Granulomatous Diseases of Orofacial Region – A Review

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ABSTRACT

Granulomatous diseases encompass a large family of disorders, sharing the histological denominator of granuloma formation. The granulomatous diseases of the head and neck are very unique entities that can mimic or hide malignant tumors and a wide assortment of diseases. They can cause a wide range of signs and symptoms in the head and neck region and also throughout the body. It poses a diagnostic dilemma for the clinician. The frequency of infectious granulomatous diseases is increasing with the increasing incidence of AIDS, multi-drug resistance and with the widespread use of immunosuppressive drugs. It is essential to find the etiology of the disease and to recognize the granulomatous pattern in a biopsy specimen. Thus, a thorough history and a complete physical examination, along with radiological, histological and laboratory evaluation may be required for the correct identification of the granulomatous disease for its specific treatment. In this review, we have highlighted the features of the various granulomatous diseases of the oro-facial region that are caused by diverse immunologic, idiopathic, neoplastic, infectious, and fungal processes and their diagnostic procedures.

Introduction

Granulomatous diseases include a large family of disorders, sharing the histological denominator of granuloma formation. '*Granuloma*' is defined as a tiny circumscribed lesion, that is about 1 mm in diameter, and is predominantly composed of collection of modified macrophages called epithelioid cells, and are rimmed at the periphery by lymphoid cells. It is an attempt to wall off substances, the body perceives as foreign but is unable to eliminate.[1] The granulomatous diseases of the head and neck are very unique entities that can mimic or hide malignant tumors and a wide assortment of diseases. The frequency of infectious granulomatous diseases is increasing with the increasing incidence of AIDS, multi-drug resistance and with the widespread use of immunosuppressive drugs. Their diagnosis is usually simple, and does not require complicated diagnostic procedures, but a high degree of suspicion is essential. The microbiological and histopathological analyses are the most specific studies that aid in the diagnosis of granulomatous diseases, but other diagnostic procedures and studies, are helpful to suggest the diagnosis or to define the extent of the disease.[1,2]

Classification of Granulomatous Diseases, Based on Etiology[3,4,5,28]

1) Infection

a. Bacterial: Tuberculosis, Leprosy, Non-tuberculous mycobacterial infections, Actinomycosis, Klebsialla rhinoscleromatis, Anthrax, Brucellosis, Cat scratch disease

b. Fungal: Histoplasmosis, Blastomycosis, Mucormycosis, Candidiasis, Cryptococosis, Rhinosporidiosis

c. Spirochetal : Syphilis

d. Parasitic : Leishmaniasis, Myiasis, Toxoplasmosis

2) Traumatic Etiology

i) Pyogenic granuloma

ii) Reparative granuloma

3) Foreign Body Etiology

i) Oral foreign body reactions (Suture, hair, amalgam, endodontic sealer, hyaluronic acid etc.)

ii) Cholesterol granuloma

iii) Cocaine induced midline granuloma

iv) Gout

4) Neoplastic

I) Histocytosis X

a) Eosinophilic granuloma

b) Hand schuller Christian Disease.

c) LettererSiwe disease.

ii) Benign Fibrous histiocytoma

iii) Neorotizing sialometaplasia.

iv) Polymorphic recticulosis (lethal midline granuloma)

5) Unknown Etiology

i) Sarcoidosis,

ii) Crohn's disease

6) Autoimmune & Vascular disease

i) Wegener's Granulomatosis

ii) Systemic Lupus erythematoses

iii) Sjogren's syndrome

7) Developmental

i) Melkerson Rosenthal syndrome

8) Congenital chronic Granulomatous disease of Childhood

Tuberculosis (TB)

Tuberculosis is a chronic granulomatous disease caused by Mycobacterium Tuberculosis. It is classified as – Pulmonary and Extra pulmonary (Lymph nodes, pleura, bones, joints, meninges, genitourinary tract, skin and peritoneum). The Head and neck TB involves larynx, middle ear nasal cavity, nasopharynx, oral cavity, parotid gland, oesophagus and spine.

Oral manifestations of TB is rare (0.1 -5 % of all TB infections) but the incidence is increasing due to the outbreak and emergence of multi drug-resistant TB and emergence of AIDS. Relative resistance of oral cavity to tuberculosis is due to presence of saliva, presence of saprophytes, and resistance of striated muscles to bacterial invasion and thickness of protective epithelial covering. Factors that facilitate invasion include small breaches in the surface epithelium (poor oral hygiene/irritation /local

trauma, self inoculation by infected sputum, Hematogenous /lymphatic dissemination and cases of immunosupression like AIDS.[6,7] The oral manifestations of tuberculosis are highlighted in Figure 1. Tuberculosis of the oral cavity mimics cancerous lesions and others like traumatic ulcers, aphthous ulcers, actinomycosis, syphilitic ulcer, or Wegener's granuloma. Thus, the chronic indurated ulcer has to be carefully distinguished from a carcinoma.

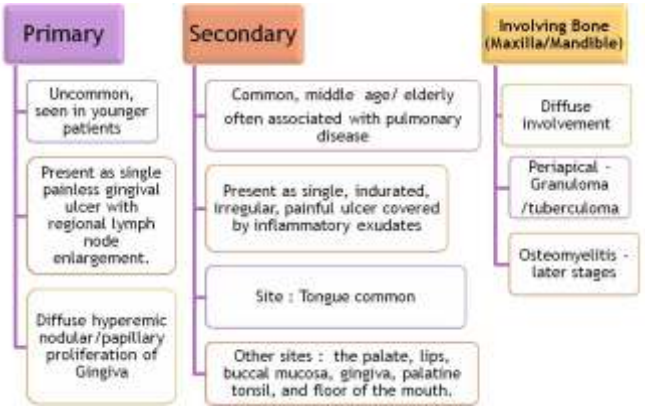

Figure 1: Oral manifestations of Tuberculosis

Histopathologically, tuberculous granulomas are composed of epitheloid cells surrounded by a zone of fibroblasts & lymphocyte that usually contains langhans giant cells some necrosis (caseation) is usually present in the center of the tubercles.[8,9] The investigations for tuberculosis include biopsy, special microbial stains, radiological examination of chest, Mantoux skin test, fine-needle aspiration cytology for identifying TB in major salivary gland. Definitive diagnosis requires isolation and identification of Mycobacterium tuberculosis in the Sputum. The first line Drugs most commonly used are Rifampicin, Isoniazid, Ethambuto, Pyrazinamide and Streptomycin.[10]

Hansen's Disease or Leprosy

Leprosy is caused by Mycobacterium leprae. It is a slowly progressive infectious disease that affects skin & peripheral nerves, resulting in disabling deformities. Cell-mediated immunity plays an important part in the pathogenesis of the disease. Mode of Transmission includes direct contact, materno-foetal transmission and through breast milk. Types of Leprosy are Indeterminate, Tuberculoid, Borderline and Lepromatous leprosy. Oral Manifestations of leprosy include ulcers, perforations and scars, papules, nodules (lepromas) and superficial erosions in palate, tongue, uvula, lips and gums. Gingival hyperplasia with loosening of teeth and Paralysis of facial and maxillary division of trigeminal nerve may be seen. Dental manifestations are called Odontodysplasia leprosa. Long standing lepromatous lesions may cause granulomatous invasion of the pulp and pinkish discoloration of crowns. Oral mucosal lesions are sources of infection in lepromatous patients.[11]

Histopathologically, the typical Granulomatous nodule consists of epitheloid cells & lymphocytes in a fibrous stroma. Langhans type giant cells and lepra cells are present, that contain the bacilli. The type of inflammatory reaction depends on the state of the patient's immune system. *Lepromatous* reaction occurs if an adequate T-lymphocyte response is lacking and *Tuberculoid* reaction is seen when the T-cell immunity remains intact, but is functionally unable to fully eliminate the bacteria.[9] Investigations for leprosy include Acid-fast (Ziehl-Neelsen) staining, Fite-Faraco staining procedure, Gomori methenamine silver (GMS) staining PCR, ELISA and IgM antibodies to PGL-1 antigen. Treatment includes Multi drug therapy – Rifampicin, Dapsone, clofazimine.[1]

Actinomycosis

Actinomycosis is a chronic suppurative disease that is caused by Actinomycetes israelii – an anaerobic bacterium. There are 4 types depending upon the anatomic location of lesions: cervicofacial, thoracic, abdominal, and pelvic actinomycosis. Cervicofacial actinomycosis is the commonest form (60%) and it is known to have the best prognosis. The tonsils, carious teeth, periodontal disease or trauma following tooth extraction facilitate entry of infection. A firm swelling develops in the lower jaw ('lumpy jaw') initially. As time passes, the mass breaks down leading to formation of abscesses and sinuses. The pus discharge contains typical tiny yellow sulphur granules. The actinomycotic infection may extend into adjoining soft tissues and can also destroy bone.[12]

Histopathologically, the actinomycotic granuloma appears as an isolated mass of Granulomatous inflammatory response or multiple suppurative fields with a central area of suppurative necrosis. Masses of filaments (sulphur granules) extend in a radiating fashion giving it a "sunburst radiation" or fiery appearance. The central core stains basophilic & the peripheral clubs stains eosinophilic with H & E stain. The colonies are surrounded by polymorphonuclear infiltration. Surrounding these inflammatory focus there are plasma cells, lymphocytes, multinucleated giant cells, macrophages and a fibrous capsule are usually seen. The organisms are gram-positive filaments, non acid-fast, and stain positively with Gomori's methenamine silver (GMS) staining.[5,9]

Cat Scratch Disease

The Causative organism is Bartonella hensalae, a gram negative bacillus (demonstrated by silver stain). It is most common in children and young adults. It is caused by traumatic break in skin due to scratch or bite of house hold cat. The primary lesion could be a papule, pustule or vesicle at site of injury. In about 1-3 weeks, painful regional lymphadenitis occurs, that may persist for 1-6 months. Other signs and symptoms include fever, headache, chills, parotid swellings, conjunctivitis, localised granuloma of eye and preauricular lymphadenopathy. Atypical manifestations of the disease lack the characteristic superficial lymphadenopathy and inoculation site papule and may be misdiagnosed initially as other infectious processes or neoplasms. Histopathologically, in early stage, reticuloendothelial hyperplasia are seen in lymph nodes. Later, destruction of lymph node architecture with focal granulomas, suppuration, necrosis with capsular thickening are seen. Epitheloid cells and multinucleated

giant cells are seen at times. Warthin Starry Silver staining and Brown Hopps Gram staining can be used to demonstrate the bacillus. It is a self limiting disease that regresses within a period of weeks and months.[13]

Syphilis

Syphilis is a venereal (sexually-transmitted) disease caused by spirochaetes, *Treponema pallidum*. The modes of transmission include sexual intercourse, intimate person-to-person contact, transfusion of infected blood and materno-foetal transmission. There are two types of Syphilis - Acquired Syphilis and Congenital syphilis. Primary syphilis present as solitary ulcers with indurated margins on lip, tongue and palate. The ulcers may be deep and are accompanied by cervical lymphadenopathy. The Chancre heals within 7 days to 2 months. Microscopically, it appears as a superficial ulcer with intense inflammatory cell infiltrate and numerous plasma cells. Mucous patches form the characteristic feature of secondary syphilis. These are painless, oval to cresentric erosions surrounded by red periphery. The maculopapular rashes and nodular mucosal lesions can be seen on lips, oral mucosa, tongue, palate and pharynx. The tertiary syphilis is characterised by Gumma formation. Swellings/nodular masses can be seen that may ulcerate resulting in bone destruction, palatal perforation and oro nasal fistula. Atrophic glossitis is also commonly seen. Microscopically, focal granulomatous inflammation with central necrosis can be seen. Congenital syphilis, is characterised by Hutchinson teeth, Mulberry molars, Frontal bossing, saddle nose and poorly developed maxilla. The Hutchinson's triad includes hypoplasia of the incisor and molar teeth, eigth nerve deafness and interstitial keratitis.[14] Investigations for syphilis include dark ground illumination, fluorescent antibody technique, silver impregnation techniques, PCR and serological tests for syphilis. Penicillin is the drug of choice for syphilis. Other drugs include doxycycline, erythromycin strearate and Ceftriaxone.[10,14]

Blastomycosis

Blastomycosis is caused by Blastomyces dermatidis, a dimorphic fungus that grows in soil and decaying wood. Three clinical forms are present Pulmonary, Disseminated blastomycosis and Cutaneous blastomycosis. Pulmonary blatomycosis can be Acute or Chronic. Acute blastomycosis presents with productive cough, chest pain, dyspnoea, fever, night sweats. Chronic type may be mistaken for TB at times. A pyogranulomatous response is seen at the initial site of pulmonary infection and at any sites of distant spread.[15] Oral involvement can be present as ulcers or exophytic mucosal lesions but is very rare. Micoscopically, a mixed inflammatory reaction is seen with clusters of polymorphonuclear leukocytes and noncaseating granulomas with epitheloid histiocytes and foreign body type giant cells.[15] The Diagnosis is usually made on identification of the fungus in a tissue biopsy or cytological smear of infected body fluid. The organism appears as round yeast cell which divides by broad based budding. The confirmation of diagnosis is through culture of the fungus. Treatment is based on the severity of disease. Itraconazole is used for mild to moderate cases. Amphotericin B is used for severe meningeal lesions and immunocompromised patients.[16]

Histoplasmosis

Histoplasmosis is caused by Histoplasma capsulatum, a dimorphic fungus found in soil. The disease spreads through inhaled spores. Disseminated histoplasmosis can be seen in immunocompromised conditions. Fever, dyspnoea, productive cough and anterior chest discomfort is seen in case of acute pulmonary infection. Granuloma formation and coagulative necrosis may result in cavitation of lung tissues. Fibrosis occurs due to healing of the granulomatous lesions. Oral involvement is usually secondary to pulmonary involvement. Oral lesions appear as papule, nodule, vegetation or an ulcer. Cervical lymph nodes are enlarged and firm. In HIV cases, ulcers with indurated border can be seen on the gingiva, palate or tongue. Investigations include culture of infective tissue on dextrose agar and biopsy. Microscopically small, oval yeasts with macrophages and reticulo-endothelial cells can be seen along with chronic granulomas with epitheloid cells, giant cells and caseous necrosis. Ketoconazole, Itraconazole and Amphotericin B are used for treatment of the infection.[17,18]

Mucormycosis

Mucormycosis is also known as Phycomycosis or Zygomycosis. It generally occurs in individuals with decreased host response. The fungus invades arteries and causes damage secondary to thrombosis and ischaemia. The symptoms include ptosis, fever, swelling of cheek, and paresthesia. Oral manifestations include ulceration of palate that may be large and deep causing denudation of underlying bone. Ulcers can also occur in the lips, gingiva and alveolar ridge. This is a chronic granulomatous infection that shows multiple granulomatous areas having lymphocytes, giant cells and epitheloid cells.[19] Broad thin walled non-septate fungal hyphae with branching at right angles are seen in the connective tissue and confirmed by by Periodic acid Schiff stain. Treatment options include a combination of surgical debridement and systemic administration of Amphotericin B.20

Rhinosporidiosis

Rhinosporidiosis, is a chronic granulomatous disease that usually presents as a polypoidal mass in the nasal cavity and nasopharynx. It is caused by *Rhinosporidium seeberi*.[21] It predominantly affects the mucus membranes of nose and nasopharynx. It also involves lips, palate, uvula, maxillary antrum, conjunctiva, lacrimal sac, epiglottis, larynx, trachea, bronchus, ear, scalp, skin, penis, vulva, and vagina. Rhinosporidiosis of the parotid duct manifests itself as a facial swelling. Microscopically, the organisms appear as sporangia containing large numbers of round or ovoid endospores. The connective tissue surrounding it shows granulation tissue and mixed inflammatory cells including lymphocytes, plasma cells, focal collection of histiocytes, and also neutrophils. Pseudocystic abscess formation, granulomatous reaction and fibrosis may also be seen.[22] Treatment options include complete excision with wide surgical margins, antifungal agents such as

griseofulvin and amphotericin B and treatment with dapsone.[23]

Oral Myiasis

Oral myiasis is caused by infestation of tissue by larvae of houseflies and it is rare as the oral cavity does not provide the necessary habitat conducive for a larval lifecycle. Maggot infestations can occur in humans in two ways - by direct inoculation in to wounds or by ingestion of infected materials like meat. Conditions leading to persistent mouth opening, accompanied with poor hygiene, suppurative lesions, severe halitosis, and facial trauma predispose the patient to oral myiasis. The growth of the larvae causes progressive destruction and cavitation. Finally a fibrous capsule is formed to which the larve firmly adheres, causing difficulty in dissection during surgery.[24,25] The dead larva may elicit an inflammatory response, with the formation of a foreign-body granuloma and, eventually, progression to calcification.[27] Diagnosis is generally made by the presence of larvae. The management of oral myaisis includes mechanical removal of the larvae, multivitamin tablets and antibiotics for secondary bacterial infections.[26]

Toxoplasmosis

Toxoplasmosis is caused by Toxoplasma gondii. The disease is devastating for developing fetus (Congenital toxoplasmosis) or immunocompromised patient (AIDS, Transplant, cancer patients). It spreads from cat feces. Patients are usually asymptomatic. Low grade fever, cervical lymphadenopathy, fatigue, muscle or joint pain (few weeks to few months), necrotising encephalitis, pneumonia, myositis can also be present. Lymphadenopathy, involves one or more of lymph nodes in the para-oral region, such as buccal lymph node. The Histopathology shows characteristic reactive germinal centers and accumulation of eosinophilic macrophages. The diagnosis is through the serum antibody titres of T.gondii and biopsy of involved node. The treatment options for Immunocompromised patients include Sulfadiazine, clindamycin and pyrimethamine.[29]

Foreign Body Granulomas

Foreign body granulomas are caused by Exogenous materials like silica, beryllium, glass, talc, or endogenous agents like hair, keratin, amyloid. In oral cavity gingiva is the most common site. Localised or diffuse erythema or ulcerations are seen. The condition does not resolve with improvement of oral hygiene. The biopsy generally shows granulomas and foreign body giant cells in absence of microorganisms. The management involves excision of the offending agent and involved tissue.[30] The term pulse granuloma (PG) has been applied to the foreign body reaction to vegetable material (leguminous crops, such as peas, beans, and lentils). It is a granulomatous response. It can occur either centrally or peripherally in the oral cavity. It is usually seen in the periapical or the sulcus area. Occasionally, the lesions may occur in the wall of the inflammatory odontogenic cysts.[31]

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease disease of unknown etiology. It is characterized by the formation of uniform discrete, non caseating epitheloid granulomas. Two clinical syndromes - Lofgren Syndrome and Heerfordt Syndrome are associated with it. The possible etiologies include Infective and non-infective agents, Mycobacterium, propionibacterium and HHV-8. It is most commonly seen in young adults or in the middle aged. The Lungs (Hilar lymphadenopathy, Pulmonary infiltration), skin, lymph nodes, salivary glands, liver, spleen and bones are involved. Clinical features include malaise, cough, cutaneous lesions like multiple, raised red patches. Oral manifestations include small papules, nodules, plaques or submucosal masses, with bleb-like appearance containing clear yellowish fluid. The common sites in the oral cavity include buccal mucosa, gingiva, lips, floor of the mouth, tongue and palate. Bilateral involvement of the major salivary glands is seen. The diagnosis is based on the clinical, radiographic, histopathological, and non caseating epitheloid granulomas. Chest radiographs show bilateral hilar lymphadenopathy and diffuse parenchymal infilterates. Increased serum ACE level is present. Kveim test and biopsy aid in confirmative diagnosis.[10,29]

Crohn's Disease

Crohn's disease is a chronic Granulomatous disorder involving any portion of the GIT including the oral cavity. The oral lesions have predilection for the labial and buccal mucosa, and the mucobuccal folds. They are generally multifocal, linear, nodular, polypoid or diffuse mucosal thickenings. The ulcers are typically persistent, linear and deep and may cause pain. Subepithelial, noncaseating granulomatous inflammation characterized by epithelioid histiocytes, giant cells and lymphocytes can be seen microscopically. Topical corticosteroid therapy or intralesional corticosteroid injections may relieve the oral lesions.[32]

Necrotizing Sialometaplasia

Necrotizing sialometaplasia is a self-limited, benign lesion of both major and minor salivary glands. It is most commonly seen in the hard palate. The underlying pathophysiology includes ischemia and infarct of mucosal salivary gland tissue that results in a self-healing inflammatory process. The predisposing factors include traumatic injuries, such as dental injection, blunt force trauma, denture wear etc. The histologic stages in the development and evolution of necrotizing sialometaplasia are - infarction, sequestration, ulceration, repair, and healing. Crateriform ulcers can be seen in the palate that can cause erosion of the palatal bone. It may be mistaken for malignancies, such as mucoepidermoid carcinoma, and invasive squamous cell carcinoma. Histopathological features include pseudoepitheliomatous hyperplasia, squamous metaplasia of the ducts and acini, preservation of the lobular architecture, lobular infarction with or without mucin spillage and inflammation secondary to the extravasation of mucin. Necrotising metaplasias resolve spontaneously within weeks.[33,34]

Histiocytosis X

Histiocytosis X is also known as Langerhans cell histiocytosis. It is classified into two variations: localized or disseminated. Its types include Eosinophilic Granuloma, Hand-Schuller-Christian Disease, Letterer-Siwe Disease. It usually occurs in children under 15 years of age. The common signs include lymphadenopathy, fever, irritability, anorexia, pallor, middle ear otitis and anemia. When the jaws are affected, radiographs show well circumscribed, osteolytic lesions with the pathognomomic –floating teeth. Oral ulcerations, swellings, gingival inflammation, tooth mobility and loss are common. It can resolve spontaneously or it can disseminate, compromising visceral organs, with a fatal outcome.[35] Microscopically, it consists of sheets of polygonal histiocytes (Langerhans' cells) with some eosinophil, plasma cells, and lymphocytes. Histiocytes contain cytoplasmic inclusions known as X bodies. Electron microscopy reveals the characteristic Birbeck granules in the lesional cells. The disease is managed by surgical intervention, radiotherapy and chemotherapy.[36]

Midline Lethal Granuloma

"Lethal midline granuloma syndrome" has been divided into the following clinical entities: Idiopathic midline destructive disease, Wegener's granulomatosis, polymorphic reticulosis and Non-Hodgkins lymphoma.[37] The idiopathic midline destructive disease is an unusual condition that resembles necrotic granulomas macroscopically and causes idiopathic progressive destruction of the nose, paranasal sinuses, palate, face and pharynx. The person affected typically appears to exhibit lack of resistance to insidious progress of the disease. Nasal stuffiness with or without nasal discharge is the major symptom. It begins as an oral or nasal ulcer and the ulceration eventually spreads. Perforation of the palate and nasal septum with mutilation of the surrounding tissues eventually occurs. Microscopically, extensive necrosis with inflammatory cell infiltration and new capillary formation can be seen. The disease is generally fatal. Chemotherapy with involved field external radiation is beneficial.[38]

Wegener's Granulomatosis

Wegener's granuomatosis is a systemic autoimmune granulomatous disease. Pathogenesis includes abnormal immune reaction, secondary to a non-specific infection, hypersensitivity reaction to unknown antigen and possible hereditary predisposition It consists of necrotizing granulomatous inflammation involving upper respiratory tract, Necrotizing glomerulonephritis and Systemic vasculitis involving small to medium sized vessels.[28] Malaise, fever, night sweats, oral ulcerations are common symptoms. Strawberry gingivitis, Gingival ulcerations, enlargements, bone loss, tooth mobility, palatal ulcerations, spontaneous exfoliation of teeth and failure of tooth socket to heal are the oral manifestations. Histopathologically, pseudo epithelial hyperplasia, subepithelial abscess and non-specific granulomatous lesion with scattered giant cells are seen. Clinical, laboratory and radiographic investigations must be done to rule out any underlying local or systemic disease. Oral foci of infection should be identified and treated. Intralesional corticosteroids or systemic corticosteroids are used for treatment.[39]

Melkersson-Rosenthal Syndrome

Orofacial granulomatosis is an entity that describes oral lesions with noncaseating granulomas. The Melkersson-Rosenthal syndrome has the elements of orofacial granulomatosis. It is a rare disorder and has an unknown etiology. It is characterized by a triad of orofacial swelling (recurrent), facial paralysis (relapsing), and fissured tongue. 'Meischer chelitis' is the term used when granulomatous changes are confined to the lips (monosymptomatic form of Melkerson Rosenthal Syndrome). Episodic with swelling and enlargement of one or both lips is seen. Firm edema of the face may be present. Soft, firm or nodular lesion or fissured, reddish-brown, swollen, nonpruritic lips may be present.[40] Facial Palsy is intermittent at first, but later becomes permanent. It can be Unilateral or bilateral, partial or complete. Microscopically, epithelioid non-caseous granulomas, edema and perivascular lymphocytic infiltrates are seen.[41] Treatment options include intralesional corticosteroids, nonsteroidal anti-inflammatory agents, mast cell stabilizers, clofazimine, tetracycline, surgery and radiation.

Conclusion

Granulomatous diseases of the oro-facial region can be caused by diverse immunologic, idiopathic, neoplastic, infectious, and fungal processes. They can cause a wide range of signs and symptoms in the head and neck region and also throughout the body. It poses a diagnostic dilemma for the clinician. It is therefore, essential to find the etiology and to recognize the granulomatous pattern in a biopsy specimen. Special stains like Ziehl-Neelsen stain, Gomori's Methenamine silver, PAS, Fite Faraco should be done whenever required. The correlation of histopathology with polymerase chain reaction (PCR) serological tests and culture, would further aid in recognizing the specific etiology. Thus, a thorough history and a complete physical examination, along with radiological, histological and laboratory evaluation may be required for the correct identification of the granulomatous disease for its specific treatment.

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