Actinomycosis in histopathology - Review of literature

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Abstract

Actinomycosis is a chronic, suppurative granulomatous inflammation caused by Actinomyces israelii which is a gram positive organism that is a normal commensal in humans. Multiple clinical features of actinomycosis have been described, as various anatomical sites can be affected. It most commonly affects the head and neck (50%). In any site, actinomycosis frequently mimics malignancy, tuberculosis or nocardiosis. Physicians must be aware of clinical presentations but also that actinomycosis mimicking malignancy. In most cases, diagnosis is often possible after surgical exploration. Following the confirmation of diagnosis, antimicrobial therapy with high doses of Penicillin G or Amoxicillin is required. This article is intended to review the clinical presentations, histopathology and complications of actinomycosis in various sites of the body.

Key words

Actinomycosis, Actinomyces, Sulphur granules, Histopathology, Filamentous bacteria.

Introduction

Actinomyces is a filamentous gram positive bacteria of genus Actinobacteria. Actinomyces species are facultatively anaerobic (except A.meyeri and A.israelii which are obligate anaerobes), and they may form endospores, while individual bacteria are rod shaped hyphae [1].
through wounds. As with other opportunistic infections, people with immunodeficiency are at higher risk. In their branching filament formation, they bear similarities to Nocardia [3]. 

*Actinomyces* species are fastidious and not easy to culture.

Actinomycosis was once a common and ultimately fatal disease [4]. Now, the incidence is decreased since the introduction of antimicrobial agents. As patients with advanced disease are rare now a days, actinomycosis has become a more diagnostic challenge [5].

Actinobacteria present in the gums and the most common cause of infection in dental procedures and oral abscesses. Many *Actinomyces* species are opportunistic pathogens of humans, particularly in the oral cavity [6]. In rare cases, these bacteria can cause actinomycosis, a disease characterized by the formation of abscesses in the mouth, lungs or gastro intestinal tract [7]. Actinomycosis is most frequently caused by *A. israelii*, which may also cause endocarditis. Actinomycosis a subacute to chronic bacterial infection, characterized by contiguous spread, suppurative and granulomatous inflammation and formation of multiple abscesses and sinus tracts that may discharge “Sulphur granules” [8]. The genus typically cause oral-cervicofacial disease characterized by a painless “lumpy jaw”. Lymphadenopathy is uncommon in this disease. Another form of actinomycosis is thoracic disease which is often misdiagnosed as neoplasm, as it forms a mass that extends to the chest wall. It arises from aspiration of organism from oropharynx. Symptoms include chest pain, fever and weight loss. Abdominal disease is another form of actinomycosis. This can lead to a sinus tract that drains to the abdominal wall or the perianal area. Symptoms include fever, abdominal pain and weight loss [9]. Pelvic actinomycosis is a rare but proven complication of use of intra uterine devices. In extreme cases, pelvic abscess may develop. Treatment of pelvic actinomycosis involves removal of the device and antibiotic treatment [10].

Actinomycosis can be considered when a patient has chronic progression of disease across tissue planes that is mass like at times, sinus tract development that may heal and recur and refractory infection after a typical course of antibiotics [9].

**Etiology**

More than 30 species of actinomyces have been described. *Actinomyces israelii* is the most prevalent species isolated in human infections and is found in most clinical forms of actinomycosis [11-15]. *Actinomyces viscoses* and *Actinomyces meyeri* are also reported in typical actinomycosis, although they are less common [15, 16] and *Actinomyces meyeri* is considered to have a great propensity for dissemination. Some species, including *A. naeslundii, A. odontolyticus, A. gerencseriae* (formerly *A. israelii* serotype 2), *A. nevii, A. turicensis* and *Actinomyces radingae* have been associated with particular clinical syndromes [17-19]. Thus *Actinomyces israelii* and *Actinomyces gerencseriae* are responsible for about 70% of orocervicofacial infections [14]. Hematogenous dissemination of actinomycosis is extremely rare and has mainly been associated with *Actinomyces meyeri, Actinomyces odontolyticus, Actinomyces israelii* [20].

Most of the actinomyces species are present in polymicrobial flora. Therefore, Actinomyces are often isolated with other normal commensals such as *Aggregatibacter actinomycetemcomitans, Ekinellacarrodens, Capnocytophaga, Fusobacteria, Bacteroids, Staphylococci, Streptococci or Enterobacteriaceae*, depending on the site of infection [21]. As such it is difficult to diagnose or isolate *Actinomyces* unless when the culture is pure and associated with neutrophils. On the other hand, *Actinomyces* infections could be polymicrobial and associated with other bacteria, named “companion microbes”, which contribute to initiation and development of infections by inhibiting host defenses or reducing oxygen tension [13]. The multimicrobial nature of actinomycosis is well described in human cervicofacial actinomycosis [21-23].
The *Actinomycetes* are ordinarily of low pathogenicity. The causative organisms, *Actinomyces* are non-motile, non-spore forming, non-acid fast, and gram positive pleomorphic, anaerobic to micro aerophilic filamentous bacterial rods [8].

A gram stain of the specimen is more sensitive than culture, especially when the patient had received antibiotics. Except *Actinomyces meyeri*, which is small and non-branching, all the other species are branching filamentous rods.

Growth of the *Actinomyces* is slow. It appears within at least 5 days and may take up to 15 to 20 days. Thus incubation of at least 10 days is required before conclusion of a negative culture. Most *Actinomyces* species are facultative anaerobes but some relevant species (such as *Actinomyces meyeri*) are strictly anaerobic, so cultures must be incubated in an anaerobic atmosphere. *Actinomyces* can be cultured on chocolate blood agar media at 37°C other enriched media can be used for *Actinomyces* isolation: brain heart infusion broth and Brucella blood agar with hemin and vitamin K1. The use of semi selective media (such as phenyl ethyl alcohol or mupirocin metronidazole blood agar) may increase isolation rates by inhibiting overgrowth of concomitant organisms [24].

*Actinomyces* can affect people of all ages, but the majority of cases are reported in young to middle aged adults (aged 20-50 years). No racial predilection exists, for unknown reasons, men are affected more commonly than women, with the exception of pelvic actinomycosis [25]. The reported male to female ratio is 3:1 [5].

Actinomycosis occurs worldwide with likely higher prevalence rates in areas with low socioeconomic status and poor dental hygiene.

**History**

Human actinomycosis was first described in the medical literature in 1857, although a similar disease in cattle had been described in 1826. Prolingh first reported the yellow granules in jaw masses of cattle in 1877. In 1878, Israel described the first human case. In 1879, Hartz first observed the microscopic appearance of granules of actinomyces infection [4].

**Incidence**

Actinomycosis has been called as “the most misdiagnosed disease” even by experienced clinicians and listed as a “rare disease” by the office of rare diseases (ORD) of the National Institute of Health (NIH). During the 1970s, the reported annual incidence in the Cleveland area of the United States was 1 case per 300000 [5]. Improved dental hygiene and wide spread use of antibiotics for various infections probably have contributed to the declining incidence of this disease [4]. The disease occurs worldwide and is mostly seen in tropical regions such as Asia, Africa, Central and South America. Infection commonly occurs in the foot of bare footed persons. Primary skin infections may develop after human bites.

**Pathology**

*Actinomyces* are prominent along normal flora of the oral cavity but less prominent in the lower gastrointestinal tract and female genital tract. As these microorganisms are not virulent, they require a break in the integrity of the mucous membranes and presence of devitalized tissue to invade deeper body structures and cause human illness. Furthermore, Actinomycosis generally a polymicrobial infection, with isolates numbering as many as 5-10 bacterial species [5]. Establishment of human infection may require the presence of such companion bacteria, which participate in the production of infection by elaborating a toxin or enzyme or by inhibiting host defenses. They may also be responsible for the early manifestation of the infection and for the treatment failures. Once the infection is established, the host produce an intense inflammatory response (suppurative, granulomatous) and fibrosis may develop subsequently. Infection typically spreads contiguously frequently ignoring tissue planes and invading surrounding tissues or organs. Ultimately, the infection produces draining sinus
tracts. Hematologous dissemination [26], to distant organs may occur in any stage of infection, whereas lymphatic dissemination is unusual.

The inflammatory reaction in actinomycosis is suppurative, with formation of abscesses that contain one or more granules (organized aggregates of filaments), 30-3000 micrometer in diameter that are bordered by eosinophilic club like Splendore-Hoeppli material.

Gram staining of pus and pathology of infected tissue is of great interest for the diagnosis of Actinomyces, as it is usually more sensitive than culture, which remains sterile in more than 50% of cases. Once Actinomyces species have invaded the tissues, they develop a chronic granulomatous inflammation characterized by the formation of tiny clumps, called Sulphur granules because of their yellow colour. These formation 0.1 to 1mm in diameter, composed of internal tangle of filaments about 1micrometer in diameter and a rosette of peripheral clubs, are stabilized by a protein-polysaccharide complex, which is supposed to provide a resistance mechanism to host defenses by inhibiting phagocytosis [27-30].

Histopathology examination discloses one to three Sulphur granules in about 75% of cases, described as basophilic masses with eosinophilic terminal clubs on staining with hematoxylin and eosin [31]. Typical microscopic findings include necrosis and yellowish Sulphur granules and filamentous gram positive fungal like pathogens. Yellowish Sulphur granules are constituted by conglomeration of bacteria trapped in biofilm [32]. Histologically chronic granulomas with fibrous stroma and cyst like spaces containing characteristic granules may be seen. Abscess like granulomas seen under epidermis which rupture forming sinuses. Gomori methenamine silver staining is also useful for demonstrating the filaments, which are not stained by the Hematoxylin and Eosin, Periodic Acid Schiff and Gridly stains.

These findings are highly suggestive of the diagnosis, but are not specific, as they can be encountered in other pathogenic conditions such as nocardiosis and chronic cervicofacial fungal infections. Gram staining can additionally show gram positive filamentous branching bacteria at the periphery of the granule that is highly suggestive of Actinomycosis.

Species identification requires culture or immunofluorescence staining because, in tissue sections, the agents of actinomycosis cannot be distinguished from each other. Both gram positive and gram negative bacilli and cocci may be found in close association with actinomycyes filaments within a granule, but it is generally believed that these bacteria are secondary pathogens.

Depending upon the site involved, pathology of actinomycosis can be discussed under the following headings.

1. Cervicofacial actinomycosis
It is the most frequent clinical form of actinomycosis and “lumpy jaw syndrome”, which is associated with odontogenic infection, the most common clinical manifestation representing approximately 60% of all reported cases [11-13, 33]. Actinomyces species could also be responsible for maxillary osteomyelitis in patients with odontogenic maxillary sinusitis [34]. The disease is often a sequel to dental caries, periodontal disease, or injury to the oral mucosa, such as tooth extraction. Actinomyces israelii and Actinomyces gerencseriae comprise about 70% of cases, but many other species have been described, such as Actinomyces meyeri, A.odontolyticus, A. naeslundii, A. georgiae, A. pyogenes or A. viscosus [14]. Actinomyces are commensals of the human oropharynx and are particularly prevalent within gingival crevices, tonsillar crypts, periodontal pockets and dental plaques as well as on caries teeth. Consequently, Actinomyces is mainly considered as an endogenous infection that is triggered by a mucosal lesion in patients with poor oral hygiene. This form of actinomycosis is in the
initial stages is characterized by soft tissue swelling of the perimandibular area, as the localized lesion enlarges, abscesses form, direct spread to the adjacent tissues occurs, along with the development of fistulas (sinus tracts) that discharge purulent material containing yellow (i.e. Sulphur) granules. If untreated, the infection may extend into the mandible, paranasal sinuses, orbit, cranial bones, brain, lungs, digestive tract, skin and other bones.

The predisposing factors include poor oral hygiene (dental caries, gingivitis, infection in erupting secondary teeth) and oral mucosa trauma (dental extraction, gingival trauma, local tissue damage caused by neoplastic condition or irradiation, cervicofacial surgery). Other predisposing factors include male sex, diabetes mellitus, immunosuppression, alcoholism and malnutrition [5, 11-13, 21, 27, 35]. Actinomycosis like other granulomatous infections like leprosy, tertiary syphilis, tuberculosis, rhino scleroderma, naso-oral blastomycosis, leishmania, histoplasmosis, coccidiomycosis and diphtheria perforate the palate [36].

Actinomyces species are considered to be involved in the pathogenesis of Bisphosphonate associated Osteonecrosis of the Jaw (BONJ). Most patients with osteoporosis receive bisphosphonate therapy, concomitant use of corticosteroids and mucosal disruption. The later may facilitate Actinomyces colonization and invasion of the jaw, as Actinomyces species have been detected in biofilm in bone samples of patients with BONJ [37, 38].

Cervicofacial actinomycosis involves mandible (50% of cases, cheek (15%), chin (15%), and submaxillary ramus and angle (10%). More rarely, the mandibular joint could be involved. In addition to odontogenic origin, other locations of primary infections are tongue, sinuses, middle ear, lacrimal pathway and thyroid gland [39-42]. In the literature actinomycosis was found to be associated with malignancy of several sites like submandibular gland, larynx, oral cavity and many other sites.

2. Respiratory tract actinomycosis:
It includes pulmonary, bronchial and laryngeal actinomycosis. Pulmonary actinomycosis is the third most common type of actinomycosis after that occurring in cervicofacial and abdominopelvic locations. Thoracic actinomycosis accounts for 15-20% of cases. In children, pulmonary involvement is uncommon [43]. The peak incidence is reported to be in the fourth and fifth decades of life [44, 45]. Males are more often affected than women, with a 3:1 ratio [31]. Pulmonary actinomycosis results mainly from aspiration of oropharyngeal or gastrointestinal secretions [44]. Consequently individuals with poor oral hygiene, pre-existing dental disease and alcoholism have an increased risk for developing pulmonary actinomycosis [27, 46]. Otherwise patients with chronic lung disease such as emphysema, chronic bronchitis and bronchiectasis and patients with tuberculosis are at increased risk. Human immune deficiency virus infection, steroid use, Infliximab treatment, lung and renal transplantation, and acute leukemia during chemotherapy have also been described as risk factors [13, 47, 48].

At early stages, there will be focal consolidation of lung which can be surrounded by pulmonary nodules with no physical symptoms. This leads to the formation of a peripheral mass with or without cavitation that invade the adjacent tissue [49, 50]. At this stage, pulmonary actinomycosis is usually characterized by fibrotic lesion with slow contiguous spread passing through the anatomical barriers [27]. The mass is often confused with malignancy.

A direct or indirect extension from cervicofacial infection to thorax may lead to pulmonary actinomycosis. Conversely pulmonary actinomycosis could be associated with extra pulmonary spread, from the lungs to the pleura, pericardium, and mediastinum and chest wall with fistula formation of sinuses that discharge Sulphur granules [48]. Finally haematogenous
dissemination with pulmonary location has been observed in patients with disseminated actinomycosis [12, 27]. Pulmonary actinomycosis can also be detected in children without any risk factors for the disease and the most common presentation is the chest wall mass [49].

Bronchial actinomycosis is rare. It may occur after disruption of the mucosal barrier, especially in patients with endobronchial stent or with a bronchial foreign body aspiration (for example, of a fish bone) [13, 50, 51].

Concerning laryngeal actinomycosis, various different forms have been described. Vocal cord actinomycosis may mimic primary carcinoma or papilloma, whereas in patients with past history of laryngeal carcinoma, and radiotherapy. Actinomycosis may mimic laryngeal cancer relapse, as it may present as an ulcerative lesion, most often without abscess or sinus tract [52, 53].

3. Extra facial bone and joint actinomycosis:
Although cervicofacial actinomycosis is the most frequent form of actinomycosis with bone involvement, Actinomyces species could also be involved in extra facial bone and joint infection. Various clinical forms of extra facial bone and joint actinomycosis have been described;
A. Hematogenous spread of localized actinomycosis.
B. Contiguous spread of pulmonary actinomycosis to the spine.
C. Polymicrobial bone and joint infection following bone explosion, especially in patients with paraplegia and osteomyelitis of the ischial tuberosity [11-13].

Few cases have been reported in the literature. Concerning hematogenous spread of localized actinomycosis, Brown etc. all reported a case of hematogenous infection of total hip arthroplasty 9 months after a non-invasive dental procedure with Actinomyces species in intra operative specimen cultures [54]. Zamenetbal reported a case of chronic hematogenous infection due to Actinomyces species of prosthetic joint in an intravenous drug user 55. Concerning y contiguous spread of pulmonary Actinomycosis to the spine [56], Tritan Ferry, et al. reported a case of contiguous spread to the spine, with thoracic spondylitis of the T3 vertebral body, associated with anterior paravertebral abscess. They also reported a case of polymicrobial bone and joint infection following bone exposition.

Most patients with extra facial bone and joint Actinomycosis have insidious onset of the disease and signs and symptoms are usually similar to those of chronic bone and joint infection and develop symptoms many months after the suspected bacteremia [55].

4. Genitourinary tract Actinomycosis
It is the second most frequent clinical form of Actinomycosis. The main clinical feature of genitourinary tract Actinomycosis is pelvic actin actinomycosis in women using an intrauterine device [56-59]. However, other clinical presentations have been described, such as primary bladder Actinomycosis and testicular Actinomycosis [60]. The prevalence of Papanicolaou smears positive for Actinomycosis organisms in women who use IUCDs is approximately 7% [61].

Actinomyces israelii is one of the most common species involved in pelvic Actinomycosis. Colonization of the female genital tract by Actinomyces species is greatly promoted by the use of an IUD [62, 63]. Moreover, IUDs have atraumatized effect on endometrium, by causing erosion, which may facilitate Actinomycosis invasion. The most common change associated with IUD is focal or extensive chronic endometritis which may be accompanied by necrosis and squamous metaplasia. IUD associated infection is infrequent, but is clearly associated with the duration of IUD use, hence it is recommended that an IUD be replaced every 5years [62, 63]. There are no data comparing copper, hormonal, or inert IUDs in terms of the risk of Actinomycosis. During IUD associated
Actinomycosis, abscess formation is frequently observed in genital tract, and creates dense adhesions with contiguous structures such as small bowel, promoting extensive fibrosis, fistulas and peritonitis [57-59]. On occasion, the inflammation spreads through the fallopian tubes to produce PID and sometimes tubo-ovarian abscess.

The symptoms of patients with pelvic IUD associated Actinomycosis may mimic the symptoms of gynaecological malignant tumors or uterine myoma or adenomyosis by presenting as genital mass without fever [57-59]. Symptoms could be lower abdominal pain, constipation and or vaginal discharge. The duration of symptoms is usually 2 months. Fever is not observed, unless complication like peritonitis occurs.

The organisms can be detected in microscopic sections or Cytology preparation, but care should be exercised in distinguishing them from pseudo actinomycotic radiate granules; the latter lack central branching filaments and diphtheroid forms. Actinomycosis can produce granulomatous inflammation in fallopian tubes and also granulomatous oophoritis particularly common after the introduction of IUD.

Actinomycosis of the cervix also occurs, but it needs to be distinguished from the more common pseudoactinomycotic radiate granules that may form around microorganisms or biologically inert substances.

A pelvic mass of about 6-7 CMS with cystic areas on CT scan, a tubo-ovarian abscess strongly suggests pelvic Actinomycosis, and similar features may also suggest malignant tumors. Lymphadenopathy is associated in 50% of cases [57-59].

The pathogenesis of primary bladder Actinomycosis is unclear, but could be due to cryptic location and usually mimics bladder carcinoma. The lesion may invade adjacent organs such as uterus and sigmoid colon. Primary bladder Actinomycosis can mimic bladder carcinoma as it is associated with macroscopic hematuria and thickening of the bladder wall [60-62]. The diagnosis of primary bladder Actinomycosis of crucial importance by guided biopsy, as it may avoid large surgical resection for suspected carcinoma [60].

5. Digestive tract Actinomycosis

Actinomycetes species are saprophytic organisms of the mouth and digestive tract. Actinomyces israelii is one of the most common species involved in abdominal actinomycosis. As with IUD associated Actinomycosis, a mucosal trauma causing erosion may facilitate Actinomycosis infection and infection. Digestive tract Actinomycosis associated Actinomycosis infection in other locations, may also mimic malignancy.

Esophageal Actinomycosis is infrequent, with only around 20 cases described in the literature. Patients with esophageal Actinomycosis are usually immunosuppressed by malignancy, HIV, or solid transplant. Most patients present with ulceration and a few had perforation, an abscess and sinus tract Actinomycosis of larynx is extremely rare; only a handful of cases have been reported.

Appendix, caecum and colon are the most common abdominal sites of Actinomycosis, which can occur is to years after gastrointestinal mucosal disruption, and for which previous surgery such as for appendicitis or colonic diverticulitis with perforation are predisposing factors [11-13]. Abdominal wall involvement with fistula may complicate abdominal Actinomycosis.

Actinomycosis of the liver, the biliary tract and the pancreas have also been described [64, 65]. Liver involvement mimic malignancy or present as an abscess could be associated with digestive tract disease such as colonic diverticular disease. Pancreatic Actinomycosis has been described in patients with pancreatic stents [64].
Actinomycosis may also anal fistulas in addition to tuberculosis, Crohn's disease and ulcerative colitis. Anal fistula is an abnormal tract having an internal opening within the anal canal, usually at the dentate line. The fistulous tract may lead to the skin or it may end blindly in perianal soft tissues. The lining of the fistula is made of granulation tissue, although epithelium may eventually grow at either end of tract. Most cases of anal fistulas are caused by an inter-sphincteric abscess originating in the anal canal and have non-specific microscopic appearance.

Signs and symptoms vary with the location of involvement. Patients with ulcerative involvement of esophageal have dysphagia, patients with appendix, caecum and colon involvement have abdominal pain with palpable mass, and patients with liver and biliary tract Actinomycosis have right upper quadrant pain and icterus [64, 65].

6. Central nervous system Actinomycosis
Actinomycosis species are mainly involved in brain abscess, but meningitis, meningoencephalitis, epidural abscess and subdural empyema have also been described. The CNS involvement occurs hematogenously from the lung or contiguously from the cervicofacial Actinomycosis or following a penetrating head injury. CNS actinomycosis usually polymicrobial [66-68].

7. Cutaneous Actinomycosis
Primary skin and soft tissue Actinomycosis is poorly described. Skin disruption may facilitate invasion of Actinomyces species. Most patients may present with an abscess or cold mass or nodular lesions with fistulas that need to be differentiated from chronic inflammatory skin disease, cutaneous mycobacterial infection and sporotrichosis [69, 70].

Clinically Actinomycosis can present as tumors mass and may be misdiagnosed as malignancy especially in cases of Actinomycosis oral cavity. Similar cases are reported in literature in which Actinomycosis mimic not only primary malignancy but sometimes even metastasis [71, 72]. In breast also Actinomycosis can cause necrotizing granulomatous masses and multiple sinus tracts.

Complications
Osteomyelitis of the mandible, ribs, and vertebrae, CNS disease including brain abscess, chronic meningitis, actinomycosis, crania, epidural infection, hepatic actinomycosis, renal actinomycosis, endocarditis [73], pericarditis [74], pneumonia (community acquired or nosocomial) [61], lung abscesses [61], bronchiectasis [61], empyema thoracis [74] etc. It also complicates other operations and situations like hip prosthesis infection [75], septic arthritis [76], endodontic infection [77], IUD infection [78], post-operative viscous endophthalmitis [79] etc. Opportunistic Actinomycosis infection has been reported in osteoradionecrosis [80] in patients having head and neck cancer. Disseminated Actinomycosis [81] by Actinomyces meyeri and Actinobacillus actinomycetemcomitans has also been reported.

Conclusion
Actinomycosis is a rare chronic disease caused by Actinomyces species. Physicians have to be aware of typical clinical presentations such as cervicofacial Actinomycosis following dental focus of infection, pelvic Actinomycosis in women with an IUD and pulmonary Actinomycosis in smokers with poor dental hygiene. They must also be aware that Actinomycosis may mimic malignancy or sometimes associated with malignancy. So, one should know the correct clinical presentations, morphological features and histopathological findings to arrive at correct diagnosis and better management of patient. Bacterial cultures and histopathology are the cornerstones of diagnosis and require attention to prevent misdiagnosis. Typical microscopic findings include necrosis with yellowish Sulphur granules and filamentous team positive fungal like pathogen. Specific preventative measures like reduction is alcohol abuse, dental hygiene may limit the occurrence
of pulmonary, cervicofacial and CNS Actinomycosis. IUDs should be changed every 5 years in women, to limit the occurrence of pelvic Actinomycosis.

References


