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Gingival swellings: A narrative review of literature

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Abstract

One of the commonest sign of periodontal disease is an abnormal overgrowth of the gingivae as a result of proliferation of submucosal connective tissue elements. There are several ways in which gingival swellings can be classified; it can be based on their distribution, gingival location or aetiopathogenesis. Forming proper diagnoses can be quite a task for the clinician. The role of taking a detailed history, clinical examination and investigations cannot be overemphasized, as occasionally they could be the presenting sign of an existing, and sometimes potentially fatal systemic disease. The aim of this research is to present a review of the literature on the etiology, clinical features and differential diagnosis of gingival swellings. Search was done via databases from Pubmed, Google Scholar, MEDLINE and CINAHL without date limit. The phrases "gingival swellings" "clinical features of gingival swellings" and "differential diagnosis of gingival swellings" were used to find related articles. Included in this review was a total of sixty-six publications and classification, clinical features, histopathological features, diagnosis, differential diagnosis, treatment and prognosis of gingival swellings were discussed. We found out that, the aetiology of gingival swelling is so extensive that a systematic approach should be taken to arrive at a correct diagnosis, however innocuous it might appear. Proper management should be followed with routine maintenance of oral hygiene and periodic follow-up.

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Introduction

Abnormal overgrowth of the gingivae due to proliferation of submucosal connective tissue elements is a frequently occurring sign of periodontal disease.[1,2] Gingival swellings can be classified in many different ways. They can be classified based on their distribution, gingival location or aetiopathogenesis. Localised gingival swellings are limited to gingivae

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adjacent to one or two teeth. They may be single, sessile or pedunculated masses. They may also be associated with a specific region of teeth. Generalised swellings, which are more commonly seen, involve gingivae associated with most or all of the teeth. Based on location, gingival swellings may present on the marginal gingivae, papillae, or may be diffusely located on the gingivae. Based on their aetiopathogenesis, they may be of inflammatory or neoplastic origin, drug-induced, congenital or inherited disorders, associated with haematological, immunological or metabolic diseases or false enlargements.[3,4] Forming proper diagnoses can be quite a task for the clinician. It is important to take a detailed history, clinical examination and investigations, as occasionally they could be the presenting sign of an existing, and sometimes potentially fatal systemic disease.[4]

The aim of this study is to present a narrative review of literature on gingival swellings.

Inflammatory Swellings

Inflammatory swellings may be acute or chronic, localized or generalized.[4]

Acute localized Inflammatory Swellings

include gingival, periodontal, periapical and pericoronal abscesses. In inflammatory swellings, microorganisms produce toxic substances such as collagenases, hyaluronidases, chondroitin sulphates and proteases. These cause epithelial and connective tissue damage.[2] Histologically, there is cellular oedema, diffuse infiltration of polymorphonuclear leucocytes, pus, engorgement of blood vessels, and occasionally ulceration.[2]

Gingival Abscesses

are located near the gingival margin or papillae.[4] They may be caused by destructive habits such as fingernail biting (*onychophagia*). The prevalence of nail-biting is especially seen in children in whom a prevalence of 12-45% has been recorded.[3] A few cases have been reported whereby patients intentionally stuck fingernail fragments into the gingival crevice. This may result in local or systemic spread of infections by auto-inoculation of bacteria such as *Escherichia coli* and *Enterobacteriaceae* into the gingivae. These bacteria have been found to be of higher prevalence in nail biters than in non-nail biters.[5,6]

Periodontal Abscesses

are located in the attached gingivae and are usually diffuse.[4] Periapical abscesses - are located close to the apex of non-vital teeth.[4] Parulis or gingival boil is a small swelling which develops at the terminus of a draining sinus. Digital pressure on the periphery will often release pus and is pathognomonic.[7] Pericoronal abscesses - involve the mucosal flap surrounding semi-erupted or impacted teeth, especially the mandibular third molars.[4]

Chronic localized Inflammatory Gingival Swellings

are solitary, pedunculated or sessile gingival swellings which does not exhibit the histological characteristic of any particular lesion.[4] They include fibrous epulis, pyogenic granuloma, and lateral periodontal cyst.[4]

Fibrous Epulis

usually presents as a painless, firm, pink, uninflamed mass extending from below the interdental papillae or free gingival margin. It typically occurs in adults. Occlusion or toothbrush trauma may lead to pain.[4] Occasionally, foci of calcification, cementum-like material or osseous material may be seen within the fibrous tissue histologically, and the diagnosis in such cases would be of peripheral calcifying fibroma, peripheral cementifying fibroma, or peripheral ossifying fibroma respectively.[4] Peripheral ossifying fibroma often occurs in young adults in the 2nd-3rd decade of life and appears to have a predilection for females. Management is by complete surgical excision and local periodontal therapy. Recurrence rate is fairly high therefore follow-up is essential.[8]

Pyogenic Granuloma

is a reactive hyperplasia of the connective tissues, especially the gingivae, due to low-grade local irritation from stimuli such as plaque, calculus, hormones or trauma. It usually presents as a reddish-blue, smooth-surfaced, highly vascular swelling extending from below the marginal gingivae.[4] About 15% may occur on the alveolar gingivae.[9] It may present as a bilobular mass, appearing both on the facial and lingual surfaces through the interdental papillae.[4] It does not often affect the underlying bone, but a case of a patient with significant bone loss has been reported.[9] It is often

ulcerated and tends to bleed easily. It typically begins as an initially rapid growth, which slows down after a few weeks, growing from a few millimeters to several centimeters but rarely exceeding 2.5 cm.[9] It mainly occurs in adult females in the second decade of life. The female sex hormones have been postulated to play a major role in its pathogenesis as they increase vascular permeability of the gingival tissues.[9] Soft, friable, bright red generalized gingival swellings often occur during puberty and pregnancy.[4] During these periods, there is an increase in gingival inflammation in the presence of irritants such as plaque, which otherwise may ordinarily cause only mild inflammation. This is so, because the gingivae contain certain cells in the stratum basale and stratum spinosum which appear to possess high affinity/low capacity receptors for sex hormones.[10] The fibroblasts and endothelial cells of small vessels in the connective tissues also possess these receptors. Studies have also shown that the sex hormones are nutrients for *Prevotella intermedius,* a dominant anaerobe isolated from the human gingivae.[10] Sex hormones are also known to affect the host's immunologic response.[11] Several authors have correlated an increase in gingival inflammation with the menstrual cycle.[10,11] Histologically, pyogenic granuloma exhibits a thickened stratified squamous epithelium, with prominent rete pegs.[4] The surface may be intact, ulcerated or may exhibit hyperkeratosis.[9] There is often dense connective tissue with mature collagen, oedema, prominent intercellular bridges and leucocytic infiltration.[4,9] Management is usually by complete surgical excision, while in pregnancy, spontaneous regression may occur after delivery.[4] If the lesion is properly removed from the base and causative factors are eliminated, recurrence can be avoided.[9]

Peripheral Giant Cell Granuloma (PGCG)

usually presents as a purplish-red, rapidly-growing, highly vascular swelling of the gingiva or edentulous alveolar ridge.[4,7] Typically, it occurs in adults with a peak incidence between 30-40 years old, though it may occur in younger patients during the mixed dentition stage.[4,12] It occurs more frequently in females and affects the mandible slightly more often than the maxilla.[7,12] It tends to bleed easily and may resorb the superficial adjacent bone (cupping) and push the related teeth apart.[4,7,12] The aetiology is unknown, but it may be associated with local irritation and trauma.[12] It is an aggressive reactive hyperplasia with a high recurrence rate.[13] Histologically, it is a multinucleated giant cell lesion, similar to the central giant cell granuloma. Thus, many pathologists believe it to be a soft tissue variant of the bony lesion.[12] PGCG associated with dental implants have been reported. In a study of peri-implant lesions, 3 out of 25 biopsy specimens were identified as PGCGs. The lesions had developed within 6 months to 3 years post-implantation, and recurrence after curettage had occurred in all cases.[13] Pyogenic granuloma and PGCG were the differential diagnoses, as these are the two lesions which had been described in literature to be associated with peri-implant mucosa. Biopsy findings were however consistent with a parulis, with a sinus tract opening on the covering epithelium. No recurrence was reported.[14]

Chronic Generalized Inflammatory Gingival Swellings

can occur as an inflammatory gingival response to irritants for example *plaque and calculus deposits, orthodontic appliances, and ill-fitting prostheses.*[4] The marginal and papillary gingivae may appear bluish or deep red, soft and swollen with a smooth shiny surface and tend to bleed easily. Occasionally, the gingivae appear generally swollen but firm, pink and fibrous. Histologically, there is an abundance of fibroblasts and collagen fibres.[4] In *mouth-breathers*, the gingivae appear red, swollen, oedematous and shiny specifically in the upper and lower anterior regions. The exact mechanism of mouth-breathing is unclear; however, the gingival swelling is thought to occur as a result of alternate wetting and drying of the gingival tissues.[4] Signs to look out for in mouth -breathers include a short upper lip, hyperactive labii superioris, proclined incisors and rhinitis.[4]

Developmental Gingival Swellings

Gingival Cyst of the Adult

is an unusual, slow-growing asymptomatic odontogenic soft tissue lesion. It arises from the rests of the dental lamina.[15,16] It most commonly occurs on the attached gingivae of the labial surfaces of mandibular teeth in the canine and premolar regions. It may also appear on the maxilla and typically occurs in females aged 50-60 years.[4,15,16] It often presents as a painless, small swelling, not larger than 6mm in diameter, but may have a bluish tinge due to the presence of cystic fluid.[15] It may cause

superficial bony erosion.[4,16] It appears radiolucent on radiographs and may be mistaken for a lateral periodontal cyst.[4] Occasionally, multiple cysts may occur in a patient, and these may occur unilaterally or bilaterally, or even on the lingual surface of the gingivae.[15,16] Gingival cysts are often so inconspicuous, that they may easily be mistaken for a normal variation of the mucosa.[15] A case of a gingival cyst <2mm in diameter discovered routinely was reported. A coincidental bilateral agenesis of the lower lateral incisors was mentioned, but this association has not been confirmed.[15] Management is typically by excision, with a good prognosis and no recurrence.[4,16] A case of gingival cyst which had recurred 4 times, each time within two weeks after excision, was reported. However, in the report, the patient had been attended to by other dentists and had only been to see the authors of the study the last time. Complete excision was done, and no recurrence was noted after 6 months' follow-up.[16] The surgical procedures during the initial 3 visits were not documented, and a wide enough excision may not have been done.

Congenital Epulis

Typically occurs as a rare solitary entity in newborns, without any other associated congenital or dental anomaly.[10] It presents on the alveolar ridge as a reddish, smooth, well-defined gingival mass which may be so large as to elevate the upper lip.[10,17,18]

Localised Neoplastic Gingival Swellings

These swellings may be benign or malignant.[4] Examples of benign swellings include fibroma, papilloma and lipoma.[4] Examples of malignant tumours include squamous cell carcinoma, melanoma and sarcoma such as Kaposi's sarcoma.[4] Odontogenic tumours sometimes present extraosseously. In a study of 406 excised gingival lesions, 6 were diagnosed as peripheral odontogenic tumours. There were 2 peripheral odontogenic fibromas, 2 peripheral calciying odontogenic cysts, 1 peripheral ameloblastoma and 1 calcifying epithelial odontogenic tumour (Pindborg tumour).[19]

Peripheral Odontogenic Fibroma

Is a rare odontogenic tumour which may mimic other exophytic gingival lesions clinically. Histologically, it may be confused with peripheral ameloblastoma or Pindborg tumour due to epithelial proliferation. It is differentiated from peripheral ameloblastoma by its smaller epithelial islands, occasional hard tissue content, and lack of hyperchromatism, intracytoplasmic vacuoles and nuclear polarisation. It is mainly found on the attached gingivae in the premolar and molar region of either jaw.[7] Management is by surgical excision, and recurrence is rare.[20]

Pindborg Tumour

Is an extremely rare benign odontogenic tumour arising from remnants of the dental lamina or the stratum intermedium of the enamel organ. It accounts for about 1% of all documented odontogenic tumours. Usually a bony tumour, a rare extraosseous presentation has been described in very few patients, with unilateral gingival swellings typically found in the canine-premolar region.[21] A bilateral presentation initially suspected to be pyogenic granulomas, has been reported. Excision of the swellings without curettage of the underlying bone was initially done. Histopathological and immunohistochemical investigations however, revealed them to be Pindborg tumours; the multifocal presentation having only been reported in intraosseous cases previously. A year later, although there were no clinical signs of recurrence, radiological investigations of the lesion sites revealed discrete calcifications, evidenced by bony resorption on surgical exploration. Excision of the soft tissues with bony curettage was then done, and no clinical or radiographic signs of recurrence noted 3.5 years later.[21]

Oral squamous cell carcinoma

Is a common malignancy worldwide, the intraoral sites most commonly affected are the tongue, floor of the mouth, and the buccal mucosa.[22] The gingiva is an uncommon site of presentation. Gingival squamous cell carcinoma (GSCC) has a predilection for the premolar-molar region of the mandible, and often occurs in edentulous areas, though it may occur where teeth are found. It often presents as a painful exophytic mass with a granular, papillary or verrucous surface or as an ulcer. It is usually preceded by long-standing leukoplakia and may be asymptomatic in the early stages. Management is by surgical excision and neck dissection. As early invasion of the underlying bone is imminent, early and proper detection is of utmost importance.[22] GSCCs tend to present with atypical appearances, and diagnoses can often be difficult. In the case of a GSCC initially diagnosed as a dentoalveolar

abscess, the patient had given a history of trauma to a related tooth. Vitality tests had confirmed the tooth as non-vital. The patient had not admitted to a history of alcohol, tobacco or betel quid usage, and there had been no preceding leukoplakia or erythroplakia; nothing to suggest a malignancy. However, there had also been no typical radiographic presentations of a periapical abscess. A root canal treatment had been performed, and after two visits, had produced no resolution. Histological and immunohistochemical tests confirmed the diagnosis of poorly differentiated GSCC. Surgical excision, partial maxillectomy, and a radical neck dissection were done with concomitant chemotherapy. No recurrence was noted.[22,23]

Non-Hodgkin Lymphoma (NHL)

Is a malignancy which commonly arises from the lymph nodes. Extra-nodal manifestations are relatively common. NHL arising primarily from the gingivae is, however, rare, but a few cases have been reported.[24,25] As they often have variable clinical manifestations, the possibilities of misdiagnosis are endless. A case initially misdiagnosed and managed as a pyogenic granuloma was reported. Following a recurrence, an excisional biopsy was done which revealed a diagnosis of primary extranodal NHL, large B-cell type.[25] Another swelling was managed as a periapical lesion because the patient had given a history of trauma to a related tooth. Following a recurrence, an incisional biopsy also revealed the actual diagnosis of NHL, large B-cell type. Chemotherapy and radiotherapy resulted in complete resolution. The same patient returned a year later with a similar gingival swelling, in a different site. Histopathology revealed it to have identical morphological and immunophenotypical features with the previous swelling, and a diagnosis of recurrent NHL large B-cell type was made. Several authors have suggested that a second occurrence of a lesion within a short period (<2-3 years) and possessing the same features as the initial lesion should be considered a recurrence, whether in the same site or not. A second lesion developing over a longer period or with different histopathological features may be regarded as a second primary lymphoma. In this case, the lesion normalized after 6 cycles of chemotherapy and there was partial remission. The patient however died of disseminated disease. There had been associated hepatitis C virus infection, which is reported, from recent studies, to be frequently associated with NHL. This may have been the reason for the fatal outcome.[24] The prevalence of NHL is increasing among the immunocompromised, organ transplant patients, patients with autoimmune disorders and patients with AIDS. Oral lesions of NHL have presented as the earliest manifestations of AIDS.[26] Management of NHL is by surgery, chemotherapy and radiation in various combinations.[24,25] Prognosis depends on the clinical stage and histological grade of the disease.[24]

Leiomyosarcoma

Is a relatively rare mesenchymal malignancy which exhibits smooth muscle differentiation. It occurs more commonly in the smooth muscles of the gastrointestinal, urinary and female genital systems.[27] Leiomyosarcoma of the oral cavity is extremely rare, probably because of the minimal amount of smooth muscle present in the oral cavity.[27,28] There is no known gender predilection, and it has been found most commonly in patients in their 30s, and patients in their 60s and 70s.[27] In a review of 23 cases of leiomyosarcoma of the oral cavity, a quarter of the cases presented on the gingiva alone.[28] It is a very aggressive lesion. Histological diagnosis may be difficult due its similarity with other spindle cell lesions such as fibrosarcoma and melanoma, and the poor differentiation of the neoplastic cells in some cases. A definitive diagnosis is obtained by light microscopy. Other useful investigations include histochemistry, immunohistochemistry and electron microscopy.2[7] Metastasis to the cervical lymph nodes, lungs and the liver may occur. Management is by radical surgery and long-term follow-up.[27,28] Chemotherapy and radiotherapy are reserved for high-grade lesions.[28] Prognosis is usually poor, with a high rate of recurrence and metastatic potential.[27]

Melanoma

is a malignancy of the neural crest cells.[29] Oral melanoma is an extremely rare, lethal disease which accounts for less than 1% of all melanomas.[29] It mainly occurs in adults over 40 years old and in females. Although it can affect any ethnic group, the Japanese appear to be most susceptible.[29] Oral melanoma mainly affects the maxillary gingivae and the hard palate.[29] Malignant melanoma of the maxillary gingiva is an aggressive lesion with a much poorer prognosis than cutaneous melanoma.[30] This is partly because detection of pigmented lesions is more

difficult in the mouth where it may be hidden, than on visible skin.[29] Oral melanoma can present in various ways and though typically pigmented, may also be amelanotic. Prompt diagnosis and early management will improve the mortality rate significantly.[29]

Metastasis of Malignancies

Originating from other organs to the gingivae is very rare but has been reported in some cases. *Carcinoma of the lungs* is one of the most commonly occurring cancers. Frequently, metastasis to the oral cavity is the first feature seen in lung carcinomas with a metastatic potential.[31] The gingiva and alveolar mucosa appear to be the most frequently involved intraoral sites of cancer metastasis. The attached gingiva is most often affected in dentate patients.[32] The average time from presentation of gingival metastasis to death is usually just a few weeks to months, hence the importance of proper and speedy investigation and management.[31] Most metastatic gingival swellings present like hyperplastic reactive lesions.[32] Several examples have been reported. A lesion resembling a pyogenic granuloma in a 76-year-old man was confirmed histologically as a metastatic deposit of lung cancer.[33] A metastatic deposit on the mandibular gingivae, similar to an inflammatory swelling, was also discovered in a 61-year old man diagnosed with lung cancer.[34] Multiple metas-tasis to the gingivae is extremely rare. A case, however, has been reported of multiple gingival swellings (1 in the mandible, 2 in the maxillae) confirmed histologically as metastatic deposits of a poorly-differentiated lung adenocarcinoma.[31]

Metastatic deposits to the oral cavity may also develop from primary tumours in other organs of the body such as the kidneys and breasts. Though rare, metastatic deposits of transitional cell carcinoma of the urinary bladder have been observed in the jaws. A mandibular gingival tumour in a 64-year-old man was confirmed on histopathology to be secondary to a *primary carcinoma of the urinary bladder.* The patient had also presented with hypoaesthesia of the lower lip on the same side.[35] *Gastric cancer metastasis* to the bony or soft tissues of the oral cavity is also very rare, but an unusual case of gastric cancer metastasis to the gingivae has been reported. The patient had undergone a gastrectomy and splenectomy due to late stage gastric cancer of the stomach. Histopathology of the gingival swelling revealed a signet ring cell cancer similar to the poorly differentiated gastric cancer. The fact that the swelling was absent prior to the gastrectomy, further confirmed the diagnosis of a direct gingival metastasis of the gastric cancer; possibly by haematogenous spread.[36]

Drug Induced Gingival Swellings

Consumption of certain drugs could result in the formation of fibrous generalized gingival swellings usually within 2-4 months of initiation of therapy.[4] These drugs include *anticonvulsants* such as *Phenytoin* and *Phenobarbitone*, immunosuppressants such as Cyclosporine and Tacrolimus; and calcium channel blockers such as Nifedipine and Amlodipine.[4] The fibrous swellings usually start as pink, firm, painless bead-like swellings with minute lobulations on the interdental papillae which may later involve the marginal gingivae. They are typically associated with the mandibular and maxillary anterior teeth but may also be found around posterior teeth. They however do not occur in edentulous areas and will disappear if associated teeth are extracted.[4] Secondary infection of the swellings will produce pain, redness and increased swelling.[4] Cyclosporine and other immunosuppressants produce more vascular swellings than swellings due to anticonvulsants such as *Phenytoin*. In situations whereby patients receive combination therapy of medications which could both potentially cause gingival swellings, the actual cause may be difficult to ascertain. In such cases, the patient's physician could substitute each potential cause with another drug one after the other, to check the effect of cessation of the drug on the gingivae. It is prudent to start with the drug with the least effect on the patient's normal routine.[4] Management of drug-induced gingival swellings is usually with periodontal surgery and oral hygiene maintenance.[37]

Tacrolimus (FK506), a macrolide drug used for immunosuppression in renal transplant patients, has been found not to produce gingival swellings, after several clinical trials by different authors. Administration of Cyclosporine A (CsA) on the other hand, has been reported to result in gingival swellings in 8-81% of patients. The prevalence and severity are further increased when patients on CsA are concomitantly given a calcium channel blocker, often administered as a remedy for the resultant hypertension caused by CsA nephrotoxicity.[37] The

swellings can be very severe and disfiguring, and recurrence after surgery is common. Tacrolimus has, therefore, been suggested as an alternative for CsA, although they produce similar side effects.[37] A report was made on four renal transplant patients with gingival swellings attributed to CsA therapy. When substituted with Tacrolimus, resolution of the swellings occurred in all the patients within the study period to an acceptable degree, and completely in one of the patients.[37] Intensive oral hygiene maintenance appeared to be a major factor in the regression of the swellings.[37] The effect of other complicating factors such as smoking was questioned in one of the patients, who, just like the others, had a similar change of medications. Failure to cease smoking may have slowed down his healing process, leading to remnant nodules on the palate. The authors suggested some reasons for incomplete regression of swellings in 3 out of the 4 patients. The short study period may have been insufficient to obtain a perfect result, although such may never have been achieved without surgery. Also, the concomitant use of a calcium channel blocker (Amlodipine and Nifedipine) by all 3 patients with incomplete regression was highlighted, especially as the only patient with complete regression of swellings, was significantly medically compromised. He was on several other medications, but none was a calcium channel blocker.[37] There have been studies, however, that have reported the appearance of gingival swellings in organ transplant patients on Tacrolimus. The frequency of such cases, though, are far less than noted on patients on CsA.[38] Other studies done have not found any appearance of gingival swellings in paediatric liver transplant patients or paediatric heart transplant patients on Tacrolimus.[39,40] The use of Tacrolimus as a substitute to CsA has been advocated because of its superiority in preventing allograft rejection and reduced costs.[39] Amlodipine, a long-acting calcium channel blocker, has also been reported to cause gingival swellings in 1.7% of patients, though not as frequently as Nifedipine (20% of patients).[41]

Another drug that has been associated with gingival swellings is Ribavirin, an antiviral agent. Intravenous (IV) ribavirin, unlike the oral and inhalational formulations, does not have US Food and Drug Administration approval. Its use is however restricted as an investigational drug for patients with serious viral infections for which no alternative treatment is yet available. A retrospective study evaluating clinical experiences of patients authorized to use investigational IV ribavirin was conducted. The reported adverse effects included gingival and lip swellings, not found in the oral and inhalational formulations. The severity, frequency and causes of these swellings, however, could not be accurately reported due to certain study limitations.[42,43]

Other Causes of Gingival Swellings

Oral Focal mucinosis

another rare localized form of gingival swelling that has been described, the aetiology is unknown, but the connective tissue is found to undergo focal myxoid degeneration.[17] An author reported a case of a firm, tender gingival swelling, presumed to be a periodontal abscess but confirmed histologically as oral focal mucinosis.[17] Some other authors reported cases of painless, pedunculated or sessile gingival swellings also confirmed histologically as oral focal mucinosis.[18] No episode of recurrence has been reported, and management is by complete excision.[18]

Lennox-Gastaut Syndrome

is a severe form of childhood epilepsy characterized by multiple seizures, delayed intellectual growth and specific EEG disturbances. Affected patients typically present with facial deformities, periodontitis and gingival swellings. Although uncommon, it is a very serious condition, with often treatment-resistant seizures and poor long-term prognosis. A few cases have been described in literature. Patients are typically on combination antiepileptic drugs, and the gingival swellings may either be as a result of these or associated with the syndrome itself.[42]

Congenital and Inherited Disorders

associated with gingival swellings include hereditary gingival hyperplasia, lysosomal storage disorders, primary amyloidosis, some vascular disorders and genetic disorders associated with characteristic dental anomalies.[3,4]

Hereditary gingival hyperplasia is an autosomal dominant (rarely autosomal recessive) inherited condition also known as congenital familial fibromatosis, heriditary gingivostomatitis or idiopathic gingival fibromatosis.[4,44] It is a rare, heterogenous disorder with no obvious known cause but appears

to result from various genetic mutations. Hence, its clinical presentations are also varied.[44] There is often a positive family history of similar presentations.[4] It presents as slowly-developing, localized or generalized painless, firm, pink or reddish bulky fibrotic gingival swellings.[4,44] It typically appears with the eruption of the maxillary and mandibular deciduous or permanent molars.[4] It tends to affect the attached gingivae in various degrees.[44,45] Oral hygiene maintenance is difficult therefore pseudo pockets develop, and bone loss occurs around the teeth. There is, however, usually no resorption of underlying bone.[4,44] There may also be retention of deciduous teeth or delayed eruption of the secondary dentition, malocclusion and a midline diastema. An abnormal swallowing pattern may develop in early childhood.[44] Recurrence after excision is common and difficult to completely eliminate, due to the tendency to develop once teeth are present. They completely disappear following extraction of teeth.[44,45] Management depends on the severity, and involves routine prophylaxis and oral hygiene maintenance, conventional gingivectomy, electrosurgery and laser treatment. Orthodontic and restorative treatment often follows. Genetic and psychological counselling of both the patient and family members is important.[44] Hereditary gingivostomatitis may occur solitarily or as part of a syndrome. Syndromes are often associated with features such as hypertrichosis, mental retardation, epilepsy, progressive hearing loss and abnormalities of the extremities.[44] Associated syndromes include Cross syndrome, Rutherford syndrome, Systemic hyalinosis, and Jones syndrome. Some cases are also associated with aggressive periodontitis.[4,44]

Another congenital syndrome which may present with gingival swellings is *Sturge -Weber syndrome*. Sturge-Weber is a rare neurocutaneous condition presenting with haemangiomas of the leptomeninges and skin of the face particularly involving the ophthalmic and maxillary divisions of the trigeminal nerve. It is caused by residual embryonic blood vessels and their effects on the surrounding brain tissues. The cutaneous presentation is called a Port-Wine stain; flat and sharply-demarcated unilateral purplish nevus flammeus lesions which may extend to the neck, back or chest. They may occasionally present bilaterally or on other parts of the body. The patient presents with neurological symptoms such as epilepsy, mental retardation and hemiplegia, hemi-hypertrophy of the face and ocular involvement. The haemangiomas may result in intraoral swellings, including gingival swellings. These may be due to the proliferation of angiomatous tissues, the use of anti-epileptic medication, or a combination of both. They may enlarge so much as to cause aesthetic and functional problems, causing impairment of nutrition and oral hygiene. Another syndrome which may present with similar features is *Klippel-Trenaunay-Weber* syndrome. Management includes symptomatic treatment, psychological counselling and complete resection of the gingival swellings.[46]

A Rare Case of Generalized Gingival Swellings Associated with Amelogenesis Imperfecta

a hereditary condition affecting the development of enamel, has been reported.[47] Regional odonto-dysplasia, an anomaly caused by a disturbance in both enamel and dentine of teeth, may also cause gingival swellings. It is caused by disturbance in the development of both the enamel and dentine of teeth, involving both deciduous and permanent dentitions. The affected teeth appear discolored and soft popularly called "*ghost teeth*" and often affect a quadrant of the mouth; rarely crossing the midline. Management is geared towards achieving an aesthetic and functional outcome and involves extractions and restorative treatments.[48]

Gingival Swellings Secondary to Systemic Diseases and Conditions

Systemic Haematological Conditions which may Present with Generalized Gingival Swellings

include leukaemia, sickle-cell anaemia and aplastic anaemia. *Leukaemia* is a neoplastic proliferation of blast cells in the bone marrow, leading to an accumulation of immature or abnormal white blood cells in the circulation.[4] The interference with normal haematopoiesis results in symptoms of anaemia, thrombocytopaenia and neutropaenia, such as weakness, fatigue, bleeding tendencies and infections.[49,50] Accumulation of leukaemic cells in tissues such as the skin, mucosa and gingivae occur.50 Gingival swellings may thus be either as a result of engorgement of the gingival tissues by leukaemic cells or secondary to thrombocytopaenia, neutropaenia or impaired granulocyte function.[50] Gingival swellings occur especially in acute myeloid leukaemia (AML) and rapidly-developing

swellings are sometimes the earliest manifestations of disease.[4,49] They usually appear similar to other inflammatory gingival swellings.[4] The affected patient typically presents with other oral symptoms including ulcerations, mucosal pallor, spontaneous bleeding and petechiae, candidal and herpetic infections. Rarely, the patient presents with numbness of the chin and/or toothache.[4] Gingival swellings due to AML, however, are very rare in children in whom they usually present as subtypes M4 (acute myelomonocytic leukaemia) and M5 (acute monocytic leukaemia).[50] An unusual case was documented of a 3-year-old boy with gingival swellings of a months' duration, fever and body pain. Haematological tests revealed the diagnosis of AML, subtype M5.[50] Generalized gingival swellings have also been reported in patients with acute lymphoblastic leukaemia, which is mainly found in children under the age of 10 years.[10] Management of acute leukaemia is with effective chemotherapy.[49,50] A phenomenon which is reported to develop in some patients with malignancies prior to, or during therapy, especially AML, is known as Sweet's syndrome (acute febrile neutrophilic dermatosis). It is characterised by fever, neutrophilia and focal infiltration of the dermis. All-*trans* retinoic acid (ATRA) and granulocyte colony-stimulating factor (G-CSF) therapies, used in the management of AML, have been associated. An interesting case of a 6-year-old child with AML was reported. She had been placed on ATRA after the diagnosis was made. She had, however developed a fever, myositis and gingival swelling, which cytotoxic therapy and antibiotics had failed to resolve. G-CSF was given, but a persistence of symptoms continued, even as bone marrow examination indicated remission. A diagnosis of a Sweet-like syndrome was made, as the patient did not have characteristic skin lesions. Regression of the swellings and muscle pain was noted within a week of Prednisolone therapy. Sweet's syndrome has also been described following some episodes of infections.[51] Gingival swellings have also been reported in sickle-cell anaemia. An example is the case of a 14-year-old boy patient who presented with a cellulitis-like facial swelling and gingival swelling due to repeated alternating episodes of haemorrhage and fibrous tissue repair.[52]

Immunological conditions such as Wegener's granulomatosis, Crohn's disease, and Orofacial granulomatosis often present with generalized gingival swellings.[3]

Wegener's Granulomatosis (WG)

is a potentially lethal, multi-organ, necrotizing granulomatous condition mainly affecting the upper and lower respiratory tracts, blood vessels and kidneys.[53] The aetiology is unclear, but genetic and environmental factors have been postulated.[53] *Staphylococcus aureus* has been implicated, its mechanism being through alteration of immune tolerance resulting in vasculitis. Exposure to silicone-containing compounds may also be associated.[53] Oral lesions have been found to occur in 10-62% of patients.[53] Intraorally, patients present with characteristic generalized reddish-purple exophytic granular gingival swellings with petechiae resembling strawberries, and hence known as "strawberry gingivitis.[4,53] These swellings initially involve the attached gingivae and may extend beyond the mucogingival junction.[53] This presentation, though rare, is almost pathognomonic for WG.[53] It is often the initial presentation and may persist for a long time before any other organ involvement is apparent.[4,53] The patient may also exhibit other oral symptoms including slow wound healing after extractions, mobility of teeth, parotid gland swelling, and cranial nerve palsies.[53] The clinical and laboratory features are varied, and each case may present uniquely. Thus, making a prompt and correct diagnosis can be difficult.[53] Three cases of WG were reported, each patient with varied presentations. The first patient initially exhibited only hyperplastic, bleeding gingivae and ulcers. He developed sinusitis, myalgia and fatigue later. The second patient had both hyperplastic, bleeding gingivae, forehead skin lesions, and mild sinusitis on initial presentation. The third patient had, apart from the gingival lesions, atypical oral ulcers, respiratory and genital lesions. The first patient had frequent exacerbations of the condition after therapy with Cyclophosphamide and Prednisolone, while the second patient had complete resolution of symptoms after the same therapy. The third patient had several significant medical disorders for which he was taking several medications, had undergone cardiac surgery, had several drug allergies and was receiving comprehensive oral care. Periodontal therapy was fairly successful, but the patient had persistent lesions. Additionally, a two-year history

of sinusitis, nasal congestion, bloody discharge and facial discomfort resulted in a diagnosis of Behcet's syndrome. A final diagnosis of WG was however eventually reached. The histological findings were consistent with WG, and antineutrophilic cytoplasmic antibodies (c-ANCA) test positive. The patient was placed on Cyclophosphamide, Infliximab, low-dose Prednisolone and Mycophenolate, and the gingival lesions resolved within four months.[53] c-ANCA detected in blood samples of majority of patients with severe WG suggests the role of B cells and plasma cells in its aetiology. c-ANCA may however not be detectable in specimen of patients with early-stage or minimal WG.[53] Other useful investigations apart from relevant organ biopsies include: chest radiograph and computed tomography (CT) scan for respiratory symptoms, full blood count, erythrocyte sedimentation rate, C-reactive protein, blood urea, nitrogen and serum creatinine, antibody testing for proteinase 3 and urinalysis.[53] Confirmatory diagnosis is made by the presence of at least two of the following signs: a. oral mucosal ulcers or nasal bleeding, b. chest radiograph showing the presence of fixed infiltrates or nodular lesions, c. abnormal urinary sediments, or d. presence of granulomas on histopathology.[4] Early management with appropriate therapy usually produces a positive outcome with occasional relapses, whereas most patients would not survive over a year after diagnosis, if no treatment is instituted.[54]

Crohn's Disease

is a chronic granulomatous lesion presenting orally as firm (almost leathery), pink, pebble surfaced gingival swellings. Patients also often present with oral ulcerations, swollen lips, bowel disorders and fever.[4] Orofacial granulomatosis (OFG) is a condition which presents with recurrent or persistent swelling of the lips, cheeks and mucosa, with hyperplastic tags in the sulci and floor of the mouth. There is often gingival swelling, ulcerations and erythema. It can present at any age, in both males and females.[55] The aetiology is unknown, but some patients exhibit sensitivity to certain foods such as chocolates, cinnamon and monosodium glutamate.[3] An unusual case of suspected OFG was reported in an 11-year old girl, who had initially been referred to the authors at the age of 9 years. This patient exhibited features suggestive of OFG right from the first visit, but it was never histologically confirmed. The initial gingival swellings and erythema had responded well to antibacterial mouthwashes and effective toothbrushing. OFG had been suspected, but there hadn't been any epithelial tags or ulceration. No further investigations had been done. Blood tests done about a year later revealed some "haematological abnormalities", when the patient had complained about continued gingival swelling. Puberty gingivitis was suspected. The findings of a biopsy specimen were consistent with a fibrous epulis with calcification, but the lesion re-appeared. The patient then developed a swollen upper lip, generalized erythematous swelling of the mandibular anterior area and ulceration. A diagnosis of OFG was made, and a history of abdominal signs and symptoms taken to rule out Crohn's disease. Several laboratory tests were also done. The original histopathology result was re-assessed, and a fresh biopsy taken. Based on clinical, histopathological and haematological findings, OFG was the most probable diagnosis. The histopathology result, however, revealed different findings from separate swellings. A right mandibular gingival swelling appeared to be a giant cell granuloma, while one on the left side appeared to be a fibrous epulis with calcification and some features suggestive of OFG. The patient presented about three months after with a recurrence of a swelling in the anterior maxillary gingivae, but the rest of the gingivae was less swollen, and the mandibular gingival swellings had regressed. New biopsy results led to the diagnosis of recurrent giant cell granuloma, as the features in this specimen were similar to those of the last biopsy done.[55] The patient was referred to the gastroenterologist to once again rule out Crohn's disease, and multiple biopsies done all came out normal. By the middle of the year, the mother of the patient claimed that the gums had become completely normal, and the patient stopped presenting for visits. After two years, inquiries about the patient revealed that the gingival condition had vastly improved, though there was still erythematous gingivae and recurrent ulcerations in the mandibular buccal sulci. She was visiting the dentist regularly for oral hygiene maintenance and was regularly taking Amphotericin B lozenges. She had, however, developed stomach cramps, diarrhoea, constipation and a tear in the anal passage.[3] These abdominal features were suggestive of Crohn's disease, which had been severally investigated and ruled out.[3]

Investigations of patients suspected of having OFG are similar to those for patient's suspected of having Crohn's disease.[3] These include a full blood count, screening for deficiencies in iron, folate, vitamin B12, calcium and albumin, anti-saccharomyces cerevisiae antibody (ASCA), and perinuclear anti-neutrophil cytoplasm antibody (p-ANCA). Referral to a gastroenterologist is mandatory if inflammatory bowel syndrome is suspected.[3] Histopathology of OFG typically reveals non-caseating granulomas and an often, intense inflammatory infiltrate deep to the epithelium, but occasionally the granulomas may be sparse, poorly formed or deep.[55] Management of patients involves simple reassurance and regular observation, diet modification, use of corticosteroids and surgery which may result in recurrence.[3]

Sarcoidosis

is a multi-system disorder characterized by pulmonary and hilar lymphadenopathy, dermal and ocular lesions.[4] Although its aetiology is unknown, it is postulated to occur due to an immunological response to an infective trigger, possibly *Mycobacteria* and *Propionibacteria*, in a genetically-predisposed individual.[56] Epstein-barr virus has been suggested as a viral trigger. Environmental and occupational factors such as exposures to mold and certain materials used in the manufacture of pesticides have also been suggested.[57] Although found in people of all races, it most frequently occurs in people of African, Afro-Caribbean or Scandinavian origin.56 It may occur in any individual regardless of age, race or sex.[57] The salivary glands are involved in 10-15% of patients, where the condition manifests as bilateral parotid gland swellings or xerostomia.[57] Intraoral lesions are rare, and occasionally, gingival swellings appear.[4,56] About a third of patients will present with non-specific symptoms of fever, fatigue, malaise or weight loss.[57] Histologically, non-caseating granulomas are seen, and diagnosis is often by exclusion of other causes of non-caseating granulomas such as tuberculosis, foreign body reactions, OFG and deep-seated fungal infections.[4,56] There may also be a significantly increased eosinophil count and increased serum ACE levels. Hilar lymphadenopathy may be seen on chest radiographs.[4] Other useful radiological investigations include CT, magnetic resonance imaging, (MRI), positron emission tomography and contrast enhancement with gadolinium.[56] Management includes observation for asymptomatic or mild cases, systemic corticosteroids sometimes in combination with antimalarials and immunosuppressants or surgical excision.[56,57] Out of six cases of sarcoidosis in which orofacial manifestations were the initial presentation reported in a study, only one of the patients presented with gingival swellings. No treatment was instituted as the patient exhibited no other symptoms. The patient however developed shortness of breath and bilateral hilar lymphadenopathy on chest radiograph five years later. A diagnosis of pulmonary sarcoidosis was made, and the patient placed on corticosteroid therapy with satisfactory results.[56]

Oral tuberculous lesions

often present as painless lesions, and rarely with gingival swellings. Primary tuberculous oral lesions are rare, but when present, are seen in younger patients. Oral lesions secondary to pulmonary tuberculosis, however, are seen in older patients. Patients typically have a history of fever, weight loss, fatigue and loss of appetite. Diagnosis is made based on the history, histological presentation of caseating granulomas, full blood count and polymerase chain reaction.[4]

A Serum Vitamin C Level Lower than 2µg/Ml can Result In Generalized Gingival Swelling

The signs and symptoms are related to the vital role vitamin C plays in collagen synthesis.[4,58] The swollen gingivae appear soft, bluish-red and friable, with a smooth surface. There may be surface necrotic slough with pseudomembrane which tend to bleed easily.[4] Patients also often present with petechiae, ecchymoses and hyperkeratosis of the skin, fatigue, lassitude, and neurologic symptoms including depression.[58] Deficiency is more usually due to diabetes, stress and smoking, rather than nutritional deficiency.[4] A case of an autistic child with swollen, bleeding gingivae diagnosed with scurvy due to nutritional dietary deficiency was however reported. The diet history had indicated a total lack of vitamin C in the diet since the onset of bone pain 3 months before the swellings.[58]

Hypoplasminogenemia (Type 1 Hypoplasminogen Deficiency)

is a rare systemic disorder presenting with ligneous conjunctivitis and ligneous gingivitis.[59] Scully and

colleagues first discovered a British patient with ligneous conjunctivitis and gingival lesions which appeared to be caused by tranexamic acid, an anti-fibrinolytic agent. After then, a few more patients, mainly in Turkey, have been discovered with gingival swellings and ulceration caused by amyloid-like deposits which only stain for fibrin. These findings have now been ascribed to hypoplasminogenemia.[60] A middle-aged patient previously diagnosed with hypoplasminogenemia was reported to have presented with a large maxillary swelling. Histopathological results confirmed the fibrinoid deposits with mixed inflammatory infiltrates consistent with this diagnosis.[59]

Plasma Cell Gingivitis

a hypersensitivity reaction characterized histologically by an abundance of plasma cells, may also cause generalized reddish gingival swellings. The swellings typically appear on the attached gingivae with a granular surface and are highly vascular, so tend to bleed easily.[4] Typical allergens include toothpaste, certain foods, especially cinnamon, chewing gum and khat.[4]

Bone Morphogenetic Protein 2 (BMP-2)

a pilot study investigated its use for osteo-inductive growth in the management of cleft lip/palate. At high doses of BMP-2 delivered by hydrogel (250 µg ml), BMP-2 showed great promise in inducing bone formation of good quality and quantity as evidenced in all treated patients, but a severe gingival swelling was noted in these patients. This led to a premature cessation of the study.[61]

Eruption Cyst

a circumscribed, translucent, fluctuant gingival swelling due to fluid accumulation may enclose an erupting tooth. If the fluid is blood and the swelling is deep blue or purplish, it is known as an eruption haematoma.[10]

Other conditions which have been reported to present with generalized gingival swellings, though rare, include Hashimoto's thyroiditis, I-cell disease and multiple myeloma.[4]

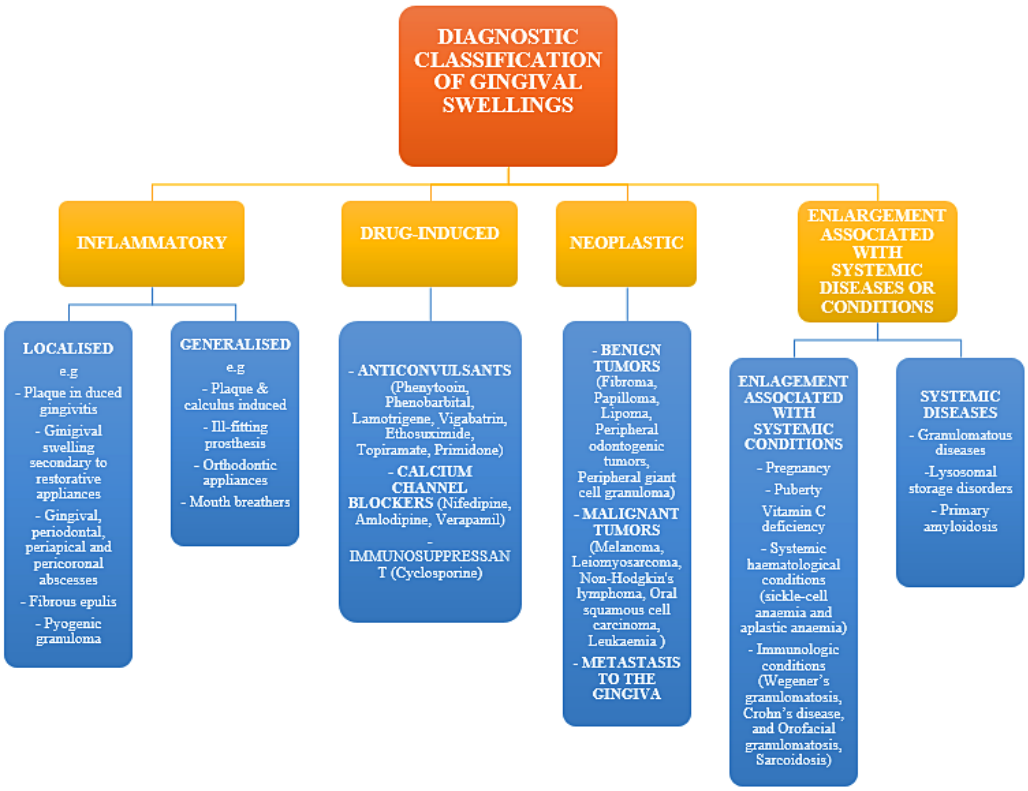

Fig. 1: A flowchart depicting the different diagnostic classifications of gingival swellings

Pseudo or False Gingival Swellings

The gingivae may appear to have increased in size in certain situations, whereas this may just be due to an overgrowth of the underlying tissues. Such conditions include tori, Paget's disease, fibrous dysplasia, cherubism and osteoma due to abnormal growth of the underlying bone.[4]

Management of gingival swellings depends on several factors, including the severity of the swellings. Several authors have proposed various indices for accurate measurements of gingival swellings in order to determine their severity and prognosis. Important factors include both the horizontal and vertical dimensions of the swellings and their aetiopathogenesis.[2] Before surgical excision, careful pre-surgical assessment should be done, including coagulation ability. This will forestall any unexpected excessive bleeding. It is also important to be prepared to manage any such complication.[62-64]

Odontogenic lesions with multifocal presentations are believed to be associated with chromosomal or genetic anomalies, as supported by reports of lesions in multiple sites in patients with known genetic disorders.[65] It may therefore be useful to carry out a genetic evaluation in patients who present with odontogenic lesions in multiple sites.

The value of advanced imaging has been emphasized in certain situations. A painless, firm, exophytic black-pigmented gingival swelling observed in a patient revealed no obvious lytic lesion on conventional radiographs. MRI however revealed a low signal intensity lesion on both T1-weighted and T2-weighted images. This led to the diagnosis of granulocytic sarcoma, a rare condition of the oral cavity, difficult to diagnose.[66]

Conclusion

Although mainly reported in adults, gingival swellings may occur in any individual, young or old. The aetiology is so extensive that a systematic approach should be taken to arrive at a correct diagnosis for any gingival swelling, however innocuous it might appear. Proper management should be followed with routine maintenance of oral hygiene and periodic follow-up.

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- **Mohammad Abubakar Kaura:** Initial conceptualization, draft write-up.
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- **Olajumoke Enahoro:** Literature review, critical appraisal.
- **Bamgbose Babatunde Olamide:** Final review and approval of the manuscript.

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