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A Review of Non-plaque-related Gingival Conditions. Part Two: Reactive Processes, Potentially Dysplastic and Malignant Neoplasms, and Pigmented Conditions

Abstract: The dental gingivae are a unique part of the oral anatomy and an integral part of the periodontal tissues. Although the vast majority of abnormalities affecting the gingival tissues are due to a simple inflammatory reaction directly related to the presence of dental plaque, a range of non-plaque-related conditions also occur due to either local or systemic factors. Such factors include developmental abnormalities, the presence of malignancy and manifestations of underlying systemic conditions. Recognition and diagnosis of non-plaque-related gingival disease is essential for comprehensive dental health care.
CPD/Clinical Relevance: This paper provides a review of the spectrum of non-plaque-related conditions that can affect the dental gingivae.
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Part two of this two-part review continues to discuss non-plaque-related conditions of the gingivae, looking specifically at reactive processes, potentially dysplastic and malignant neoplasms, and pigmented conditions. An updated classification system for non-plaque-induced gingival diseases was introduced at the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases. (Table 1).[1]

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Reactive processes

Fibrous epulis

Fibrous epulis is a localized hyperplasia of the gingival tissues, often in response to local trauma or irritation, such as calculus or an overhanging restoration.[2] The overlying epithelium is smooth and pink, with the bulk of the swelling being composed of fibrous tissue (Figure 1). The inter-dental papilla is the most frequently affected site.[3] Fibrous epulides are often asymptomatic but may occasionally, if large, cause cosmetic problems. Diagnosis can be made on the history and clinical features. Local excision is required if there is any doubt in diagnosis or there is aesthetic concern.

Pyogenic granuloma

Pyogenic granuloma arises as a localized swelling often with an ulcerated surface (Figure 2). The aetiology is not known, although it is accepted that some cases are associated with pregnancy, where the term 'pregnancy epulis' is used.[4] The vascular nature of the condition is reflected by the onset of bleeding when the area is touched. The name of this mucosal abnormality is a misnomer, since it is not associated with either suppuration or formation of granulomas, but rather involves granulation tissue. Clinically, it is difficult to distinguish

1 Genetic/developmental disorders
1.1 Hereditary gingival fibromatosis (HGF)
1.2 Peutz-Jeghers syndrome
1.3 Cowden syndrome
2 Specific infections
2.1 Bacterial origin
Necrotizing periodontal diseases (*Treponema* spp, *Selenomonas* spp, *Fusobacterium* spp, *Prevotella intermedia*, and others)
Gonorrhoea (*Neisseria gonorrhoeae*)
Syphilis (*Treponema pallidum*)
Tuberculosis (*Mycobacterium tuberculosis*)
Streptococcal gingivitis (strains of *Streptococcus*)
2.2 Viral origin
Hand, foot and mouth disease (coxsackie virus)
Primary herpetic gingivostomatitis and recurrent herpes simplex (herpes simplex type 1 and 2 virus)
Chicken pox and shingles affecting the trigeminal nerve (varicella zoster virus)
Kaposi's sarcoma (human herpes virus 8)
Molluscum contagiosum (molluscum contagiosum virus)
Squamous cell papilloma, condyloma acuminatum, verruca vulgaris, multifocal epithelial hyperplasia (human papilloma virus)
2.3 Fungal origin
Candidosis
Other mycoses (histoplasmosis, aspergillosis)
3 Inflammatory and immune
3.1 Hypersensitivity reactions
Contact allergy
Plasma cell gingivitis
Erythema multiforme
3.2 Autoimmune
Pemphigus vulgaris
Mucous membrane pemphigoid
Oral lichen planus
Lupus erythematosus
3.3 Granulomatous inflammatory conditions
Orofacial granulomatosis and oral Crohn's disease
Sarcoidosis
Granulomatosis with polyangiitis
4 Reactive processes
4.1 Localized
Fibrous epulis
Calcifying fibroblastic granuloma
Pyogenic granuloma (vascular epulis)
Peripheral or central giant cell granuloma
4.2 Generalized
Drug-induced gingival overgrowth
5 Potentially dysplastic and malignant neoplasms
5.1 Potentially dysplastic
Leukoplakia
Erythroplakia
Erythroleukoplakia
5.2 Malignant
Squamous cell carcinoma
Leukaemia
Lymphoma
Malignant melanoma
6 Nutritional, endocrine and metabolic diseases
6.1 Vitamin deficiencies
Scurvy (vitamin C deficiency)
6.2 Endocrine
Addison's disease
7 Traumatic
7.1 Physical/mechanical insults
Frictional keratosis
Toothbrush-induced ulceration
Factitious injury (self-harm)
7.2 Chemical (toxic) insults
Etching, chlorhexidine, aspirin (acetylsalicylic acid), cocaine, hydrogen peroxide, dentifrice detergents, paraformaldehyde or calcium hydroxide
7.3 Thermal insults
Burns
8 Other pigmentation
8.1 Physiological
Physiological (ethnicity related)
Melanotic macule
8.2 Acquired
Smoker's melanosis
Drug induced (including heavy metals)
8.2 Iatrogenic
Amalgam tattoo
Graphite tattoo (pencils)

Table 1. Adapted from Holmstrup *et al.* [1]

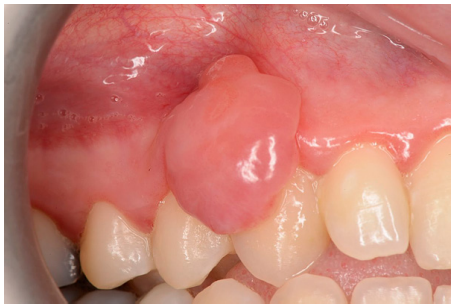

Figure 1. A fibrous epulis on the gingival margin with normal overlying mucosa.

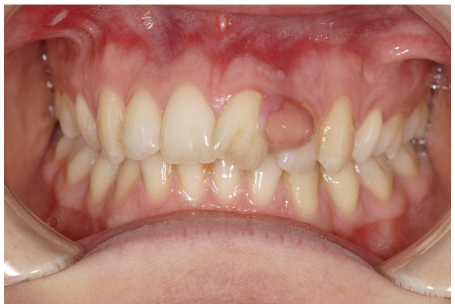

Figure 2. A pyogenic granuloma on the gingival margin with ulcerated overlying mucosa.

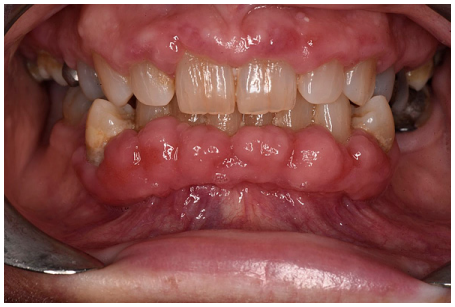

Figure 3. Drug-induced gingival hyperplasia following amlodipine therapy.

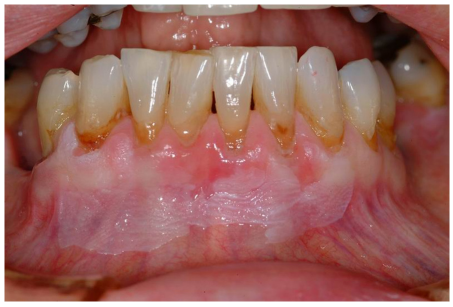

Figure 4. Leukoplakia presenting as a homogeneous non-raised white patch on the gingivae.

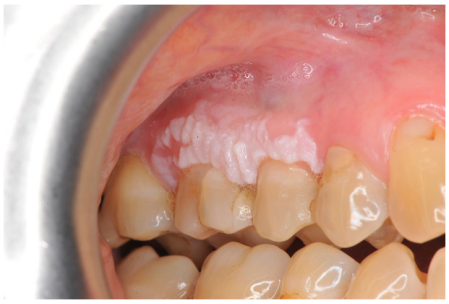

Figure 5. Leukoplakia presenting as a raised irregular white patch on the gingivae.

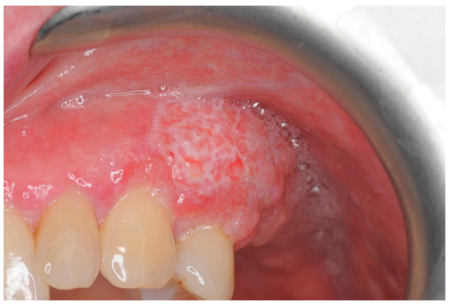

Figure 6. Squamous cell carcinoma presenting as a localized and slowly enlarging erythematous gingival swelling.

pyogenic granuloma from peripheral giant cell granuloma, although the latter should be suspected if there is radiographic evidence of underlying bone loss.[5]

Pyogenic granuloma develop most frequently on the gingivae.[6,7] Diagnosis is primarily based on history and clinical features. Excisional biopsy should be performed to obtain a definitive diagnosis and exclude alternative conditions. The patient should be warned of the risk of gingival recession when excising gingival pyogenic granulomas. Possible causes of local irritation should be identified and corrected. If present in pregnancy, and not concerning the patient, the mucosal abnormality may be left since it may resolve post-partum.[8] If excision is carried out during pregnancy, there is a potential for recurrence due to the ongoing hormonal factor.[9]

Drug-induced gingival hyperplasia

A number of medications have been reported as inducing gingival hyperplasia as an adverse event, in particular nifedipine, amlodipine, phenytoin, and ciclosporin. These drugs induce enlargement of the gingival tissues due to stimulation of fibroblasts.[10] The medication dose, duration of therapy, drug serum concentration, concomitant medications, oral hygiene, age, gender and genetics are all factors that may determine the presence and degree of gingival enlargement.[11] The anterior of the mouth is most frequently involved and in severe cases the crowns of the teeth may become covered (Figure 3).[12] Plaque control becomes difficult, which further increases gingival enlargement due to inflammation

The diagnosis is made on the basis of the onset of the gingival changes occurring within a few weeks of the start of a new medication. Mild overgrowth that is not causing cosmetic concern or impeding oral hygiene requires no intervention. When active intervention is required, the patient's medical practitioner or specialist should be consulted to determine whether alternative medication is possible since a change may result in resolution.[13–15] Periodontal treatment involving surgery may still be required.[16,17]

Potentially dysplastic and malignant neoplasms

Leukoplakia and proliferative verrucous leukoplakia

Leukoplakia may be defined as 'a white patch affecting the oral mucosa that cannot be diagnosed clinically or histopathologically as a specific disease.' It is included in the World Health Organization list of oral potentially malignant disorders. By definition, no aetiological factor can be identified. Leukoplakia may range from a homogeneous smooth plaque (Figure 4) to a raised papillary patch (Figure 5). Proliferative verrucous leukoplakia (PVL) is a subtype of oral leukoplakia where there is invasion of the surrounding tissue and exophytic growth.[1] PVL has a higher risk of malignant transformation than homogeneous leukoplakia and is more likely to occur on the gingivae.[18–22]

It is important to eliminate any tobacco and alcohol habit since these factors increase the potential for malignant change. The affected

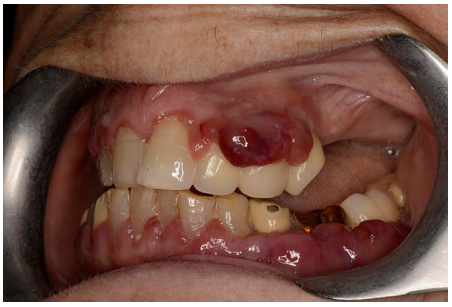

Figure 7. Leukaemia presenting as multiple swellings of the gingivae that bleed easily on touch.

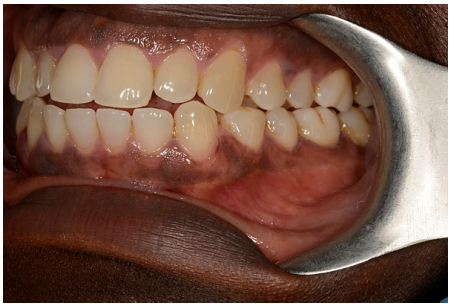

Figure 8. Diffuse and variable physiological pigmentation of the gingival tissues.

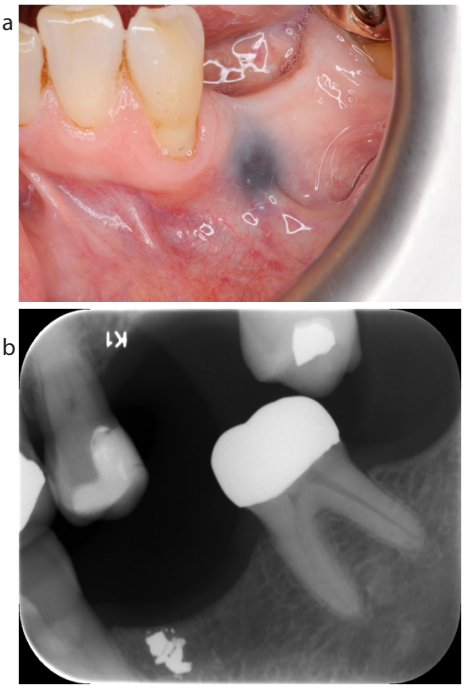

Figure 9. (a) An amalgam tattoo presenting as a localized, flat area of slate-grey pigmentation on the gingivae. **(b)** Intra-oral radiograph revealing a radio-opacity consistent with amalgam.

mucosa should be photographed and closely monitored. A biopsy is required to determine the presence and extent of any dysplasia. If present, then the area may require excision, although recurrence may occur, particularly in PVL.[23–25]

Squamous cell carcinoma

Although the aetiology of oral squamous cell carcinoma (SCC) is not fully understood, a number of risk factors associated with its development are recognized, in particular tobacco habit, alcohol consumption, areca nut use, human papilloma virus infection (type 16 and 18), and immunosuppression. In addition, malignant transformation within a pre-existing leukoplakia, erythroplakia or erythroleukoplakia is recognized.[26,27] SCC does also occur in the absence of any of the presently known risk factors.[28]

SCC can arise at any mucosal site, with the posterior lateral margin of the tongue, ventral surface of the tongue and floor of mouth being affected most frequently.[29] The gingivae are involved relatively rarely.[30–32] Presentation of SCC is highly variable and includes erosion, ulceration and swelling (Figure 6), which may mimic inflammatory conditions, such as periodontal abscess, leading to misdiagnosis.[33–37] SCC on the gingivae can involve loss of underlying bone and mobility of the associated teeth.[33]

Diagnosis of SCC can only be made on the basis of histopathological examination of biopsy tissue. The management of SCC is primarily surgical excision, sentinel lymph node biopsy or neck dissection, with or without adjuvant radiotherapy and/or chemotherapy, followed by close monitoring for recurrence.[38,39]

Leukaemia

Leukaemia is a haematological malignancy, affecting bone marrow, white blood cells and their precursors. It is classified as acute or chronic (depending on clinical aggressiveness) and lymphocytic/lymphoblastic or myeloid (depending on the type of white blood cells affected). The oral manifestations, which may be the initial presentation, include gingival oedema (Figure 7), spontaneous bleeding, petechiae, purpura and ulceration.[40–43] The patient may also have lymphadenopathy, pallor, fever, lethargy, recurrent infections, night sweats and weight loss.[44,45] A full blood count (and blood film) will give an initial diagnosis, which will subsequently be confirmed by bone marrow biopsy. Management will be dependent on the type of leukaemia, and includes medication, such as tyrosine kinase inhibitors, chemotherapy, radiotherapy, antibiotics, blood transfusion, bone marrow transplant and stem-cell transplant.[46,47]

Pigmented conditions

Physiological pigmentation

Although physiological pigmentation is a variation of normal anatomy rather than a 'disease', it is important to recognize it in order to differentiate it from a number of pigmentary disorders, especially malignant melanoma. Increased melanocyte activity causes an increased amount of melanin within the epithelium, which results in colour changes of the oral mucosa.[48] Pigmentary changes can occur in any individual but are seen more frequently in darker-skinned races. The presentation involves asymptomatic and unchanging diffuse or multifocal brown pigmentation of the oral soft tissues, most often on the gingivae (Figure 8).[49–51] No active intervention is required for benign physiological pigmentation and the patient can be reassured. Gingival depigmentation techniques do exist if the pigmentation causes cosmetic distress.[48,52]

Acquired pigmentation

Stimulation of melanocytes and deposition of melanin within the oral mucosa can be a response to external factors, including local irritation, and systemic influences. The chemical and heat irritation associated with smoking can produce asymptomatic patches of brown pigmentation on the palate, gingivae and buccal mucosa.[53,54] The pigmentation may improve following smoking cessation.[55]

Several drugs, including chloroquine, hydroxychloroquine, quinidine, minocycline, chlorpromazine, oral contraceptives and cyclophosphamide can induce pigmentation of the oral mucosa. The pathogenesis of the mucosal pigmentation differs depending on the causative drug, but may involve causing increased melanin synthesis or accumulation, deposition of the drug or its metabolites, or iron deposition

due to drug-induced vessel damage.[56] Cessation of the causative drug, where possible, can result in a reduction of the pigmentation.[57]

While minocycline is known to cause direct discolouration of oral soft tissues, it also produces discolouration of alveolar bone, which gives a pigmented appearance to the overlying gingival tissues.[58–61] Occupational exposure to heavy metal vapours or medications containing heavy metals can also cause oral mucosal pigmentation.[62]

The clinical presentation is variable depending on the drug involved, but includes asymptomatic patches of grey, blue, black or brown discolouration. The hard palate and gingivae are the most frequently affected sites. The diagnosis is made on the history and clinical features.

A tissue biopsy should be undertaken whenever there is uncertainty about the cause of pigmentary changes in the mouth to exclude malignant melanoma.

Amalgam tattoo

Amalgam tattoo represents unintentional implantation of particles of amalgam restorative material into the oral soft tissues during placement, modification or removal of an amalgam restoration. In addition, pieces of amalgam can fall unnoticed into a tooth socket at the time of a tooth extraction.

The clinical presentation is characteristically a single asymptomatic slate grey-blue macule (Figure 9a), most frequently on the gingivae where a tooth has been lost, or where an apicectomy, involving a retrograde filling has been performed.

Diagnosis is usually made on the characteristic clinical features. A radiograph may show a radio-opaque area, confirming presence of amalgam within the soft tissues (Figure 9b). Differential diagnoses must include malignant melanoma, melanocytic naevi, and Kaposi's sarcoma.[63] Amalgam tattoo does not require any active treatment.

Conclusion

This article, the second part of a two-part review, has outlined reactive processes, potentially dysplastic and malignant neoplasms and pigmented conditions that may affect the gingivae. Many of these gingival conditions are asymptomatic, and, therefore, will only be identified on routine dental examination. Furthermore, as discussed, some gingival abnormalities can be a manifestation of a malignant process, or of systemic disease, and may be the initial, or indeed the only presenting feature. It is therefore imperative that dental practitioners carry out a thorough examination of the oral mucosal soft tissues as part of a routine dental check-up. It is hoped that the updated classification system for non-plaque-induced gingival diseases (Table 1) from the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases[1] provides a useful surgical sieve for dental practitioners when considering differential diagnoses of gingival abnormalities.

Compliance with Ethical Standards

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

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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