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Systematic Review: Pigmented Odontogenic Lesions

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ABSTRACT

Introduction: Pigmented odontogenic lesions are rare; to date, only 60 cases have been reported in the literature. Melanocytes have been detected in a wide variety of odontogenic lesions. Several studies have discussed melanocyte presence and melanin production in odontogenic lesions, but its origin is still unclear. Therefore, the present systematic review aimed to gather information on such cases.

Materials and Methods: An electronic search was performed in PubMed Central's database The search strategy was limited to human studies (case reports and case series) and full-text English articles published till June 2021. Irrelevant articles were omitted.

Results: Pigmented odontogenic cysts (66.66%) are more common than pigmented tumors. The most common pigmented cyst was calcifying odontogenic cysts (22 cases), followed by odontogenic keratocysts (10 cases). The most common pigmented neoplasm was mixed odontogenic tumors (10 cases). Pigmented lesions are more common in the Asian race.

Conclusion: The melanocyte presence in odontogenic lesions has no particular prognostic importance. Some possible factors in this field include ethnicity, dental hard tissue induction, neural crest cells, and dental lamina's origin. Further documentation of such cases helps to improve the available information on these lesions.

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Introduction

Melanocytes originate from neural crest cells and are commonly spread in the skin, nervous system, certain types of the mucosa, and other regions.(1) They are characterized by intracellular granules (melanosomes) that release melanin into the surrounding epithelial cells through a unique "cytocrine" mechanism after maturation.(2) Melanin has antioxidant and reactive oxygen species (ROS)-dependent cytotoxic effects.(3) The presence of melanocyte and melanin pigmentation in gingiva and oral mucosa is well documented.(2) Oral melanocytes may be inherently active or activated in certain situations. Non-physiological changes in oral pigmentation are associated with genetic, metabolic, endocrine, chemical, or physical factors, infective agents, and inflammatory or tumoral conditions.(3) The presence of melanin pigmentation in odontogenic lesions has an unknown etiology and is uncommon even in dark-skinned persons. However, it has been detected and reported in some odontogenic cysts and neoplasms.(4,5) In these lesions, melanin is seen in the cytoplasm of tumor cells or cyst epithelium. Several studies have discussed the presence of melanocytes and melanin production in odontogenic lesions, but its origin is still unclear.(4) In the present systematic review, we assessed the microscopic variation of the reported pigmented odontogenic lesions and discussed the possible origin of these pigmentations.

Materials and Methods

Search strategy

An electronic search of the PubMed database was performed using the following keywords: (odontogenic tumor OR odontogenic cyst OR odontogenic lesion) AND (pigmented OR melanocyte). Two independent authors screened the articles' titles and abstracts, and unrelated studies were omitted. The bibliography of the selected articles was also searched manually to find any related articles which might have been missed in the primary search.

Eligibility criteria

The inclusion criteria were those human case reports or case series that reported the cases with sufficient demographic information (having at least one other characteristic in addition to the microscopic diagnosis), articles being in English, full-text availability, published till June 2021, the article type being human case reports or case series. Studies on peripheral odontogenic lesions were excluded from the study.

Data collection

Data were extracted from the included articles by two independent authors. The following information was collected (if available) and is presented in Table 1: (1) Gender, age, and ethnicity of the patients; (2) microscopic diagnosis; (3) lesion's location; (4) associated lesions.

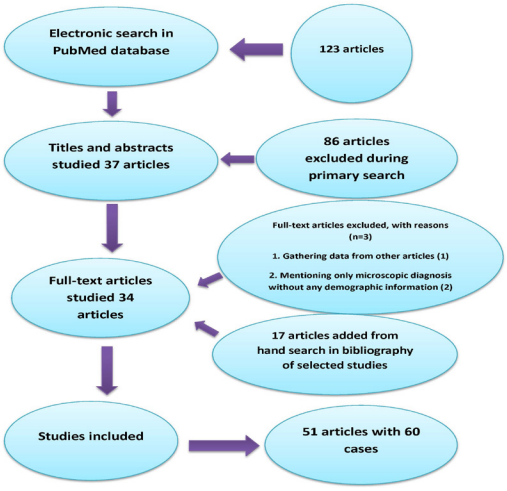
Statistical analysis

Based on the data extracted from the included article, a descriptive statistical analysis was performed using SPSS software version 21 (IBM Corp., Armonk,

N.Y., USA).

Results

The data extraction chart is shown in Figure 1.



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In the first step, the titles and abstracts were removed from unrelated articles. In the second step, after reviewing the full text of the articles, one article was deleted due to gathering information from other articles and not presenting a new case. Two articles were removed because of mentioning only microscopic diagnosis without any demographic information. Then 17 articles were added from a hand search.

Fifty-one articles were included, which presented 60 cases which were divided into three groups: cysts (40 cases, 66.66%) (Table 1), benign tumors (15 cases, 25%) (Table 2), and malignancies (4 cases, 6.66%) (Table 3).

Table 1: Reported cases of pigmented odontogenic cysts.

Cyst types	N (%)	Mean age (Years)*	Gender		Cyst location**		Associated lesion (N)	Nationality***
			Female	Male	Mandible	Maxilla		
Calcifying odontogenic cysts	22 (55%)	22.31	13	9	11	11	Odontoma (7)	14 Asian, 3Black, 1White, 1Hispanic
Odontogenic keratocyst	10 (25%)	14	6	4	8	1		7Asian, 2Black, 1White
Dentigerous cyst	3 (7.5%)	26.33	1	2	3			2Asian, 1White
Lateral periodontal cyst	4 (10 %)	47.5	1	3	1	2		4Black
Inflamed odontogenic cyst with verrucous proliferation	1 (2.56%)	13		1		1		1Asian

*The age was not known in the two patients. **The location was unknown in 3 cases & one patient had OKC in both mandible and maxilla. *** The nationality was not known in 3 cases. In the Asian group, 23 cases were Japanese.

Table 2: Microscopic subtypes of reported pigmented benign odontogenic tumors.

Benign Tumor type	Subgroup	N (%)	Mean age (Years)	Gender		Tumor location*		Nationality
				Female	Male	Mandible	Maxilla	
Nationality (n=10)	Ameloblastic fibro odontoma/ dentinoma	5 (33.33%)	13.6	3	2	2	1	4Asian, 1Black
	Odontoma	3 (20%)	31.66	1	2	1	2	3Asian
	Ameloblastic fibroma	1 (6.66%)	18	-	1	1	-	1Black
	Odontoameloblastoma	1 (6.66%)	11	1	-	-	1	1Asian
Epithelial (n=4)	Adenomatoid odontogenic tumor	2 (13.33%)	13.5	1	1	1	1	1Asian,1Hybrid
	Pindborg tumor	2 (13.33%)	20	2	-	1	1	1Asian, 1Black
Ectomesenchymal	Central odontogenic fibroma	1 (6.66%)	28	1	-	-	1	1Black

* The location was not known in 2 cases.

Table 3: Reported cases of pigmented odontogenic carcinomas.

Malignant tumor type	N (%)	Mean age (Years)	Gender		Tumor location		Nationality
			Female	Male	Mandible	Maxilla	
Ameloblastic carcinoma	2 50%)	51.5	-	2	1	1	1Asian,1Black
Malignant ameloblastoma	1(25%)	63	1	-	-	1	Asian
Odontogenic carcinoma	1(25%)	6	-	1	-	1	Asian

There was a hybrid case (dentigerous cyst (D.C.) + adenomatoid odontogenic tumor (AOT)) in a black male patient (8 years old, mandible), which showed melanin deposition in both parts and was considered separately as a hybrid lesion (not shown in table). Calcifying odontogenic cysts (COCs) associated with odontoma were included in the cyst group because the odontoma parts of all lesions were melanin-free. The case reported by Grant & Marwah(6) as a gingival cyst was reclassified as a lateral periodontal cyst (LPC) because of the bone involvement. The most common lesion was COC (36.66%), followed by odontogenic keratocyst (OKC) (16.66%) and ameloblastic fibro-odontoma/ fibro-dentinoma (AFO/AFD) (8.33%). Mixed odontogenic neoplasm (n=10) was the most common benign pigmented tumor (Table 1,2). Malignant pigmented tumors were more commonly reported in men and the maxilla (Table3). Pigmented lesions were more common in the Asian race (61.66%), especially in Japanese (41.66%), followed by Blacks, and only about 5.17% (n=3) were European.

Discussion

The origin of melanocytes in odontogenic lesions is hypothetical. Melanocytes are naturally present in the oral epithelium's basal layer, even in areas without obvious pigmentation.(2) Melanocytes and keratinocytes make epidermal melanin units, and keratinocytes show the capacity to control melanocyte melanogenesis. Histologically and ultrastructurally, the melanocytes of the epidermis and the oral mucosa are similar. Oral melanocytes' baseline metabolic activity is lower than the epidermis'. However, oral melanocytes can be more active in melanin biosynthesis in response to genetics, smoking, drug, injury, infection, inflammation, hormonal dysfunction, neoplasm, and other environmental factors.(3)

The infrequent existence of melanocytes in odontogenic lesions can be expected as the dental lamina's origin is the primitive oral epithelium.(1) Lawson et al.(7) detected the melanocytes within the ducts of minor salivary glands, dental lamina, and tooth buds of 12- to -18- week human fetuses and demonstrated that mucosal melanocytes tended to gather around the attachment area of the dental lamina to the oral epithelium. Takeda and Uyeno(8) also found melanocytes in mesenchymal tissue around the dental anlage in dog fetuses.

Neural crest cells play a dual role in tooth anlage development and melanocyte differentiation.(4,7,9) Their main role in odontogenesis is reflected in the reciprocal induction between the inner enamel epithelium and the dental papilla cells.(10) Both melanocytes and tooth germs develop at 5-6 weeks of gestation, so it is possible that the former erratically gains entrance into the latter.(11) Although melanocytes are ordinarily present in the oral epithelium, intraepithelial pigmented lesions such as pigmented oral squamous cell carcinomas (SCCs) are rare.(12) It is suggested that, like the oral mucosa, which can contain inactive melanocytes, the odontogenic epithelium also has inactive melanocytes that are activated in certain situations.(13) For example, TP53 promotes skin pigmentation by stimulating melanogenic cytokine synthesis.(14) Satomura et al. (15) found that the higher expression of stem cell factor and endothelin-1 on SCC cells may lead to melanocytes' stimulation in pigmented SCC. In melanocytes, an increase in metabolic activity may be seen in response to environmental causes such as hormones, inflammation, or injury.(3)

Ethnicity is considered one significant aspect of the development of melanotic jaw lesions.(1) In the present study, Asian races, especially the Japanese, accounted for most cases, followed by blacks.

It should be noted that most pigmented odontogenic tumors have epithelial elements accompanied by a mesenchymal component with dentin formation and calcification. The mesenchymal element and hard tissue formation may play a role in melanocytes' activity.(11) Melanocytes have also been reported to be associated with odontoblasts on the surface of the dental papilla. When the dentin matrix is made, odontoblasts and melanocytes retract, but

melanin pigment remains in the processes that are entrapped between the newly formed dentin.(2,7)

In our review, the most common pigmented lesion was COC. There is an inductive effect by the odontogenic epithelium on the adjacent mesenchymal tissue in COC, leading to dentinoid material production.(16) This may explain the higher frequency of pigmented COC compared to other odontogenic lesions. Furthermore, the most common group of pigmented tumors, including the mixed group, contained odontogenic epithelium and mesenchyme with induction of dental hard tissues or calcification. This theory can confirm higher numbers of AFOs in this study. Previous theories can also justify pigmentation in AOT because of dental hard tissue formation and dental lamina origin.

The second most pigmented lesion was OKC. The squamous epithelium of OKC typically does not contain melanocytes. Takeda et al.(17) reported two patterns of pigmentation in pigmented OKC: a) in the common pattern, many melanocytes are scattered in the basal layer, and unremarkable melanin pigment exists in the basal cells. b) Dendritic melanocytes are inconspicuous within the epithelium, but the cytoplasm of basal cells includes plenty of pigmentation. As mentioned earlier, melanocytes are found at the base of the dental lamina and may rarely be found in odontogenic lesions with dental lamina origins such as OKC and LPC.(4,13,18)

Ameloblastoma is a locally aggressive epithelial odontogenic neoplasm with a high recurrence rate.(19) The origins of these tumors can be considered the dental lamina, the developing enamel organ, an odontogenic cyst's epithelial lining, or the oral mucosa's basal cells.(20) Melanocytes have not been reported in ameloblastoma, which is the most common odontogenic tumor after odontoma in all races.(21) Nevertheless, cases of pigmented epithelial carcinomas without producing any dental hard tissue, such as ameloblastic carcinoma, odontogenic carcinoma, and malignant ameloblastoma, have been reported.(21-23) Takeda(21) mentioned that melanocytes appeared in the malignant-transformed ameloblastoma, and no melanocytes were in the pre-existing benign ameloblastoma.

Pigmented odontogenic tumors seem to have a biological behavior similar to conventional odontogenic neoplasms.(21) In addition, it was suggested that pigmentation in odontogenic cysts might be a physiologic phenomenon rather than a pathologic process; therefore, pigmentation does not contribute to the prognosis.(24) On the other hand, Mikami et al.(25) mentioned that pigmented SCC seems to have a better prognosis than conventional SCC, and the pigmentation lets patients become alert of the mucosal change.

Conclusion

Melanin pigmentation's etiology and pathogenesis in odontogenic lesions are unclear, but the presence of melanocytes in these lesions does not seem to be of any particular prognostic importance. Some possible factors in this field include ethnicity, dental hard tissue induction, and the origin of the neural crest cells and dental lamina. Pathologists should be familiar with these rare phenomena to avoid misdiagnosis. More documented cases help to improve information about these lesions, and this issue could be considered for future research.

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None

Authors' contributions

Saede AtarbashMoghadam: Conceptualization, Methodology, Writing - Review & Editing **Niloofar Jalali:** Resources, Investigation, Visualization **Soran Sijanivandi:** Data curation, Writing - Original Draft **Shaghayegh Dawdani:** Project administration, Supervision, Funding acquisition

Conflict of Interests

The authors declare no conflict of interest.

Ethical declarations

Not applicable

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None

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

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