Granulomatous Diseases of Nose

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Abstract

A focal compact leukocytic, especially mononuclear cells collection termed is known as granuloma. Any scenario resulting in building up of granuloma is called granulomatous inflammation/disease. In case of nasal cavities, it is a chronic inflammatory condition, histologically having characteristic chronic inflammatory cells aggregation. These can be of varied nature, i.e. infectious and non-infectious. The definitive diagnosis in such cases needs to rely on visual examination using endoscope, radiography, histopathology and microbiological assays. Clinical management includes medicinal as well as surgical interventions. Clinical management can be successful and time effective if the diagnosis is definite. Due to varying etiologies of granulomatous diseases in the nose a thorough knowledge of the etiologies to reach the definitive diagnosis after differentiation the clinically similar cases yet having different clinical remedies is crucial. Researchers have published many articles on these conditions, however, this chapter will cumulatively highlight different aspects of granulomatous nasal diseases. This chapter will help the medical students, clinicians and researchers to quickly review the aforementioned clinical condition in a single document.

Keywords: Granuloma, Nasal cavity, Mononuclear cells, Chronic inflammation, Endoscopy, Radiology, Microbiology

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Introduction

An inflammatory condition of the nasal mucosa known as Rhinitis is highly prevalent, with significant morbidities posing a substantial burden economically to the health care departments all over the world. The reason that it has been considered just a source of annoyance has become underestimated and neglected. The etiologies of rhinopathies are enormous and are overlapping and the failure can be attributed to the lack of clear and standardized diagnostic guidelines. It is very important to have a well-developed classification of the subtypes in order to precise the remedial therapies. The clinical and research communities are appreciating the efforts of cytologists in improving the differential diagnosis of rhinitis and defining distinction in the nasal pathologies (Gelardi et al., 2023). On etiological grounds, rhinitis can be non-allergic or allergic (Agnihotri & McGrath, 2019). Despite a heavy morbidity rate and prevalence, it is still merely considered a source of annoyance in the population around the globe (Papadopoulos & Guibas, 2016). Many such thinkings have been hindering the development of well-designed classification system for the differential diagnosis of various nasal pathologies over time and there are a number of independent classifications guidelines which overlap and make the diagnosis and management very challenging in this modern world as well. However, cytologists have played a crucial role in differentiating these pathologies and newer types have been identified and already mixed-up pathologies have been redefined in a much better way (Gelardi et al., 2022). This chapter will focus on granulomatous diseases of nose. Different etiologies and their differential diagnostic features will be discussed in the succeeding paragraphs. This manuscript will definitely help the modern-day clinician in better understanding of the various granulomatous conditions of nose in human health practices.

Granuloma

Granuloma is named as 'granul' circular granular structural contour and 'oma" a tumorous condition. But it is actually a collective compact mass made by macrophages which is a chronic type of inflammatory condition (Mohan, 2018). Granuloma refers to round mass compactly formed by cells of inflammation, especially the mononuclear cells (James, 2000). Any scenario resulting in formation such structures is known to be a granulomatous condition (Nwawka et al., 2014). A granuloma is the product of a complex interactions and mechanisms involving the foreign invader, drugs, chemical mediators, other endogenous or exogenous irritant components, a long-lasting circulation of antigen in body, immunological activities especially associated with macrophages, Type-I helper T-cells activity, Plasma (B-cells) cellular response, circulating immunoglobulins and other extensive mediators of biochemical nature (James, 2000). On histological grounds, there are accumulations of mononuclear leukocytes, which can also be termed as modified macrophages having an immediate outer layer of lymphocytes and some giant cells. The purpose of these shields around the invader is to protect the human body of continuous inflammatory stimulations from the invader, which can otherwise result in local destructive inflammation of the tissue (Nwawka et al., 2014). These broadly classified as foreign body granulomas and immune granulomas (Kameswaran, 1999; Molina-Ruiz & Requena, 2015; Pagán & Ramakrishnan, 2018). These glaucomatous conditions are common in head and neck, specifically in nose and associated sinuses (Hughes & Drake-Lee, 2001). Many scenarios like

autoimmune, neoplasms, traumatic conditions, inflammation and drug abuse can result in nasal and sinuses granulomas (Fuchs & Tanner, 2009). Among the granulomas of infective origin there are bacteria, i.e., mycobacterial infections including tubercular and non-tubercular, leprosy, scleroma, actinomycosis and sypholos. There can be fungal sources, i.e. blastomycosis, histoplasmosusm, paracoccidioidomycosis and cryptococcosis. Besides, some non-infective cases are there, like sarcoidosis and Wegener's granulomas (Watkinson & Clarke, 2018).

Nasal Granulomas

Trauma, drug abuse (cocaine), neoplasms along with infective and inflammatory diseases account for the occurrence of granulomatous nasal lesions. All these have different management protocols, that's why it is highly recommended that the clinician should be able to differentiate the conditions effectively and then progress towards surgical or medicinal treatment. E.g. the fungal rhinoscleroma, rhinitis and sinusitis need extensive medicinal and surgical treatments, the wegener's granulomatosis has shown negligible response to etanercept but other alternatives like methotrexate and leflunomide the members of prolonged cyclophosphamide are showing some promising effects. Similarly, the drug abused, especially the cocaine associated destructive lesions of the midline aspect, have a significantly higher anti-neutrophilic cytoplasmic antibodies, and is decreasing the sensitivity of the test in differentiating it from wegener's granulamtosis (Fuchs & Tanner, 2009).

Classification of Nasal Granulomatosis

The nasal granulomatous lesions are broadly classified as; infective, inflammatory/allergic and neoplastic (Shah et al., 2017). This differentiation in some literature is a bit different, but it looks like these broad divisions have been further unveiled and more types have been given.

Infective Granulomatous Diseases

Bacterial

The bacterial of diseases having granulamtous nasal lesions includes actinomycosis (*Actinomyces israeli*), leprosy (*Mycobacterium leprae*), tuberculosis (*Mycobacterium tuberculosis*), syphilis (*Treponema pallidum*) and rhinoscleroma (*Klebsiella rhinoscleromatis*) (Richtsmeier & Johns, 1982; Holliday Jr et al., 2022).

Fungal and Protozoal

The fungal and protozoal etiologies of diseases resulting in granulomatous lesions of nose include; *Aspergillus* (*A. fumigatus, A. flavis* and *A. niger*), zygomycosis (*Conidiobolus coronatus, Rhizophus oryae*), *Dermatacietes* (*D. curvularia, D. alternaria, D. bipolris*), rhinosporidiosis (*Rhinosporidium seeberi*), bastomycosis (*Blastomycetes dermatitidis* and *Cryptococcus neoformans*), sporotrichosis (*Sporotrichum schenkii*), histoplasmosis (*Histoplasma capsulatum*), coccidioidimycosis (*Coccidioidi immitis*) and the protozoal leishmaniasis *(Leishmania donovani*) (Andrews et al., 1996; Lessa et al., 2007).

Inflammatory and Allergic

The inflammatory reasons for granulomatous lesions of the nose will account, wegener's granulatomosis, churg-strauss syndrome, cholesterol granuloma, sarcoidosis and eosinophilic granulomas (Ferguson, 2000; Ellis & Keith, 2006; Noor & Knox, 2007; Cannady et al., 2009).

Neoplastic

The most common and lethal neoplastic granulomatous condition of the nose is the one caused by T cell lymphoma, also termed as lethal midline granuloma (Mallya et al., 2013).

Few of the above-mentioned causations will be discussed below.

Sarcoidosis

It is multiple systems involving granulomatous condition. Around 6% of the cases complain about the nasal obstruction and that is usually as a result of inferior turbinate swelling along with facial pain. The mucosae in such cases usually are dry, crusted, granular (strawberry skin) usually non-ulcerated. Microscopically, these are revealed as CD4þ T lymphocytes associated non-caseating and giant cells gramulomatous lesions (Mallya et al., 2013). According to some reports, the condition is attributed to peanuts dusts, pine pollen, zirconium and beryllium exposure. In such patients, the Type 4 delayed type hypersensitivity is usally seen depressed while the cell mediated immunity works normally. The gama globulins are usually high. The reason behind persistence of granuloma seems to be a failure of suppressor regulatory mechanism (Greaves et al., 2020). The diagnostic options include, Nickerson-kveim test, high levels of angiotensin converting enzymes, chest radiograph, biopsy of nasal mucosa, nasal radiograph to see rarefaction or osteolysis (Ungprasert et al., 2019). Clinical management usually relies on nasal steroids spray, oral steroids e.g. methotrexate or hydroxychloroquine, nasal saline douching for crust removal while there is contraindication to surgical intervention (Drent et al., 2021).

Wegener's Granuloma

Wegner's granuloma is an inflammatory condition involving both the respiratory and renal system. In wegner's granuloma, there are evidence of necrotizing vasculitis in small to medium vessels in effected organ systems. The common sites include lungs, triad of airway and renal system. There is no age limitation to this condition. The definite etiology is still not known. However, it is thought to be associated with inflammation associated with a hypersensitivity reaction against some unknown stimuli, e.g. bacteria, and the resultant vasculitis is thus

attributed to immune complexes. The anti-neutrophil cytoplasmic antibody (cANCA) is usually found elevated in such cases (Csernok & Gross, 2013). As this is involving multiple organ systems that is why the clinical features are usually disproportional. Patients complain of general malaise, fever and ill thriftiness. As the disease is of a lethal nature, the patients usually die of renal failure in a span of around 6 months. Besides nasal septal disruption, nasal obstruction, epistaxis, collapse of nasal bridge and facial pain can be evident in such patients. This can also accompany the ocular tissue and add symptoms like conjunctivitis, dacryocystitis, etc. The oral mucosa can show granular lesions of hyperplastic nature on gums and interdental spaces, tooth loosening, failure of dental cavities to heal, and ulcerative stomatitis. The otological aspects include AOM, facial nerve paralysis, effusive otitis media with middle year filled with necrotizing granulation mass and conductive or sensorineural hearing loss and thus these needs to be asked in history and be observed keenly in the clinical examination (Comarmond & Cacoub, 2014). The diagnostic options in case of wegener's granuloma relays on cANCA test, elevated ESR, CRP, RFTs, Biopsy, CT-imaging along with a history of previous surgery with bone destruction followed by reformation can be diagnostic feature (Erickson & Hwang, 2007). The managements usually based on steroids, cytotoxic drugs like azathioprine, cyclophosphamide, mycophenolate mofetil. These are helpful only before the initiation of the renal damage (Comarmond & Cacoub, 2014).

Churg Strauss Syndrome

Churg strauss syndrome is a systemic vasculitic condition with evident bronchial asthma. On examination and cytology, there is obvious eosinophilic granulomatous lesion. The vasculitis can be small to medium size and the clinical picture shows nasal crusting, polyposis and septal disruption. The condition can be successfully managed with oral steroids (Greco et al., 2015).

Eosinophilic Granuloma

This condition may also be considered a manifestation of histiocytosis x. Which involves Langrenus cells associated clonal proliferation with heterogeneous inflammatory cellular infliltrates of eosinophils, lymphocytes, histiocytes, neutrophils, plasma cells? It can involve organs but predominantly bones, especially the frontal, temporal and parietal bones. Studies show that this condition commonly happens in the first three decades of life. It is clinically characterized by painful swelling of affected bones and cervical adenopathies, gum ulceration, tooth loosening, mandibular lesions. If there is involvement of temporal bone, there will be stimulation of mastoiditis of acute nature. Cranial radiograph is usually of value in diagnosis of this condition, which reveals punched out bony lesion over jaw with radiolucent areas around teeth. The skull shows beveled margins due to angular destruction (Angelini et al., 2017). The condition can be locally managed by curettage and irradiation, dosing with steroids and etoposide for over a 12 months' course. Recently trends also include alpha interferon and bone marrow transplantation (Emmi et al., 2023).

Cholesterol Granuloma

This condition is usually associated with trauma and hemorrhage. Granulomatous reactions are believed to be directed against cholesterol particles. The incidence is higher in males without age distinction. The condition usually involves the maxillary and frontal sinuses disturbing the facial looks and proptosis can also be evident. The bone appears to have cystic expansion. On radio-imaging, the sinuses appear opaque. The biopsy finding usually reveals giant cells granuloma. The only management method is surgical, i.e. curettage of the lesion (Kuperan et al., 2012).

Lethal Midline Granuloma

This condition is also known by synonyms like T-cell lymphoma and Stewart granuloma. This results in widespread destruction of the facial middle aspects. Some studies have reported predominance in males without any age discrimination. Some researchers have implicated EB viral infection in the cases. In prodromal stage, which may last for years with characteristic clinical features of rhinorrhea and nasal obstruction. In the active period there are evidents of necrosis, purulent nasal discharge, crusting and tissue loss. This also accompanies progressive destruction of the facial contour, upper lips palate, orbit and base of the skull. There may or may not be a fever along with the aforementioned conditions but usually because of secondary infectious complications. In terminal stage there is bleeding, visible disruption of the face and death may occur (Trindade et al., 2020). Diagnosis is usually challenging in such cases because of the dispersed atypical cellular population in necrotic areas. The biopsy may be preferably taken from beneath the crust. Immunohistochemistry is a groundbreaking tool. There is usually an absence of granuloma or giant cells. An association with thrombosis and necrosis is always there (Ribeiro et al., 2012). The clinical management previously was through a low dose radiotherapy. In recent times, the protocols include a full course of radiotherapy over the entire affected area. If there is disseminated lymphoma that is a problem, in such and worst cases, chemotherapy is highly recommended (Trindade et al., 2020).

Nasal Tuberculosis

It is a rare condition which exclusively always associated with primary TB patients. The nasal features include ulcers, polypoidal and nodular lesions. The ulcerative lesions are more typically seen in the anterior portion of nasal septum and inferior nasal turbinate. Another condition the lupus vulgaris which is an indolent infection of the skin and mucosa of the nasal cavity. The common cause ruled out is nose picking. The clinical features include, a profuse nasal discharge and obstruction, an odorless crust, nasal bleeding, ulceration of nasal mucosa followed by fibrosis and stenosis of nares. Extensive spread may lead to atrophic rhinitis. Another finding may be jellying nodules, which is an early lesion of reddish-brown color at mucocutaneous junction and as a result there is destruction of the cartilaginous part of the nasal septum (Khan et al., 2017). In the case of lupus, there is extensive scarring of the vestibules extending up to face skin with nodular appearance. The lesions usually blanch on palpation. Microbiology and biopsy is always diagnostic. The associated complications include Atrophic rhinitis, lupus of face, dacryocystitis and very rarely development of epithelioma (Couppoussamy et al., 2024).

Nasal Leprosy

It is also called as 'tuberculoid leprosy, which is a skin lesion extending to nasal vestibule however, the nasal mucosa is not involved. The spontaneous cutaneous anesthesia is a usual feature. Another term is 'lepromatous leprosy' where there is a highly infectious nasal discharge followed by encrustation. The discharge is of serosanguinous nature however the nodular thickening of the nasal mucosa is the earliest feature in this case. The nodules are seen in the anterior and inferior turbinate. There is collapse of the anterior bridge with destruction of the nasal spine is a usual feature. The destruction is both bony and cartilaginous structures. Radiological views are usually concluded in diagnostic investigations. Another term is borderline leprosy, which refers to a condition with poor immune tolerance. The skin around the nose and eyes is usually affected while nasal mucosa is free of any lesion (Samra et al., 2024).

Nasal Syphilis

The nasal syphilis can be primary, secondary or tertiary. In case of primary syphilis, the lesions are seen in the nasal vestibule. The lesions are non-painful, hard ulcerated papule. These lesions are associated with enlarged robbery and non-tender lymphadenopathy. The resolution is usually spontaneous, which may take around 6 weeks. In secondary syphilis, also termed as the infective stage, there is a catarrhal rhinitis with crusting and fissuring of nasal vestibule and a non-tendered enlarged lymph node (Patton et al., 2014). In the tertiary syphilis the nasal septum, particularly the bony portion, is involved. Septal perforation in the bony portion is usually seen in this case (Prasad & Mokamati, 2016). The symptoms include headaches which are usually intense at night or colder times of the day, obstruction of the nose associated with swelling, diminished smell sensation, bony portion of the nasal septum is perforated, tenderness over the bridge of the nose is characteristic. The nasal swelling usually does not respond to nasal decongestant. Secondary atrophic rhinitis and unilateral presentation is also characteristically evident (Prasad & Mokamati, 2016).

Congenital Syphilis

The congenital syphilis is also termed as snuffles. This usually initiates during the first 3rd week of life. The early manifestations are serous rhinorrhea followed by purulent discharge. This is also accompanied by excoriation of the nasal vestibule and upper lip (Sankaran et al., 2023).

Rhinoscleroma

Rhinoscleroma is granulomatous conditions arising at the nose and extending to the nasopharynx, larynx, trachea and lower respiratory tract however, the latter can be very rarely involved. There is age related discrimination. The reported etiology is *Klebsiella rhinoscleromatis*. Pathophysiology explains infiltration of the granulomatous nature in submucosa. The cells of granuloma include eosinophils, lymphocytes, plasma cells and scattered mikuliz cells (foam cells). The foam cells are identified as centrally nucleated and vacuolated cytoplasm containing bacilli (Umphress & Raparia, 2018). The clinical course runs from the atrophic to cicatrizing stage. In atrophic stage, the changes initially appears in the mucosa of nose, which clinically resembles atrophic rhinitis. Next stage is the granulation or nodular stage, where there are non-ulcerative nodular lesions which are initially bluish red and rubbery in consistency and later become paler and harder. The last stage is termed as the cicatrizing stage which has characteristic features of adhesion and scaring. This results in stenosis of the nasal cavity and disturbance of the nasal anatomy. The nose structure changes and is named after a classic presentation of 'Tapir's nose'. At this stage, it can extend to nasopharynx, maxillary sinuses and lower air tract (Gaafar et al., 2011). Levin test, which is a type of complement fixation test (CFT) a reaction of subject's serum with known suspension of *Klebsiella rhinoscleromatis* is assessed. In positive cases, the antibodies titter in the subject is significantly high. Another tool is tissue biopsy and histopathological observations (Ahmed et al., 2015).

Rhinosporidiosis

Rhinosporidiosis is a chronic granulomatous disease clinically characterized by the development of nasal polyps and hyperplastic nasal mucosae. The hypothetical etiology is *Rhinosporidium seeberi*. Its appearance has been termed as strawberry like mulberry mass. The disease is observed to be prevalent in India and Srilanka and is attributed to taking a bath in ponds which are also used by cattle bathing. The mode of spread reported is through some theories, i.e. direct (Demellow's theory of direct transmission), autoincoulation theory, hematogenous route, lymphatic spread the latter is a rare route of transmission (Arseculeratne, 2002). The nasal features of rhinosporidiosis are nasal lesions with polyploid reddish and granular, which can be multiple, friable, and pedunculated. The surface is usually studded with whitish dots known as sporangia. The lesions are hypervascular and bleed on touching the lesion. The lesions are covered by mucoid secretions. The lesions are exclusively limited to nasal mucosa (Bandopadhyay et al., 2015). The treatment option solely relies on surgical intervention followed by therapy with Dapsone @100mg/day for a period of 06 months (Janardhanan et al., 2016).

Conclusion

Any scenario resulting in building up of granuloma is called granulomatous inflammation/disease. In case of nasal cavity, it is a chronic inflammatory condition, histologically having characteristic chronic inflammatory cells aggregation. These can be of varied nature, i.e. infectious and non-infectious. The definitive diagnosis in such cases needs to rely on visual examination using endoscope, radiography, histopathology and microbiological assays. In many cases, the complication and worsening of the cases is exclusively as a result of clinical errors in diagnostic of the granulomatous nasal condition. However, with the advancement of the diagnostic investigation tools and gadgets, these hurdles have now been very narrowed. After this comprehensive discussion on the subject matter, it is very obvious that clinicians should take the diagnostic aid as and when required to safeguard the patients in a peaceful way and when possible, give them the required relief at the earliest.

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