Research article

Clinicopathological spectrum of cervicofacial actinomycosis

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ABSTRACT

Introduction and Aim: Cervicofacial actinomycosis is a rare chronic granulomatous disease caused by *Actinomyces* and is the commonest subtype of actinomycosis. Due to the similarities in clinical presentation, cervicofacial actinomycosis is almost always suspected as malignancy or tuberculosis. Histopathological evaluation is crucial in diagnosis and management of these cases. The aim of the study was to evaluate the clinicopathological features of cervicofacial actinomycosis in the biopsy specimens.

Methodology: This is a retrospective cross sectional observational study of 17 years duration. All cases of cervicofacial actinomycosis diagnosed on biopsy specimens were analyzed. Clinical presentations and histomorphological features were evaluated on hematoxylin and eosin-stained slides with confirmation of organism on special stains.

Results: Out of 36 diagnosed cases of actinomycosis during the study period, we evaluated 16 cases (44.4%) of cervicofacial actinomycosis. Mean age of presentation was 38 years. Male to female ratio was 1:0.9. The anatomical sites of eight (50%) were in the oral cavity, six (37.5%) on the face and two (12.5%) in the neck. Two cases (12.5%) had sinuses discharging sulphur granules. Six cases (37.5%) were clinically suspected as malignant and among them two cases (12.5%) also had differential diagnosis of tuberculosis. All cases on histomorphology showed sulphur granules consisting of basophilic filamentous bacterial colonies with *Splendore Hoeppli* phenomenon and mixed inflammation. On special stains, the bacterial colonies were Gram, PAS and GMS stain positive, and acid fast negative.

Conclusion: Cervicofacial actinomycosis are uncommon. Their presentation can mimic carcinoma or tuberculosis. Consistent histomorphological features can direct towards identification of organisms by special stains for confirmation of diagnosis.

Keywords: Cervicofacial; actinomycosis; sulphur granules; sinuses; granulomatous.

INTRODUCTION

Actinomycosis is a chronic granulomatous infectious disease caused by an endogenous infectious agent *Actinomyces israelii* (1). These are anaerobic/ microaerophilic, non-sporulating, nonmotile gram-positive bacteria that have a filamentous and branching structure (2,3). These are found in the oral cavity, colon, and genitourinary tract as commensals. Break in mucocutaneous barrier causes invasion of these organism into the underlying structures, thus causing disease in humans. Based on anatomical sites involved they are categorized as cervicofacial, pelvic, thoracic, and abdominal actinomycosis in the order of prevalence (3).

Cervicofacial actinomycosis often follows dental caries and tooth extraction, dental implants, periodontal disease, or infections associated with tooth eruption (1,2,4). The disease may present as chronic, slowly progressive, nontender indurated swelling and may progress to become abscess. As these organisms care less for the anatomical barriers such as fascial planes and lymphatic drainage, they invade directly into the underlying structures. As a result, multiple fistulae and discharging sinuses can also be the clinical presentation(1,2). Clinically, it is a great mimicker of malignant neoplasms as well as granulomatous diseases (2). Cervicofacial actinomycosis being the commonest subtype, in this study we analyzed 16 cases diagnosed on the biopsy specimens.

MATERIALS AND METHODS

This was a retrospective cross sectional observation study conducted in the department of pathology, at tertiary care hospital, in southern India. All the cases reported as actinomycosis involving the cervicofacial region on histopathological examination of biopsy specimens were included. The study period was from January 2005 to December 2022. The clinical details of the patients provided on the request form were recorded. Hematoxylin and eosin-stained slides were evaluated to study the morphological features of the disease and identify the Actinomyces bacterial colonies. Associated host immune response patterns were also evaluated. Bacterial colonies were evaluated using special stains such as acid-fast stain, Grocott's methenamine silver (GMS), Periodic Acid Schiff (PAS) and Gram stains. Descriptive statistical analysis was done.

RESULTS

Over 17 years of study duration, a total of 36 actinomycosis cases involving various sites were reported, out of which 16 (44.4%) cases are localized to the cervicofacial region. Our study population has individuals as young as 11 years to as old as 80 years of age and with the mean age of 38 years. There were nine males and seven females with male to female ratio of 1:0.9. Out of 16 cases, most involved was oral cavity comprising eight (50%) cases followed by six (37.5%) on face and two (12.5%) cases in the neck region (Table 1). Clinically, four cases involving oral cavity, two cases involving neck, with a total of six (50%) were suspected as malignancy. Two cases (16.6%) involving the neck also had a differential of tuberculosis. Biopsy specimens were available in all the cases. Hematoxylin and eosin-stained paraffin block sections had filamentous bacterial colonies and *Splendore Hoeppli* phenomenon within the tissue of all the cases (Fig.1).

Table 1: Clinical summary of the lesions

S. No.	Site	Clinical presentation	Clinical diagnosis/suspicion	Number of cases	Total (in %)
1	Oral cavity	Adenotonsillar hypertrophy	Chronic Adenotonsillitis	4	8 (50%)
		Upper molar swelling	Malignancy	2	
		Gingivobuccal swelling	Malignancy	1	
		Induration at the lateral border of tongue	Malignancy	1	
2	Face	Swelling over mandible	Inflammatory process	1	6 (37.5%)
		Radiolucent lesion in the maxillary sinus	Inflammatory process	1	
		Abscess over temporal region	Post traumatic abscess	1	
		Nasal cavity mass	Benign neoplasm	1	
		Swelling with discharging sinus over eyebrow	Actinomycosis	1	
		Left eye canaliculitis with discharge	Actinomycosis	1	
3	Neck	Submandibular swelling	Tuberculosis/ Metastatic lesion	2	2 (12.5%)

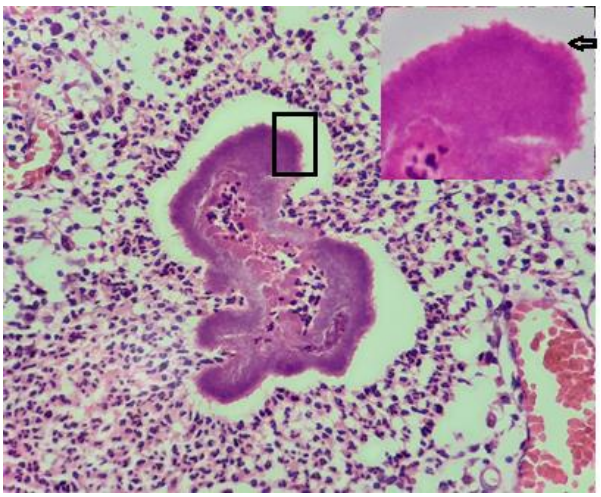

Fig.1: Sulphur granules consisting of basophilic bacterial colonies with peripheral eosinophilia *Splendore Hoeppli* phenomenon (inset, arrow) surrounded by dense mixed inflammatory cells. (Hematoxylin and eosin stain, 40X magnification)

Table 2: Summary of histomorphological findings in cervicofacial actinomycosis

Sl. No.	Histomorphological findings	Total number of cases (in percentage)
1.	Bacterial colonies	16 (100%)
2.	Lymphocytes	16 (100%)
3.	Plasma cells	16 (100%)
4.	Histiocytes	14 (87%)
5.	Neutrophils	10 (62.%)
6.	Eosinophils	2 (12.5%)
7.	Fibrosis	4 (25%)

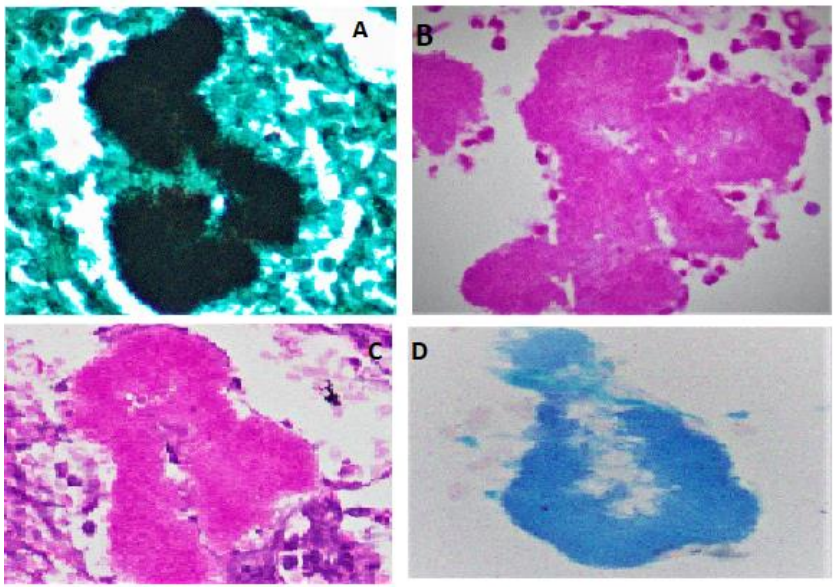

Fig. 2: A. Filamentous bacterial colonies as seen in GMS stain. B, C. Gram stain and PAS stain positive. D. AFB negative (40 X magnification).

Coexisting granulomatous inflammation consisting of lymphoplasmacytic infiltrate mixed with neutrophils, histiocytes, occasionally eosinophils was also seen. Few cases showed fibrosis (Table 2). The bacterial colonies were PAS, Gram and GMS stain positive and acid fast negative in all the cases (Fig. 2).

DISCUSSION

Actinomycosis is a rare slowly progressive granulomatous infectious disease. It can affect individuals of all age groups. Based on the limited available data in the literature, the age group of 20-60 years are most affected, with peak incidence at 40-50 years. (2,5) In our study, 37.5% (6 cases) were beyond 40 years of age. One of the studies has documented male to female ratio of 2.4:1 (7,8). We witnessed almost equal distribution among genders in our study population.

Cervicofacial actinomycosis accounts for 50% cases of actinomycosis (1,2,4). In our study, cervicofacial site was the most common site involved comprising in 44.4% of the cases, thus correlating with the frequency reported in other studies. Actinomyces are normal oral commensals and become pathogenic on providing microaerophilic environment following mucosal damage attributed to dental procedures, maxillofacial surgical interventions, and poor oral hygiene (1-5). Incidentally more than one third of the cases will seldom be associated with this precedent event(2). The most common site involved in our study was oral cavity (50%), however, due to the disadvantage of limited clinical data, oral health status of the subjects could not be assessed.

Actinomycosis is of clinical concern as they pose clinical challenges by mimicking primary or metastatic carcinomas, abscesses, cysts, tuberculosis, and other infectious diseases (6, 7). We were provided with clinical diagnosis of neoplasm in six cases (37.5%), of which five (31.2%) were suspected as malignant and one (6.2%) as benign lesion. Among them, histopathological examination was asked to rule out tuberculosis in two cases (12.5%).

We had four (25%) pediatric cases of adenotonsillar hypertrophy with nasal obstruction, snoring and mouth breathing. Actinomyces are normally present in tonsillar crypts, where the mechanical mucosal barrier is at the weakest, hence tonsils are a potential site for colonization and entry point by these organisms (9,10). Osborne *et al.*, are of the opinion that organisms like *Staphylococcus aureus* and beta hemolytic *Streptococcus* have complementary effects to form an anaerobic environment for the Actinomycetes to proliferate (11). Pransky *et al.*, also hypothesized that lymphoid hyperplasia observed in adeno- tonsillectomy specimens probably have some

kind of association with Actinomyces colonization (12).

As the organisms gain access to the underlying soft tissue, fistulas and sinuses are formed, discharging visible sulphur granules which, microscopically, are the bacterial colonies (1-5). Sulphur granules was observed on clinical examination in two of our cases (12.5%), one of which had canaliculitis and the other hand swelling with sinuses over the left eyebrow. Presence of sulphur granules are highly suggestive of actinomycosis (2), nevertheless, other grain forming infectious agents such as nocardiosis, chromomycosis and botryomycosis needs to be ruled out (13).

Due to the inherent nature of the organisms to invade directly, tissue surrounding in and around the mandible and the mandible itself is the most common site of cervicofacial actinomycosis (2,14). In our study two cases (12.5%) involving the submandibular region were clinically diagnosed as metastatic carcinoma/ tuberculosis. One case had mandibular soft tissue swelling that was suspected as an inflammatory process.

One of our cases had presented as nasal mass and one as a radiolucent lesion(3x6cm) with bone necrosis in maxillary sinus. It is exceptionally rare for cervicofacial actinomycosis to involve nasal cavity and paranasal sinuses as there are only few case reports in the literature (15-18).

Our study had a case of canaliculitis associated with discharging sulphur granules in an 80-year-old lady. Explosive sneezing or blowing of nose could be one of the reasons that bacteria reach the lacrimal canal. Also, direct inoculation can happen upon habitual touching and cleaning the eyes with hands that are contaminated by saliva (19).

Actinomycosis is clinically, a diagnostic challenge. Although isolation of the organism in the culture is the definitive way to diagnose, only in less than 50% of the cases organisms are isolated. Culture test may be wearying, as a strict anaerobic environment is required to transport the sample. Also, it is a slow growing organism, and needs examination of the culture up to 3 weeks (16). While sulphur granules are highly suggestive of the diagnosis, their presence in the sample does not always lead to growth of Actinomyces upon culture(8,20). A history of prior antibiotic therapy may also interfere with the culture outcome (20).

Microscopic examination of the sulphur granules, on hematoxylin and eosin stain will show bacterial colonies in the form of basophilic masses with radiating filaments that have an eosinophilic inert terminal club representing *Splendore Hoeppli* phenomenon (20). All the cases in our study group were diagnosed based on these characteristic features of the bacterial colonies. It's not uncommon to miss these organisms on histopathology sections as they barely manage to be present in less than one percent of the total tissue of a given lesion. Hence, necessity of repeated biopsies for the diagnosis might put both the clinician and the patient at unease (21).

Along with bacterial colonies, host immune responses in the form of subacute or chronic inflammation consisting of neutrophils, lymphocytes, plasma cells and histiocytes may be seen. With the chronicity of the disease a dense fibrosis may also be noted (5,7). We observed consistently chronic inflammatory cells in all the cases. Depending on the disease process fibrosis and acute inflammation with suppuration was also identified (Table 2).

Sulphur granules are also characteristic of other infectious diseases (5, 20). Modified acid-fast stain, GMS, PAS and gram stains are helpful in differentiating these from other organisms. The advantage of histopathology lies in that it allows to run a series of special stains on the available small biopsy tissue. Nocardia is a closest differential to be considered and unlike Actinomyces, these species stain positive with acid fast stains. Also, the filaments of Nocardia appear separate whereas those of Actinomyces are cemented together. Most importantly, *Splendore Hoeppli* is absent in nocardiosis (20). Sulphur granules in botryomycosis shows bacterial colonies with *Splendore Hoeppli* phenomenon. Nevertheless, when stained with gram and GMS stain there will be absent filamentous bacterial colonies. Fungal hyphae that are GMS positive and gram stain negative will be seen in chromomycosis along with pigmented fungal elements as observed on hematoxylin and eosin stain (7,20).

In recent times, a molecular amplification of 16S rRNA and sequencing the product has become an ancillary test to identify the organism (1,2,7). Even though Actinomyces responds very well to broad spectrum antibiotics, missing the diagnosis at its early stage may worsen the disease, leading to deterioration or even relapse (2). Due to its pathological nature of direct invasion, rarely these organisms may reach the central nervous system (2%) through facial sinuses, orbits, ear canal or by perineural invasion, resulting in worse prognosis (7, 21, 22).

CONCLUSION

Actinomycosis commonly presents as a mass forming lesion with least clinical suspicion. Identification of filamentous bacterial colonies with inflammatory reaction is the most consistent histopathological feature for diagnosis of actinomycosis. Lymphocytes and neutrophils are the predominant inflammatory cells seen. This study stresses the need to consider actinomycosis in clinical and histopathological evaluation of patients presenting with mass forming lesions in sites that are common for the disease. Actinomycosis is an uncommon but not rare disease.

CONFLICT OF INTEREST

Authors have no conflicts of interest.

REFERENCES

1. Kononen, E., Wade, W.G. Actinomyces and related organisms in human infections. Clin Microbiol Rev. 2015; 28(2):419-442.
2. Brain, T. Fisher. Actinomyces. In: Robert M. Kliegman, Joseph W. St Geme, Nathan J. Blum, Samir S. Shah, Robert C. Tasker and Karen M. Wilson, editors. Nelson textbook of pediatrics, 21st ed. Pennsylvania: Elsevier; 2020.1465-1467.
3. Chandler, F.W., Watts, J.C. Fungal Diseases. In: Damjanov, I, James L editors. Anderson's pathology, Volume I, 10th ed. Noida: Elsevier; 2009.975-976.
4. Feder, H.M. Jr. Actinomycosis manifests as an acute painless lump of the jaw. Pediatrics. 1990; 85(5):858.
5. Stajer A, Ibrahim B, Gajdacs M, Urban E, Barath Z. Diagnosis and management of cervicofacial actinomycosis: lessons from two distinct clinical cases. Antibiotics. 2020; 9(4):139.
6. Volpi, L., Ferreli, F., Bignami, M., Pistochini, A., Meloni, F., Karligkiotis, A. A rare localization of actinomycosis mimicking ulcerative malignancy. Case Rep Otolaryngol. 2013; 2013:323210.
7. Mallmann, L., Boff, R., Koth. V., Salum. F., Figueiredo, M A., Cherubini, K. Cervicofacial actinomycosis: Important considerations on a mimicking disease. Rev. Estomatol. Hered. 2020; 30:126–133.
8. Pulverer, G., Schutt-Gerowitt, H., Schaal, K.P. Human cervicofacial actinomycosis: microbiological data for 1997 cases. Clin Infect Dis. 2003; 15; 37(4):490-497.
9. Walter, J.B., Gurndy, M.C. Body's defence against infection. In: Walter, Hamilton, Israels, editors. Principles of pathology for dental students, 5th ed. Churchill Livingstone, London; 1992.70.
10. Bhargava, D., Bhusnurmath, B., Sundaram, K.R., Raman, R., Al Okbi, H. M., Al Abri, R., *et al.*, Tonsillar actinomycosis: a clinicopathological study. Acta Tropica 2001; 80:163-168.
11. Osborne, J.E., Blair, R.L., Christmas, H.E., Mckenzie, H. Actinomycosis of the nasopharynx: a complication of nasal surgery. J. Laryngol. Otol. 1998; 102: 639-640.
12. Pransky, S.M., Feldman, J.I., Kearns, D.B., Seid, A.B., Billman, G.F. Actinomycosis in obstructive tonsillar hypertrophy and recurrent tonsillitis. Arch. Otolaryngol. Head Neck Surgery. 1991; 117, 883-885.
13. Smego, R.A. Jr, Foglia, G. Actinomycosis. Clin Infect Dis. 1998; 26:1255-61; 62-63.
14. Lerner, P.I. The lumpy jaw. Cervicofacial actinomycosis. Infect Dis Clin North Am. 1988; 2(1):203-220.
15. Sakuma, Y., Yamashita, Y., Shiono, O., Oridate, N. Actinomycosis arising from the nasal cavity, with rare fatal progression. BMJ Case Rep. 2016; 2016:bcr2015213747.
16. Park, K.S., Lee, D.H., Lim, S.C. Actinomycosis of the nasal cavity. Braz J Otorhinolaryngol. 2021; 88: S128-132.
17. Kingdom, T.T., Tami, T.A. Actinomycosis of the nasal septum in a patient infected with the human immunodeficiency virus. Otolaryngol Head Neck Surg. 1994; 111:130-133.
18. Lee, D.H., Yoon, T.M., Lee, J.K., Lim, S.C. Nasal septum actinomycosis mimicking mucocele. J Craniofac Surg. 2020; 31:e147-e149.
19. Pine, L., Hardin, H., Turner, L., Roberts, S.S. Actinomycotic lacrimal canaliculitis. A report of two cases with a review of the characteristics which identify the causal organism. *Actinomyces israelii*. Am J Ophthalmol. 1960; 49:1278-1288.
20. Guarner, J., Anaerobic Bacterial Infections. In: Gary W. Procop, Bobbi S. Pritt,editors. Pathology of infectious diseases. Saunders, Pennsylvania: Elsevier. 2015;341-343.
21. Burns, B.V., Al-Ayoubi, A., Ray, J., Schofield, J.B., Shotton, J.C. Actinomycosis of the posterior triangle: a case report and review of the literature. J Laryngol Otol. 1997; 111(11):1082-1085.
22. Lubomski, M., Dalgliesh, J., Lee, K., Damodaran, O., McKew, G., Reddel, S. Actinomyces cavernous sinus infection: a case and systematic literature review. Pract Neurol. 2018; 18(5):373-377.