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Original Article

Clinical manifestations of actinomycosis in Southern Taiwan

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Background and Purpose: Actinomycosis is an uncommon and frequently misdiagnosed infection that may present as an acute or indolent process. Even when clinical suspicion is high, the disease is commonly confused with other chronic inflammatory diseases and malignancy. An early diagnosis helps the clinician in deciding treatment and can avoid physical morbidity such as unwarranted surgery.

Methods: We retrospectively evaluated the histopathology and selected clinical information on all cases of actinomycosis that occurred at Kaohsiung Veterans General Hospital in Taiwan from 1993 to 2005. Data on the demographic characteristics, predisposing conditions, clinical presentations, diagnosis and treatment were analyzed.

Results: A total 36 cases of actinomycosis were identified and evaluated. The mean age of patients was 52.14 ± 13.28 years, and the male-to-female ratio was 1:1.1. Only three types of actinomycosis were found in this study: cervicofacial, at an incidence of 31%; thoracic (33%); and pelvic (36%). The clinical manifestations depended upon the region of infection; the most frequent presentations of cervicofacial, thoracic and pelvic actinomycosis were cutaneous soft tissue swelling with drainage sinus formation (55%), hemotypsis (75%) and abnormal vaginal spotting (54%), respectively. The most common initial laboratory abnormalities were normochromic anemia (69%) and leukocytosis (25%). While most patients had no history of a foreign body, all pelvic actinomycotic patients had a history of intrauterine device use. Nineteen patients (53%) had no comorbid conditions and 11 patients (31%) had malignancy. Most patients were initially diagnosed as malignancy (56%). All patients with actinomycosis were diagnosed by histopathologic findings. Twenty two patients (61%) were treated by surgery combined with antibiotics, 11 patients (31%) by surgery only and 3 patients (8%) by antibiotics only. No recurrence or mortality occurred.

Conclusions: Actinomycosis should be included in the differential diagnosis when patients present with chronic drainage sinus, chronic hemoptysis and abnormal vaginal spotting with use of intrauterine devices.

Key words: *Actinomyces*; Actinomycosis; Chronic disease; Risk factors

Introduction

Actinomycosis is usually a chronic, suppurative disease characterized by the formation of multiple abscesses, fibrous tissue, abundant granulation tissue, and drainage sinuses. The disease occurs in healthy individuals and immunocompromised patients [1], and should not be considered an opportunistic infection. The three common clinical manifestations are cervicofacial, thoracic and pelvic actinomycosis. There are no specific laboratory tests available for the diagnosis of human actinomycosis. A definitive diagnosis can be made by isolating *Actinomyces* species in microbiological cultures of clinical specimens or by histopathological examination of sections of tissue. The lesions of actinomycosis can usually spread extensively to adjacent structures and organs [2]. Therefore, early diagnosis or high suspicion will prevent the morbidity associated with delayed or missed diagnosis, even though actinomycosis is a rare disease with a very low mortality rate [3]. This retrospective study describes the clinical characteristics of 36 patients with actinomycosis.

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Methods

We retrospectively reviewed the medical, microbiological and histopathological records in Kaohsiung Veterans General Hospital from January 1993 through December 2005, of all patients diagnosed with actinomycosis with pathologic evidence of: (1) an outer zone of fibrous tissue and central foci of acute inflammation with polymorphonuclear cells; and (2) an amorphic central area surrounded with a rosette of filamentous organisms that often show branching (Fig. 1).

Statistical analysis

Kruskal-Wallis test was used to analyze the differences in clinical symptoms, underlying diseases, and laboratory findings among three types of actinomycosis. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (Version 12.0; SPSS Chicago, IL, USA) software package. A p value <0.05 was considered statistically significant.

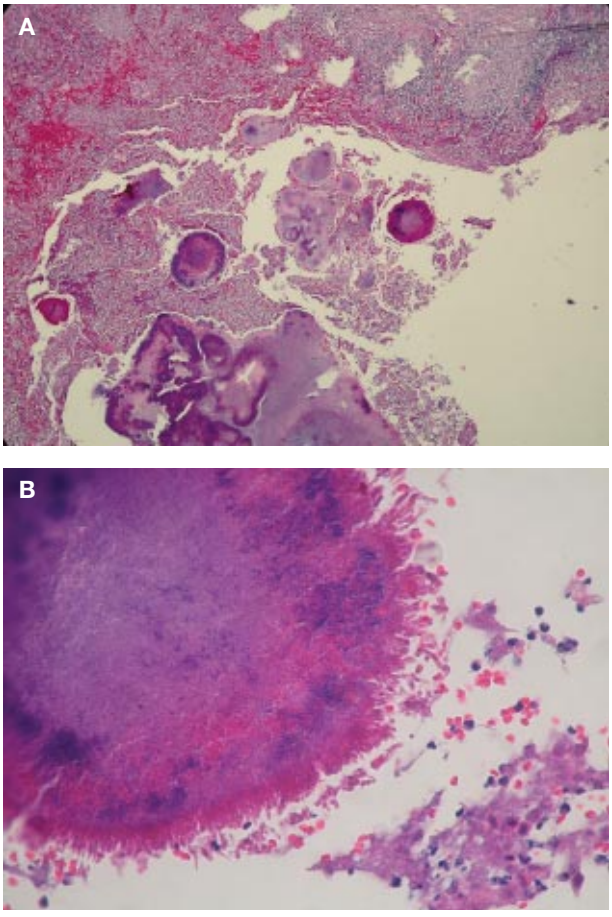

Fig. 1. Lung biopsy disclosed sulfur granules and *Actinomyces* colonies dispersed in lung tissue. (A) Hematoxylin and eosin stain, × 100; and (B) hematoxylin and eosin stain, × 400.

Results

Demographic and clinical characteristics

There were 36 cases of actinomycosis diagnosed and treated at Kaohsiung Veterans General Hospital in Taiwan from 1993 to 2005. The departments in which these patients were initially evaluated included dental, chest medicine, gynecologic, ear-nose-throat and general surgery departments. There were 17 men (47%) and 19 women (53%), with a male-to-female ratio of 1:1.1, as shown in Table 1. The male-to-female ratio was about 3:1 in cervicofacial and thoracic actinomycosis, and all patients with pelvic actinomycosis were female. Patients with pelvic actinomycosis seemed to be more frequent than others. The predisposition of male and female patients to acquire the disease varied with age and appeared to be especially pronounced in female patients aged 40-60 years (Fig. 2). The median age was 50 years (range, 27-85 years).

Predisposing conditions

Pelvic actinomycosis cases were all associated with use of an intrauterine device (IUD) [100%], but there was no association with foreign body in cervicofacial and thoracic actinomycosis (Kruskal-Wallis test, p<0.05). Periodontitis was present more frequently in cervicofacial actinomycosis (Kruskal-Wallis test, p<0.05). Underlying malignancy was present in 5 (45%), 2 (17%), and 6 patients (46%) with cervicofacial, thoracic and pelvic actinomycosis, respectively. No underlying conditions were found in 5 (45%), 7 (58%), and 7 patients (54%) with cervicofacial, thoracic and pelvic actinomycosis, respectively.

Clinical and laboratory manifestations

The clinical and laboratory manifestations among patients with cervicofacial, thoracic and pelvic actinomycosis are shown in Table 2. In cervicofacial actinomycosis, the most frequent clinical manifestations were soft tissue swelling and sinus tract formation (Kruskal-Wallis test, p<0.05). The lesion sites of the 11 cases of cervicofacial actinomycosis were located over the mandible (n = 6), oral cavity (4) and neck (1). Hemoptysis, cough, chest pain and leukocytosis were frequently seen in thoracic actinomycosis (Kruskal-Wallis test, p<0.05). The lesion sites were located in right-middle lung (4, 33%), right-lower lung (3, 25%) and left-lower lung (5, 42%) on chest X-ray. Symptoms in pelvic actinomycosis were abnormal vaginal spotting, lower abdominal pain and menorrhagia (Kruskal-Wallis

Table 1. Demography, predisposing factors, diagnosis, treatment and outcome of 36 patients with actinomycosis in southern Taiwan from 1993 through 2005

Variable	No. of patients (%)			
	Cervicofacial (n = 11)	Thoracic (n = 12)	Pelvic (n = 13)	Total (n = 36)
Gender				
Male	8 (72)	9 (75)	0 (0)	17 (47)
Female	3 (28)	3 (25)	13 (100)	19 (53)
Age (years)				
Mean ± SD	57.09 ± 16.93	53.25 ± 13.31	46.92 ± 5.73	52.14 ± 13.28
Median	55	51.5	46	50
Range	27-85	37-81	39-59	27-85
Predisposing factors				
Foreign body				
Yes	0 (0)	0 (0)	13 (100)	13 (36)
No	11 (100)	12 (100)	0 (0)	23 (64)
Malignancy	5 (45)	2 (17)	6 (46)	13 (36)
Periodontitis	8 (73)	3 (25)	0 (0)	11 (31)
Abdominal surgery	0 (0)	0 (0)	0 (0)	0 (0)
Smoking	0 (0)	4 (33)	0 (0)	4 (11)
Pre-existing tuberculosis	0 (0)	1 (9)	0 (0)	1 (3)
No underlying conditions	5 (45)	7 (58)	7 (54)	19 (53)
Initial diagnosis				
Malignancy	9 (82)	8 (67)	3 (23)	20 (56)
Cellulitis	1 (9)	0 (0)	0 (0)	1 (3)
Epidermoid cyst	1 (9)	0 (0)	0 (0)	1 (3)
Pneumonia	0 (0)	4 (33)	0 (0)	4 (11)
Menorrhagia	0 (0)	0 (0)	7 (54)	7 (19)
Tubo-ovarian abscess	0 (0)	0 (0)	3 (23)	3 (8)
Diagnostic tool				
Microbiologic	0/1 (0)	0/7 (0)	0/5 (0)	0/13 (0)
Histopathologic	11 (100)	12 (100)	13 (100)	36 (100)
Treatment				
Antibiotics only	0 (0)	3 (25)	0 (0)	3 (8)
Surgery only	4 (36)	1 (8)	6 (46)	11 (31)
Antibiotics and surgery	7 (64)	8 (67)	7 (54)	22 (61)
Outcome				
Cure	11 (100)	12 (100)	13 (100)	36 (100)

Abbreviation: SD = standard deviation

test, $p<0.05$). Ovary (4, 31%), uterus (8, 62%) and vagina (1, 7%) were the lesion sites. Three cases were found incidentally due to general health examination. Normocytic anemia (69%) was the most obvious abnormal laboratory finding in all three forms of actinomycosis.

Diagnosis and treatment

Patients with cervicofacial, thoracic and pelvic actinomycosis were initially diagnosed as malignancy in 9 (82%), 8 (67%), and 3 patients (23%), respectively. Four cases (33%) initially presented as pneumonia in thoracic actinomycosis, and 7 cases (54%) as menorrhagia in pelvic actinomycosis. Diagnosis in all 36 cases was from histopathology via biopsy or surgery. The specimens of 13 cases were sent for aerobic and anaerobic culture, but no actinomyces were isolated. Surgical treatment was employed in 11 patients with cervicofacial (100%), 9 patients with thoracic (75%) and 13 with pelvic actinomycosis (100%). Thirty three patients received surgery and 3 cases were treated with antibiotics only without surgery. Fifteen patients received 4-6 months of treatment with intravenous penicillin and oral amoxicillin; 10 cases received preoperative and postoperative antibiotics with variable duration, ranging from 3 days to 21 days; 11 cases received surgery only without antibiotics. None of the patients had recurrence or had died at 6 months after treatment.

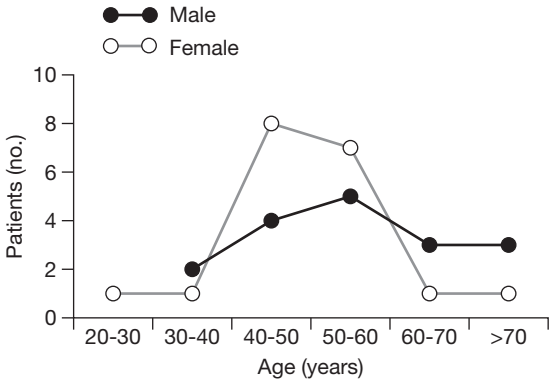

Fig. 2. Age distribution of male and female inpatients with actinomycosis.

Discussion

The causative organism of human actinomycosis was differentiated by Waksman and Henrici [4] in 1943. The annual incidence of actinomycosis in the Netherlands and Germany in the 1960s and in the Cleveland area in the 1970s was 1:100,000 and 1:300,000, respectively [5]. Members of *Actinomyces* are Gram-positive, nonspore-forming, predominantly anaerobic prokaryotic bacteria. Fourteen *Actinomyces* spp. have been identified and 6 can cause disease in humans, including *Actinomyces israelii, Actinomyces naeslundii, Actinomyces odontolyticus, Actinomyces viscosus, Actinomyces meyeri* and *Actinomyces gerencseriae*. *Actinomyces* are difficult to culture because they are fastidious bacteria and sensitive to most antibiotics. Even a single dose of an antibiotic before culture may inhibit the organism's growth [6,7]. All of the *Actinomyces*, except *A. viscosus*, are fastidious bacteria that require brain-heart-enriched agar media and grow best at 37°C in an atmosphere of 6-10% ambient carbon dioxide [8]. The differentiation of species is difficult and fluorescein-conjugated antibody typing is now available in some centers [8]. Wolff and Israel [9] postulated the endogenous infection theory on the basis of the observation that this microorganism was an anaerobe only in animals or humans and never in nature. The human pathogenic *Actinomyces* is part of the normal flora of the mouth, colon and female genital tract. The causative actinomycetes in primary lesions are always accompanied with other microorganisms from the mucosal flora. Therefore, actinomycosis is considered to be an endogenous, obligatorily synergistic mixed infection [10,11]. We isolated microorganisms other than *Actinomyces* in 5 of 13 cases in this study.

Due to its inability to penetrate mucosa, *Actinomyces* lacks virulence and has low potential to produce disease in the absence of tissue trauma. The first step in the development of actinomycosis is the disruption of the mucosal barrier, allowing invasion. A polymicrobial environment and tissue trauma are thus required for proliferation and clinical infection, since these concomitant synergistic flora destroy vascularized tissue

Table 2. Clinical and laboratory findings of 36 patients with actinomycosis in southern Taiwan from 1993 through 2005

Variable	No. of patients (%)		
	Cervicofacial (n = 11)	Thoracic (n = 12)	Pelvic (n = 13)
Clinical manifestations			
Fever	1 (9)	2 (17)	2 (15)
Drainage sinus tract	7 (64)		
Soft tissue swelling	11 (100)		
Cough		10 (83)	
Chest pain		5 (42)	
Hemoptysis		9 (75)	
Dyspnea		3 (25)	
Lower abdominal pain			4 (30)
Abnormal vaginal spotting			7 (54)
Menorrhagia			3 (23)
Vaginal discharge			2 (15)
Incidental finding	1 (9)	1 (8)	1 (8)
Laboratory findings			
Leukocytosis (WBC >10^4/mm^3)	0 (0)	7 (58)	2 (15)
Anemia (Hb <12 g/dL)	7 (64)	8 (67)	10 (77)
Thrombocytopenia (platelet <150 K/mm^3)	1 (9)	0 (0)	0 (0)

Abbreviations: WBC = white blood cells; Hb = hemoglobin

and create anaerobic-like conditions, supporting the growth of *Actinomyces* [11,12]. Poor oral hygiene, aspiration of oropharyngeal or gastrointestinal secretions into the respiratory tract and the presence of IUDs are also important risk factors for actinomycosis [13]. In our series, 8 among 11 cases (73%) of cervicofacial actinomycosis had poor oral hygiene and all cases of pelvic actinomycosis had a history of IUD usage; however, history of aspiration was not found among our patients with thoracic actinomycosis.

The clinical manifestations of actinomycosis include cervicofacial, thoracic and pelvic infection. Cervicofacial, thoracic and pelvic actinomycosis infections represent 60%, 15% and 20%, respectively, of all cases of actinomycosis [14]. Cervicofacial actinomycosis may take the form of acute, painful pyogenic abscesses or an indolent disease evolving into a painless indurated mass in the face or neck, often accompanied by draining sinus tracts that discharge sulfur granules [8]. This lesion is often located at the mandible or submandibular region and may extend to the underlying bone tissue, resulting in the development of osteomyelitis. Thoracic actinomycosis may involve the lungs, pleura, mediastinum, or chest wall and leads to the development of chronic pneumonia with or without pleural effusion [8]. The clinical presentations of thoracic actinomycosis often mimic that of tuberculosis or malignancy, with cough, low-grade fever, body weight loss and chest pain [15]. Previous studies of computed tomography findings of thoracic actinomycosis have emphasized extensive consolidation that extends to the pleura, mediastinum, and chest wall, with a tendency toward transfissural, transfascial extension [16,17].

In our study, only 1 among 12 cases initially mimicked adenocarcinoma of lung with extension through the diaphragm to the right lobe of the liver. Pelvic actinomycosis is usually insidious and easily confused with other inflammatory or malignant pelvic disorders. Nonspecific symptoms, such as lower abdominal pain, may persist for months or years. Endometrial actinomycosis with extension to the adjacent organs (e.g., the ovaries) is the usual form of actinomycosis that develops in association with an IUD [8].

Microbiologic identification is often difficult because the recovery rate in culture is less than 30%. In our study, aerobic and anaerobic pus culture was done in 13 (36%) of these 36 cases and none isolated *Actinomyces*. The reasons for negative results for *Actinomyces* may be inappropriate procedures at the bedside or in the operating room. Morphologically, *Actinomyces* are filamentous and the thin filaments may be V shape branching. Sulfur granules are macroscopic, yellowish grains of firm consistency that are visible on a gauze sponge. When stained with methylene blue, Gram's stain, periodic acid-Schiff, or silver methenamine, Gram-positive branching mycelia and filaments are visible. Granules may not always be present or may be few in number. One study found only 1 to 3 granules in 56% of specimens and none at all in 7 cases, which were confirmed by culture [18]. In our series, sulfur granule was visible in all pathologic specimens (100%).

The treatment of actinomycosis included antibiotics and surgery. For mild cervicofacial infections, a 2-month course of oral penicillin V or one of the tetracyclines is adequate [19]. For complicated forms, parenteral penicillin G, 10-20 million U/day should be administered for 4-6 weeks, followed by oral penicillin V, 2-4 g/day for 6-12 months [20]. In cervicofacial actinomycosis, the basic principles of surgical incision and debridement have been demonstrated to be curative in cases with acute and localized presentation. Surgical intervention alone can cure cases with limited infection by complete removal of the infection foci, and antibiotic therapy is unnecessary.

In conclusion, actinomycosis is a frequently misdiagnosed disease and this study from southern Taiwan suggests that clinicians should be alert to the possibility of actinomycosis if patients present with chronic drainage sinus, chronic hemoptysis and abnormal vaginal spotting with history of IUD usage.

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