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Review Article

Oral Granulomatous lesions: a Review

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Abstract: Oral granulomatous diseases are frequently observed due to a wide variety of infections. These represent a unique form of the chronic inflammatory response. Granulomatous diseases of the oral tissues are uncommon and are difficult to diagnose due to various etiological agents. Over the years, emergence of accurate molecular diagnostic techniques has enabled identification of causative organisms of oral granulomatous diseases which were previously unknown. Oral granulomatous diseases are a large group of lesions which share similar histogenesis of granuloma formation. Therefore an extensive clinical, microscopic and laboratory evaluation is required to identify the source of the oral granulomatous diseases. This article highlights the etiology and histopathological features of granulomatous diseases of the oral cavity.
Keywords: Chronic inflammation; granulomatous inflammation; granulomatous diseases; oral granulomatous lesions

INTRODUCTION

A granuloma can be defined as a firm, tumour like granulation with compact collection of epithelioid cells and inflammatory cells formed as a reaction to chronic inflammation due to foreign bodies, fungi, bacteria etc. Granulomas are usually formed due to continual existence of a nondegradable product or hypersensitivity reactions. These two mechanisms are found to be combined in most infectious diseases since microorganisms can function as foreign bodies as well as antigens for immunological responses. Thus granulomas are normally the result of defensive mechanisms and form when acute inflammatory processes are unable to destroy invading agents. The formation of a granuloma is an end result of series of events[1]. Due to immunological response, macrophages are activated which either fuse to form giant cells or transform into epitheloid cells[2].

A wide variety of granulomatous disorders can involve the orofacial tissues[3]. The lesions range from infections, immunological, reactive to foreign body granulomas. Most granulomatous lesions of the oral cavity present as small, non-necrotising / noncaseating granulomas with peripheral lymphocytes, central epithelioid histiocytes and multinucleated giant cells[4]. The common term "granuloma" is also used to describe oral diseases even with little or no resemblance to true granulomas, such as pyogenic granuloma, periapical granuloma, peripheral giant cell granuloma, eosinophilic granuloma, foreign body granuloma and periapical granuloma. These lesions are considered to be reactive than neoplastic [5]. Granulomatous lesions of the oral cavity usually present themselves as sessile, lobulated, moderately firm and relatively nontender nodules and papules with normal coloration and with little or no surrounding inflammatory mucosal erythema. With progressing time, some of the granulomas may ulcerate centrally and are presented as a squamous cell carcinoma. The treatment of these oral granulomas depends on the systemic cause. Localised lesions without systemic connection can be treated by conservative surgical removal[6]. No therapy is proved to be universally effective. Laser is a new approach for the treatment of various disorders. Treatment of mucosal oral granulomas by laser is without local anaesthesia and is therefore distinct from the traditional method of surgical excision[7]. This review paper summarise the details related to the most common oral granulomatous lesions.

Classification of oral granulomatous diseases

Based upon etiology and type of necrosis classification of oral granulomatous diseases is given in table1 and table 2.

1. Bacterial Infections

Bacterial infections are the most common cause of oral granulomatous disease. But in some the causative agent remains undetected. Advances in molecular diagnostic techniques have facilitated the identification of previously unrecognizedcausal organisms.

Tuberculosis

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. It is transmitted primarily through the respiratory tract and mainly affects the pulmonary system but it can also involve extra-pulmonary sites, including head and neck region. The clinical presentation of tuberculosis may appear invarious forms. The non-specific nature of the oral lesions in tuberculosis delays its diagnosis and is an unexpected finding[8]. The granulomas in case of oral tuberculosis are likely to be necrotizing / caseating in nature (Figure 1). Despite the large numbers of bacilli contacting the oral cavity mucosa in a typical case of pulmonary tuberculosis oral lesions are rare. This may be as a result of saliva which is said to be a protective agent. But this may not be a case always as poor oral hygiene, leukoplakia, local trauma and irritation by tobacco chewing favour the deposition of mycobacteria through infected sputum[9].Immunosuppression may also be another likely cause of the oral tuberculosis[10].Oral tuberculosis lesions may be either primary or secondary in occurrence. Although primary lesions are uncommon, secondary lesions are found to be common in vestibule, corner of the mouth, tongue and lip. Theyusually appear as a single, irregular, painful ulcer covered by inflammatory exudates in patients of any age group but relatively more common in middle aged and elderly patients. The common symptom observed is a pain during eating sometimes accompanied by dysphonia, speaking difficulty[11]. Tuberculosis-specific symptoms help clinicians towards suspecting and diagnosis of a mycobacterial infection. During the diagnosis of the tuberculosis, when acid-fast bacilli are not identified from the oral granuloma, culture of the biopsy specimen may show*M. tuberculosis*. PCR and radiographic evidence of tuberculosis are recent techniques used for diagnosis of the tubeculosis bacilli[1].

Leprosy

Leprosy is a contagious and chronic granulomatous disease caused by *Mycobacterium leprae* (Hansen's bacillus)and has a long incubation period nearly between two to six years. The disease is presented as lepromatous leprosy, a low resistance form, and tuberculoid leprosy, the highly resistant form, as well as other intermediate forms with combined characteristics. The lesions are usually observed on the hard and soft palate of the uvula, on the lips and gums and on the underside of the tongue. Oral lesions of leprosy occur more frequently in areas of the mouth with lower surface temperature[12]. Oral lesions usually appear in lepromatous leprosy cases. They may take the form of multiple nodules (lepromas) that progress to necrosis and ulceration[13].Oral lesions are nonspecific in their presentation and are often overlooked by clinicians or misdiagnosed. Lepromatous leprosy usually begins in the form of chronic rhinitis. The diagnosis of leprosy is based on a combination of clinical and histological findings.[1]Clinical examination of the oral mucosa does not necessarily confirm disease involvement, and can be confirmed only with histopathological examination[14].

Syphilis

Acquired syphilis in adults is an important public health issue caused by *Treponema pallidum*, a spirochetal microorganism. *T. pallidum* is usually transmitted through sexual intercourse. For therapeutic procedures, syphilis is divided into a series of clinical stages such as primary syphilis, secondary and tertiary syphilis. Primary syphilis lesions are called as chancre of the oral mucosa which arise followed to venereal contact as a result of orogenital sexual practice. The lesions appear as painless ulcers. The secondary syphilis appears after six weeks to six months if the patient of primary syphilis is untreated. The signs and symptoms of primary and secondary syphilis resolve spontaneously and patients then enter the latent stage of infection and in one third of the untreated patients development of tertiary syphilis becomes in evident. Manifestations may take up to 10 years to appear and then appear as gummatous lesions, cardiovascular syphilis, or neurosyphilis. Oral lesions in primary and secondary syphilis are nonspecific and characterised by squamous hyperplasia and a plasma cell infiltrate that extends deep into the submucosa[15].

The confirmation of primary or secondary syphilis cases is difficult as the Venereal Disease Research Laboratory Test (VDRL), Fluorescence Treponemal Antibody Test are usually negative in these early stages and therefore these should be repeated one to two weeks after development of primary lesions[15]

Cat Scratch Disease

Cat scratch disease is known as regional granulomatous lymphadenitis which only occurs in humans, especially those who are scratched or bitten by kittens. Primary manifestation is lymphoid hyperplasia in lymph node. The disease further shows multiple granuloma formation undergoing central necrosis which coalesces to form abscess. *Bartonella henselae* is the responsible gram negative bacillus. It is identified by PCR hybridisation and indirect fluorescent antibody assay.

2.Fungal Infections

There are only few fungi which are capable of invading human tissues. The main obstacles for these fungi to grow in human body are the elevated temperature and cellular immunity. Fungal lesions are particularly observed in common parts of the respiratory tract. Oral fungal infections (mycoses) have come into particular prominence since the introduction of HIV infection. Candidosis is the most common mycotic infection of oral cavities of human beings but others also must be considered.

Histoplasmosis

Histoplasmosis is a granulomatous systemic mycosis was first described by Samuel Darling in 1905[15]. It is caused by H. capsulatum which is a dimorphic fungus growing at ambient temperatures[16,17]. Oral lesions are seen with the chronic disseminated form of the disease but sometimes they may present as the initial or the only mucocutaneous manifestation of the disease[18]. The fungus can spread via blood, with the involvement of phagocytic system. The disease can be severe in immunocompromised patients, and it is an important cause of death in AIDS[16] and was added to the list of 'AIDS defining' diseases in 1985[18]. In the chronic form it can be localised in the lungs, causingrespiratory dysfunction. The oral lesions are generally papillary, ulcerated or nodular, granulomatous, involving the tongue, palate andbuccal mucosa and are rarely observed[16]. Histoplasmosis can be diagnosed by clinical sign and symptoms, histopathology, cultures, serological and histoplasmic skin test. Direct immunofluorescence is diagnostic in case of HIV patients[19].

Blastomycosis

Blastomycosis is an uncommon male-predominant disease caused by the fungus *Blastomyces dermatitidis.* Oral blastomycosis is uncommon[16].This is mainly found in USA, Southern Canada, but also in Africa, India and Middle East[18]. Transmission of the disease is usually by spore inhalation and the lungs are the most commonly affected organ. Clinically presents as acute and chronic. In the chronic form granulomatous lesions of oropharyngeal mucosa and skin are observed. The signs of pulmonary infection mimic the tuberculosis infection. Skin and mucosal lesions are characterised by proliferative verrucous growth, ulceration, and scarring. Mucosal lesions may mimic carcinoma. Mucocutaneous disease indicates spread of the disease. For the diagnosis of blastomycosis, cytological or histopathological examination of tissue with identification of organism is important with culture of sputum or fresh biopsy material as additional methods for diagnosis.

Paracoccidiodomycosis

It is often a sub clinical infection frequently involving the mouth. In many cases, the main clinical symptoms are oral lesions. It is caused by *Paracoccidioides brasiliensis*, a fungus found in soil. Itis dimorphic, and in human tissues presents only in the yeast form. This is observed as aprimary infection of the lungs classified as acute, subacute and chronic forms and dissemination via lymphatic and blood vessels[18]. While invading the oral tissues, especially the lips and cheeks, this infection may cause severe reduction in facial mobility and radically inhibit movement of the lower jaw or the jaw bone[16]. Oral involvement in Paracoccidiodomycosis was first described by Lutz in 1908 in two patients with cervical lymphadenopathy. The oral lesions observed are in single or multiples, granulomatous or ulcerative typically showing an erythematous granular hyperlasia with detectable hemorrhages. The lesions can spread thought the oral cavity extending to the hard and soft palate[20]. This disease is surprisingly not common in immunosupressed patients[21]. The fungus can be observed in routine Haematoxyline and Eosin (H&E) staining, but are readily seen with Periodic Acid -Schiff Stain (PAS) or methenamine silver nitrate[18]. Immunohistochemistry and In-situ hybridisationare also recent techniques involved in its diagnosis.

Aspergillosis

Aspergillosis is caused by *Aspergillus*, a very common group of fungi.In people with healthy immune systems, it usually causes mild or moderate lung problems. In people with suppressed immune systems, it can be life threatening. Patients with acute leukemia are particularly susceptible to invasive aspergillosis. Aspergillosis is the second most frequently seen fungal infection of the face and mouth in patients receiving chemotherapy. It affects predominately male patients; however few cases are of female gender[22]. Myoken *et a*l[23]studied the pathologic features of oral aspergillosis. During the early stage, isolated areas of marginal gingiva show degenerated epithelium and infiltration of the connective tissue by fungal hyphae (Figure 2,3). In the advanced stage, the violaceous marginal gingiva becomes transformed into gray necrotic lesions that extended to the attached gingiva. In general, oral aspergillosis lesions are yellow or black in color, with a necrotic ulcerated base, typically located on the palate or posterior tongue[16]. Aspergillosis is difficult to diagnose in an early stage of infection[24]. Diagnosis of oral aspergillosis depends on a combination of clinical, microbiological and histological characteristics. The recent developments in the early detection methods have been promising which involve modern techniques like serodiagnosis, polymerase chain reaction and detection of galactomannan, a cell wall component of *Aspergillus* species[22].

Others

Orofacial granulomatosis (OFG) is a generic term applied to manifestations of several diseases including sarcoidosis, Crohn's disease,

cheilitisgranulomatosa and foreign-body reactions. Chronic granulomatous disease (CGD) is another extremely rare congenital immune deficiency syndrome. The causative agent of this syndrome is also unknown but poor oral hygiene is found to be the main cause for the same.

Sarcoidosis

Sarcoidosis is a systemic non-necrotizing / non-caseating granulomatous disease of unknown etiology but immunological disturbance plays a major part. It is a multisystem disease most commonly affecting young adults. It was first reported in the 19th century, by Jonathan Hutchinson (1875), but the term sarcoidosis was introduced later by Boeck in 1899[2]. Although the etiology of sarcoidosis is unknown, infectious agents like Mycobacterium, Propionobacteria, Epstein–Barr virus (EBV), Human herpes virus-8 (HHV-8) and environmental factors such as wood dust, pollen, clay, mold, silica etc. and occupational exposures have been considered as possibleetiological agents[25]. Oral involvement during the disease generally appears in patients with chronic multisystem sarcoidosis and rarely occurs in the acute stage. In some cases, oral involvement is the first and the only symptom of the disease and appears as a nontender well-circumscribed brownish red or violeceous swelling, as papules or as submucosal nodules that can occasionally either show superficial ulceration or be symptomatic[26].The diagnosis of sarcoidosis is established when clinical features are supported by histopathological evidence of typical non-caseating epithelioid granulomas (Figure 4,5) and other laboratory tests[26].

Crohn disease

Crohn's disease is a chronic Granulomatous disorder that may involve any portion of the GIT including the oral cavity. Microscopically, nonspecific chronic inflammation is seen and in older long-standing lesions, noncaseating / nonnecrotizing granulomas are observed[27].The etiology of the disease is unknown. Oral manifestations of the disease are often present in patients with advanced intestinal disease with granulomatous inflammatory lesions in the intestinal tract[28].

Proximal and oropharyngeal gastrointestinal tract Crohn's disease is difficult to diagnose. Thorough history-taking, direct visualization, and tissue biopsy are all important steps in establishing the diagnosis[29]. Gastroscopy by experienced gastroenterologists will identify oropharyngeal Crohn's disease in only 50% of patients[30]. This could be due to limited examination of the oro-and hypo-pharynx by endoscopists. Indirect laryngoscopy can provide initial identification of the oral ulcerations and in the absence of neoplasia on biopsy, a careful search for luminal Crohn's disease should be undertaken[31].

Chelitisgranulomatosa

Cheilitisgranulomatosa (CG) is a rare granulomatous disorder of unknown origin, initially described by German dermatologist Miescher in 1945.Clinically it manifests as diffuse, non tender, soft to firm swelling of one or both lips. Macrocheiliais caused by swelling of the minor salivary glands, and mucous and ⁄ or purulent discharge through an enlarged ductal orifice[32].Histopathology of this disease shows non necrotizing granulomas of varying degrees with dilation of lymphatic vessels and perivascular lymphocytic infiltration. Other sites of involvement are buccal, labial (70%) mucosa and palate, clinically presenting as corrugated/lobulated appearance and as papillary hyperplasia[32,33]. Fibrosis may also be present in long term lesions[33].The non-specific histopathology of the disease and the wide variety of possible clinical differential diagnoses highlight the diagnostic challenge posed by this lesion and the need for clear clinico-histopathological correlation for establishing the correct diagnosis.

Eosinophilic granuloma

Since eosinophils may not always be present, and therefore, the name eosinophilic granuloma, despite being a commonly accepted term, is a misnomer and is known to simulate malignancy

Wegener's granulomatosis

Wegener granulomatosis (WG) represents an inflammatory destructive disease that may have widespread systemic involvement which was first categorised as a distinct syndrome by Friedreich Wegener in 1936. This is characterised by the triad of systemic vasculitis of small arteries and veins, necrotizing glomerulonephritis and necrotizing granulomatous inflammation of the upper and or respiratory tracts. The middle ear, gingiva, and nasal mucosa are also commonly affected[34].Wegener's granulomatosis may initially manifest in the oral mucous membrane as petechiae and hyperplastic gingival lesions or strawberry gingivitis[34].Limited mucosal inflammation, ulcerative stomatitis, granulomata, oroantral fistulae, osteonecrosis of the palate and labial mucosal nodules are described as the common symptoms in case of involvement of oral cavity[35]. Since very few deposits of immune complexes are typically provable during biopsy, WG is classified as vasculitides. A thorough clinicopathological correlation coupled with serological workup should help in diagnosis of WG.

4. Reactive Lesions

Most of localised outgrowths of the oral cavity are considered to be reactive in nature than neoplastic[5] and can be classified as vascular and fibrous. The localised lesions of the oral cavity have been broadly categorised as pyogenic granuloma, peripheral giant cell granuloma, perapical granulomaetc.

Pyogenic granuloma

Pyogenic granuloma (PG) is one of the inflammatory hyperplasias of the oral cavity. This term is referred as a misnomer because pus is infrequently found in the lesion and is unrelated to any infection. This arises in response to various stimuli such as chronic mild local irritation, traumatic injury or even hormonal factors[36]. It is predominantly observed in young females in their second decade of lifemay be because of the vascular effects of their hormones[37]. The lesions manifest as exophytic growth which are generally sessile commonly seen in gingival[36]. Pyogenic granuloma lesions show three distinct phases such as cellular phase, capillary phase and involutionary phase[38]. The clear diagnosis of PG is based upon biopsy findings and the treatment is based upon complete surgical excision.

Peripheral giant cell granuloma

Peripheral giant cell granuloma (PGCG) also known as osteoclastoma, is one of the reactive hyperplastic lesions of the oral cavity. The term 'peripheral' is included in the name to separate this lesion from a histologically similar lesion which occurs inside the jaws. It is not a true neoplasm but rather a benign hyperplastic reactive lesion occurring in response to local irritation such as tooth extraction, poor dental restorations, ill-fitting dentures, plaque, calculus, food impaction and chronic trauma. Chronic trauma can induce inflammation leading to granulation tissue with endothelial cells, chronic inflammatory cells and increased number of fibroblasts[39]. The PGCG lesions can present as polypoid or nodular lesions of varying size with, a smooth shiny surface, soft or rubbery to touch[40].In rare cases, PGCG lesions are oral manifestations of hyperparathyroidism[39].The biopsy is a reliable method for diagnosis of PGCG with the differential diagnosis as pyogenic granuloma.

Periapical granuloma

Periapical granuloma (PG) is a localized mass of chronic granulation tissue in response to low grade infection caused as a sequele of pulpitis. It is a misnomer as it does not have features of granuloma. Clinically, tooth is nonvital, pain on biting and slightly tender on percussion. Microcroscopically, these lesions are composed of fibrocellular stroma, numerous blood vessels, chronic inflammatory cells (lymphocytres and plasma cells), macrophages and sometimes cholesterol clefts[41].

5. Foreign body granulomas

Foreign bodies (FB) or materials are the most common source of granulomatous inflammation in the oral cavity. Various foreign bodies and locations such as wood in the orbit, impression material in the maxillary sinus, tooth fragments in the orbit could be the reasons for granulomas[42].The implantation of an FB into tissues results in an inflammatory reaction[43] (Figure 6). The foreign material is composed of particles that are usually too large to bephagocytosed by macrophages. Because the material is typically inert, it usually does notinducean immune response. Instead macrophages are recruited to the site for the elimination of the foreign substance where they become activated and are transformed into epitheliod macrophages to form granuloma[44]. Foreign bodies sometimes migrate within the tissues and become symptomatic after a certain period of time[42]. The hyaline ring granuloma is also a distinct oral entity characterized as foreign body reaction[46]. The removal of FBs is often a surgical challenge due to a combination of difficulty in access and close anatomical relationship to vital structures[42]. It is necessary that the FBs should be diagnosed and removed on time to avoid further complications.

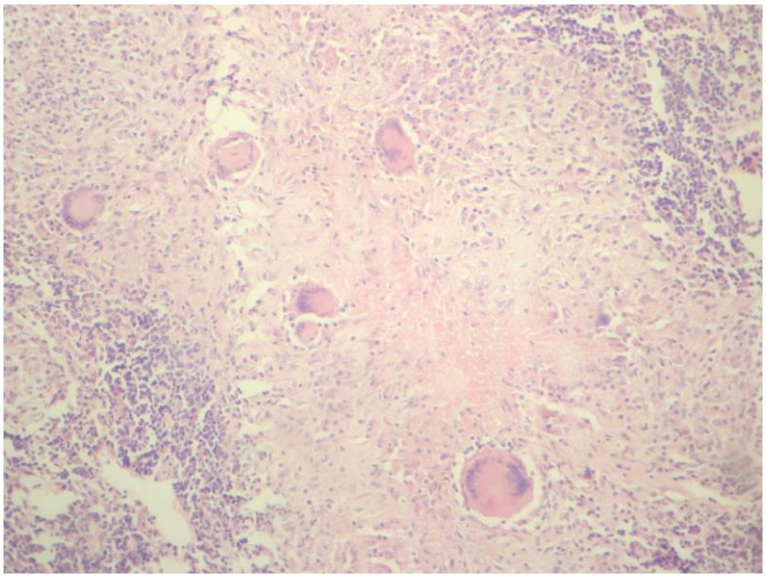

Fig-1: Tuberculous granulomatous lesion showing Langerhans giant cells, necrosis and chronic inflammatory cell infiltrate (Hematoxylin and Eosin stain, x100).

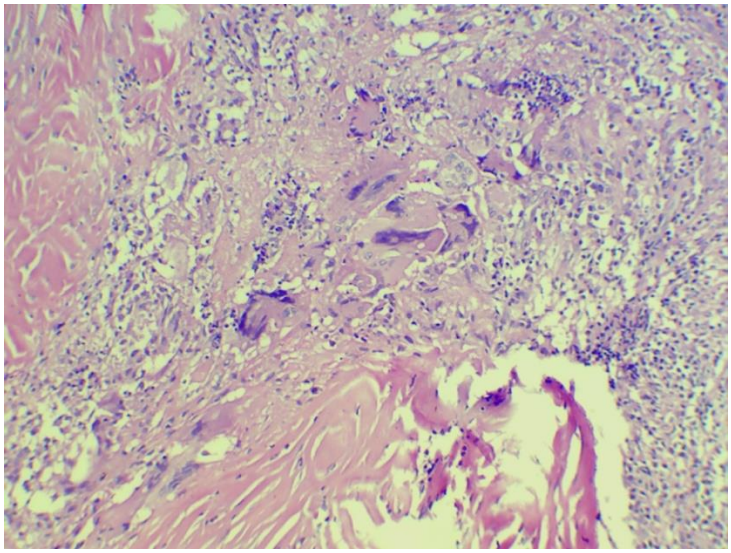

Figure 2: Oral aspergillosis of marginal gingiva showing degenerated epithelium and infiltration of the connective tissue by fungal hyphae (Hematoxylin and Eosin stain, x100).

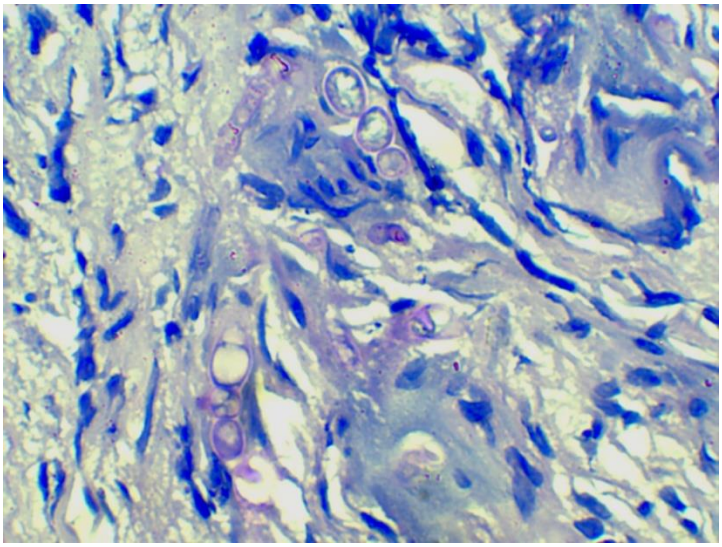

Fig-3: PAS stain showing fungal hyphae (PAS stain,x400)

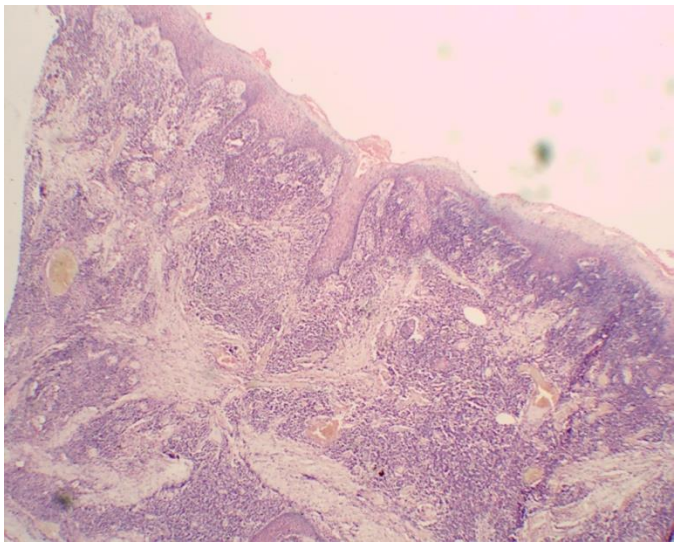

Figure 4: Small non-caseating epithelioid granulomas of sarcoidosis(Hematoxylin and Eosin stain, x40).

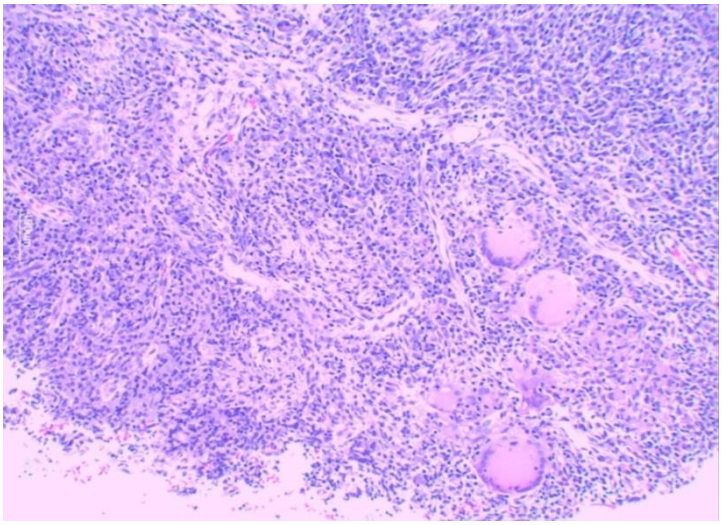

Figure 5: Giant cells and chronic inflammatory cell infiltrate in sarcoidosis (Hematoxylin and Eosin stain, x100).

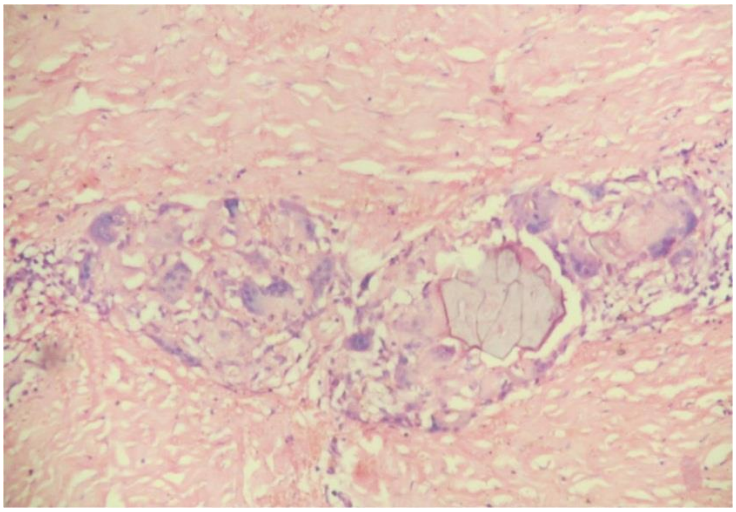

Figure 6:Foreign body granuloma against suture material showing foreign body giant cells and chronic inflammatory cells (Hematoxylin and Eosin stain, x100).

Table 1: Classification of oral granulomatous lesions

SN	Etiology	Name of the Disease
1.	Bacterial	• Tuberculosis
		• Leprosy
		• Syphilis
		• Cat-scratch disease
2.	Fungal	• Histoplasmosis
		• Blastomycosis
		• Paracoccidiodomycosis
		• Aspergillosis
3.	Others (Unknown, autoimmune & Vascular)	• Sarcoidosis
		• Crohn's disease
		• Chelitisgranulomatosa
		• Eosinophilic granuloma • Wegener's granulomatosis
4.	Reactive lesions (Trauma, hypersensitivity)	• Pyogenic granuloma
		• Peripheral giant cell granuloma
		• Periapical granuloma
5.	Foreign bodies	• Oral foreign body reactions

Table 2: Classification based on type of necrosis:

Type of Necrosis	Granulomatous lesions
Caseating granulomas/suppurative	Tuberculosis, Syphilis, Cat scratch disease, Actinomycosis, Blastomycosis, Cryptococcosis, Coccidiodomycosis
Non-caseating granulomas/ non-suppurative	Leprosy, Sarcoidosis, Crohn's disease, silicosis, foreign body granulomas

Table 3: Diagnostic criteria of granulomatous diseases

SN	Disease	Diagnostic criteria
	Bacterial	
1.	Tuberculosis	• Fever,Gradual loss of weight,Chest pain, persistant cough with or without hemoptysis, Lymphadenopathy, Chest X-Ray. • Ziehl-Neelsenstaining,Culture for bacilli,Sputum AFB direct smear and culture • Elevated ESR
2.	Leprosy	• Loss of sensation of temperature, touch, pain, deep pressure. • Relatively painless ulcers, skin lesions of hypopigmented macules (flat, pale areas of skin), and eye damage (dryness, reduced blinking) • Hypopigemented reddish skin with definite loss of sensation • Thickened peripheral nerves • Acid fast bacilli on skin smears or biopsy material
3.	Syphilis	• Pimary syphilis - Sore (chancre) -non tender, Palpable non lymph nodes in the groin. • Secondary syphilis - Common symptoms such as headache, achiness, loss of appetite and reddish brown rash. It may be scaly, flat or raised. (vary individual to individual) • Tertiary syphilis - fever, gumma, bone pain, liver disease, anemia. • Demonstration of *T. pallidum* by dark filed microscopy. • Reactive VDRL test and reactive treponemal blood test (TP-PA)
4.	Cat-scratch disease	• Blister or pustule at the site of injury, Fever, chills, nausea, vomiting, Fatigue, Lymphadenitis, Malaise, Loss of appetite, sore throat, weight loss, Enlarged spleen, occasionally infected lymph node may form a tunnel (fistula) through the skin and drain (leak fluid) • Detection of *Bartonellahenselae* IgG antibody by IFA test
	Fungal	
5.	Histoplasmosis	• Fever, chills, dry cough, malaise, sweats, abdominal pain, small scars in lung x-ray, Patchy infiltrates on lung x-ray seizures, mouth ulcers, encephalopathy • Localized granuloma in lungs on biopsy • Positive serology with high complement fixation titres
6.	Paracoccidioidomycosis	• Productive cough, dyspnea, malaise, fever, weight loss, lymphadenopathy, hepatosplenomegaly, multiple skin lesions • Pulmonary fibrosis, bullae and emphysematous changes leading to pulmonary hypertension and corpulmonale • Demostration of large multiple budding yeast in KOH Complement fixation and immunodiffusion test for circulating antibodies
7.	Blastomycosis	• Bone pain, chest pain, cough (may produce brown or bloody mucus), fatigue, fever, malaise, joint pain, muscle pain, night sweats, rashes, shortness of breath, weight loss • Broad based budding organisms in sputum or tissues in KOH preparation • Urine antigen testing • Lung biopsy
8.	Aspergillosis	• Cough, fever, wheezing, weight loss, hematuria, decreased urine output, aspergillus antibody test, chest x-ray, sputum stain for

		Aspergillus, • IgE blood level and complete blood count • Lung function tests • Tissue biopsy
	Others	
9.	Sarcoidosis	Dyspnea on exertion, non-productive cough, chest pain, wheezing, nasal congestion, Hemoptysis, Angiotensin Converting Enzyme(ACE).
10.	Crohn's disease	Lower right quadrant pain, diarrhea, periods of constipation Episodic obstruction
11.	Chelitisgranulomatosa	Swelling of face and lips, partial facial paralysis Tongue abornmalities, Tongue folds and furrows(Scrotal tongue), Episodes of facial paralysis, facial edema, swollen lip, swollen cheeks, swollen chin, swollen tongue, lymphaedema
12.	Wegener's granulomatosis	Rhinitis, sinusitis, cough, hemoptysis
	Reactive lesions	
13. 14. 15.	Pyogenic granuloma Peripheral giant cell granuloma Periapical granuloma	Tumor like growth
16.	Foreign body	Difficult to diagnose as foreign bodies may remain undisclosed

CONCLUSION

The rate and severity of oral disease varies across different studies. Isolated granulomas may be identified from a variety of infectious and non-infectious disease processes. Granulomatous inflammation often presents a diagnostic difficulty for the clinician. Therefore an extensive clinical, microscopic and laboratory evaluation is required to identify the sourceof the oral granulomatous diseases.

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