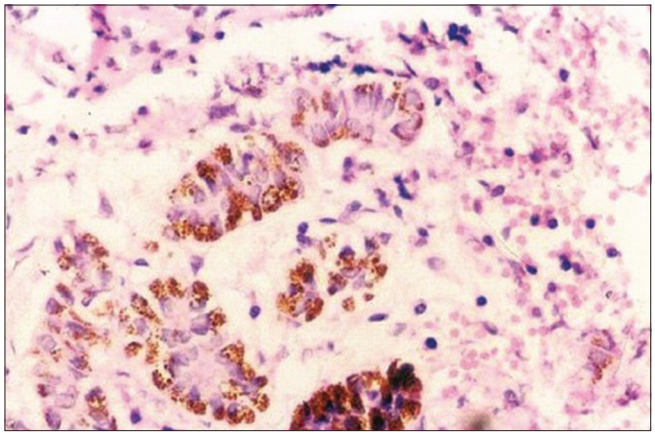

Figure 3: Photomicrograph of odontogenic epithelial cell rests stained using Masson Fontana, exhibiting the presence of intracellular melanin pigmentation (Masson Fontana, x100)

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

Table 1: Cases of pigmented odontogenic tumors reported till date

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.*[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	Hispaniac
Takeda *et al.*, (1985)[4,5]	CCOT	21	M	Maxilla	Japanese
Keszler and Guglielmotti (1987)[4,5]	CCOT with composite odontome	15	F	Maxilla	Unknown
Siar and Ng (1987)[4,5]	CCOTwith compound odontome	16	F	Maxilla	Chinese
Siar and Ng (1987)[4,5]	CCOT	31	M	Maxilla	Indian
Siar 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)[4,5,6]	AOT	12	F		Japanese
Warter *et al.*, (1990)[7]	AOT with DC	8	M	Right mandibular cuspid area	Nigerian
	AOT	29	M	Mandibular retromolar area	Japanese
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)[5]	Fibroodontoma	27	F		Japanese
Gurkiran *et al.*[11]	Odontoma	23	M	Lower right posterior region	Indian
Takeda and Yamamoto 1989[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 Goubran (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				Negro

CCOT: Calcifying cystic odontogenic tumor, AOT: Adenomatoid odontogenic tumor, DC: Dentigerous cyst, AFD: Ameloblastic fibrodentinoma, CEOT: Calcifying epithelial odontogenic tumor, F: Female, M: Male

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

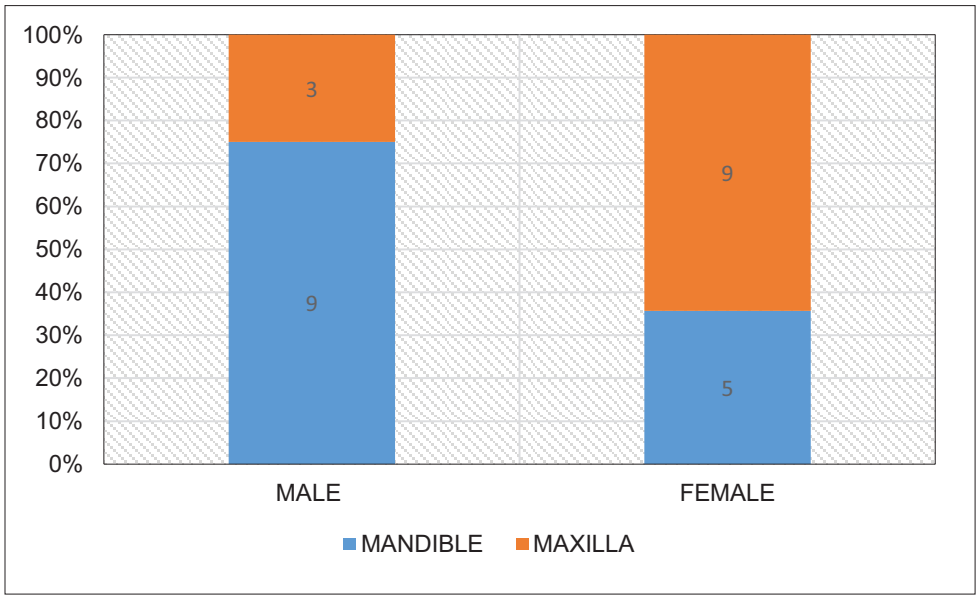

Figure 4: Bar graph showing the increased tendency for pigmented tumors to occur in the maxilla in females and the mandible in males

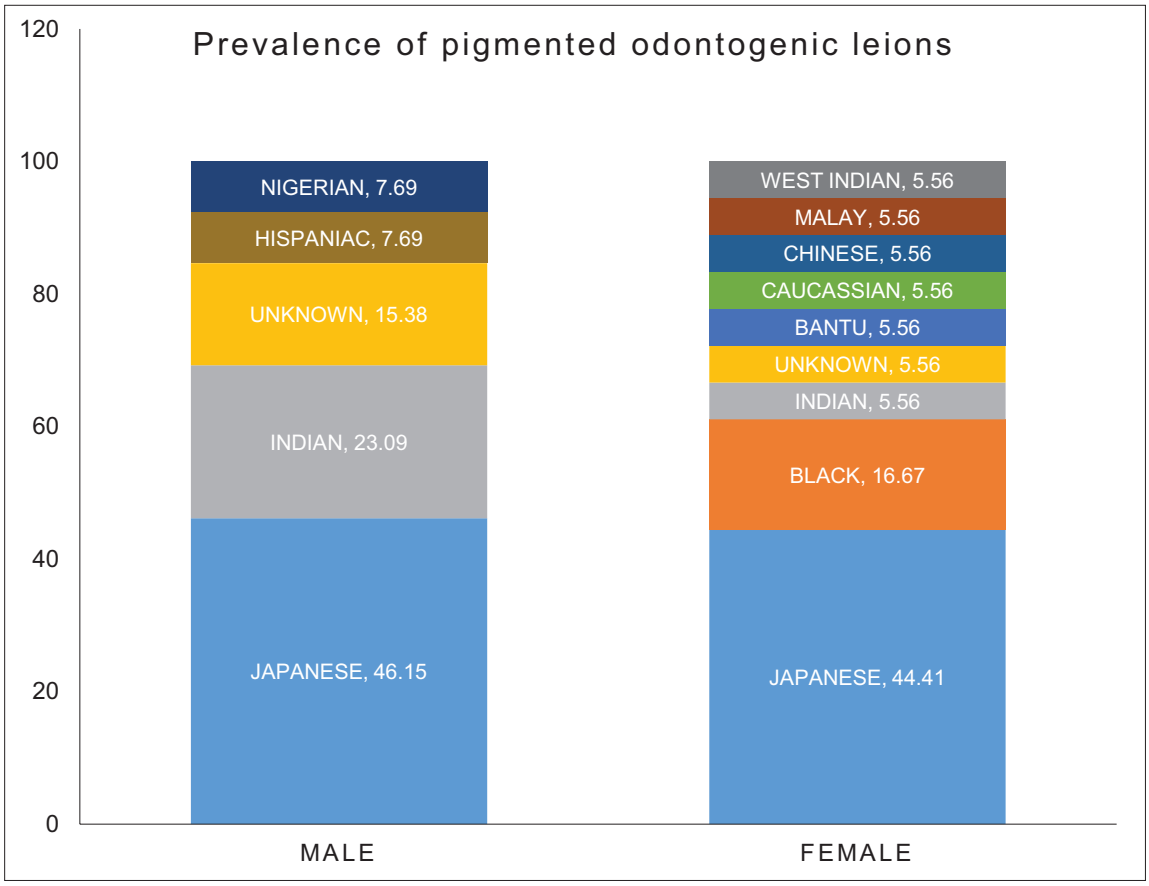

Figure 5: Bar diagram showing racial preponderance for occurrence of pigmented odontogenic tumors

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, Srikant N. Pigmented odontogenic tumors: Adding color to diagnosis?. J Oral Maxillofac Pathol 2014;18:398-402.

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