International Journal of Infectious Diseases 29 (2014) 74–79

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Invasive actinomycosis: surrogate marker of a poor prognosis in immunocompromised patients

Isabelle Pierre [a], Virginie Zarrouk [a], Latifa Noussair [b], Jean-Michel Molina [c,d], Bruno Fantin [a,d,*]

[a] Service de Médecine Interne, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, 100 boulevard du général Leclerc, 92110 Clichy, France
[b] Service de Microbiologie, Hôpital Beaujon, Assistance Publique Hôpitaux de Paris, Clichy, France
[c] Service de Maladies Infectieuses et Tropicales, Hôpital Saint Louis, Assistance Publique Hôpitaux de Paris, Paris, France
[d] Université Paris-Diderot, Sorbonne Paris Cité, Paris, France

ARTICLE INFO

Article history:
Received 21 March 2014
Received in revised form 12 June 2014
Accepted 13 June 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Actinomyces sp
Immunosuppression
Beta-lactams
Surgery

SUMMARY

Objectives: Actinomycosis is a rare disease favored by disruption of the mucosal barrier. In order to investigate the impact of immunosuppression on outcome we analyzed the most severe cases observed in patients hospitalized in three tertiary care centers.

Methods: We reviewed all cases of proven invasive actinomycosis occurring over a 12-year period (1997 to 2009) in three teaching hospitals in the Paris area.

Results: Thirty-three patients (16 male) were identified as having an invasive actinomycosis requiring hospitalization. The diagnosis was made by microbiological identification in 26 patients, pathological examination in eight patients, and by both methods in one. Twenty patients (61%) were immunocompromised. Actinomycosis localization was abdominal or pelvic in 17 patients, thoracic in 11, cervicofacial in three, and neurological in two. Twenty patients (61%) underwent surgery. All strains were susceptible to amoxicillin. All patients were treated with a beta-lactam antibiotic, for a median length of 82 days. Twenty-eight patients (85%) were considered as cured. Overall mortality at hospital discharge was 21% (7/33). Mortality was higher in immunocompromised patients (7/20; 21%) compared to non-immunocompromised patients (0/13) ($p = 0.027$). However, six of seven deaths were directly related to the underlying disease.

Conclusions: Actinomycosis is a cause of severe infection in immunocompromised patients and a surrogate marker of a poor prognosis in this specific population

1. Introduction

The genus *Actinomyces* is a heterogeneous group of Gram-positive bacteria, mainly anaerobic facultative or microaerophilic rods with various degrees of branching. *Actinomyces* species are frequently found as members of the normal microbiota in open cavities, especially the oropharynx, upper respiratory tract, gastrointestinal tract, and female genital tract.[1]

Among the different species of *Actinomyces* identified, *Actinomyces israelii* is the most commonly encountered in clinical infections; other species can also produce infection in man, such as *Actinomyces naeslundii*, *Actinomyces viscosus*, and *Actinomyces odontolyticus*.[1]

The clinical presentation varies according to the anatomical location. Classical features are cervicofacial cellulitis in patients with poor dental hygiene,[2] thoracic infections after esophageal lesion,[3,4] abdominal infection after surgery or gastrointestinal perforation,[5] and pelvic infection favored by the presence of an intrauterine device (IUD).[1] Cases mimicking cancer are frequently reported because of the torpid presentation of the infection.

Penicillin is the treatment of choice, and should be administered for a long duration (3–12 months), according to the anatomical location.[1]

Actinomyces have a low virulence potential and can cause invasive disease only when the normal mucosal barrier is disrupted. Therefore, because of this low virulence, we hypothesized that actinomycosis could be an opportunistic infection in

* Corresponding author. Tel.: +33 1 40 87 58 90; fax: +33 1 40 87 10 81.
E-mail address: bruno.fantin@bjn.aphp.fr (B. Fantin).

http://dx.doi.org/10.1016/j.ijid.2014.06.012

severely immunocompromised patients. In order to investigate this point, we analyzed the most severe cases of actinomycosis observed in three tertiary care hospitals and studied the relationship between immunosuppression and outcome.

2. Patients and methods

We recorded all cases of invasive actinomycosis diagnosed in three tertiary care and teaching hospitals in the Paris area (Beaujon hospital, 500 beds; Saint-Louis hospital, 700 beds; Saint Joseph hospital, 600 beds) that occurred over a 12-year period (January 1997 to March 2009).

Invasive actinomycosis was defined as a deep-seated infection with an identification of Actinomyces from the site of infection by microbiological and/or a pathological examination. A deep microbial sample growing *Actinomyces spp* was required. Identification to the species level was done using morphological and biochemical characteristics, and when needed by sequencing methods. A biopsy leading to a pathological diagnosis of actinomycosis was considered; the presence of actinomycotic granules in exudates or in histological sections of tissue was highly indicative of actinomycosis.

All adult patients with reliable medical charts and meeting these criteria were included. Outpatients or patients with incomplete medical records, and patients with samples growing *Actinomyces sp* without a related focus of infection or with a superficial infection were excluded (Figure 1).

For each patient, demographic characteristics, underlying diseases, clinical and radiological manifestations, microbiological results, and treatment and outcome data were collected retrospectively and reviewed.

Statistical analyses were done with Epi Info 3.5.1. Means were compared with a Mann–Whitney test. Qualitative variables were compared with a Fisher's exact test.

3. Results

3.1. Study patients

As shown in Figure 1, 97 patients were screened for actinomycosis by pathology or bacteriology. Data were missing for 30 of them (mostly outpatients). Of the remaining 67 medical records that were examined, the clinician did not retain the diagnosis of infection due to actinomycosis in 19. These cases were systematic cultures of vaginal tract samples from the gynecology ward, or of bronchoalveolar lavage samples from pulmonary transplanted patients.

Forty-eight patients met the criteria for actinomycosis, but 15 were considered to have focal and superficial infections and were finally excluded. The remaining 33 patients were considered to have an invasive actinomycosis and represented the study population (Table 1).

3.2. General condition and presentation

The median age at presentation was 47 years. Seventeen patients were female. Twenty patients (61%) had at least one severe underlying condition and were considered as immunocompromised: seven had solid cancer, six were receiving immunosuppressive treatments, five had uncontrolled diabetes mellitus, five had a hematological malignancy, four had an autoimmune disease, two were bone marrow transplant recipients, and one had an HIV infection with a CD4 count of <200 cells/mm^3 (Table 1). Local trauma was reported in six patients (including previous surgery in three); an IUD was reported in five of the 17 patients with abdominal actinomycosis. Twenty-six patients (79%) had fever and 15 (45%) had lost weight. Focal symptoms varied according to the anatomical location of the infection.

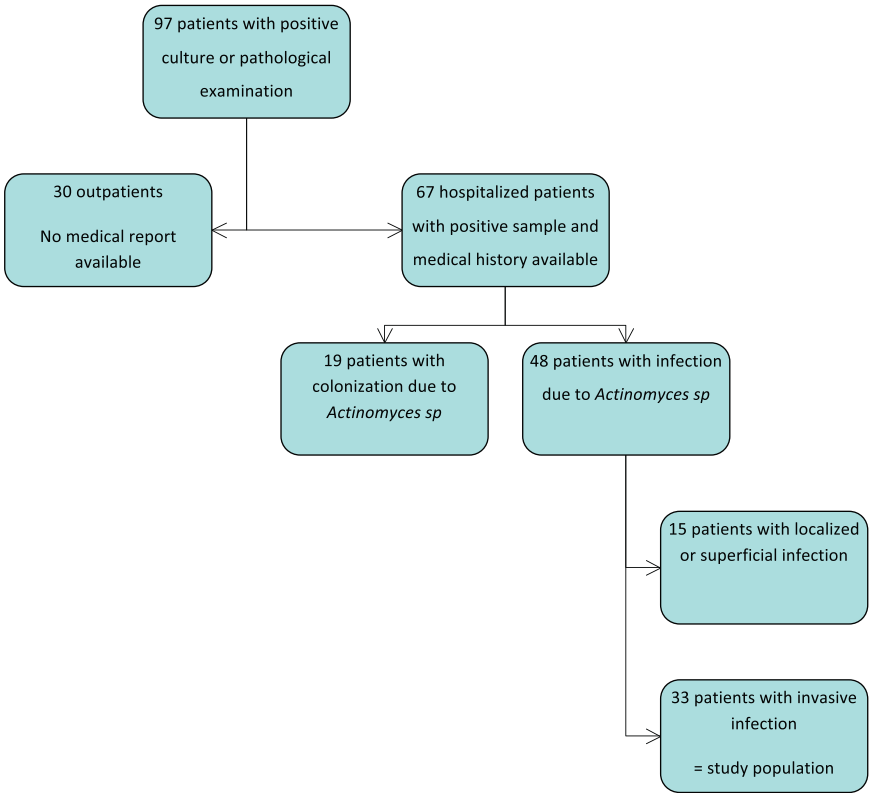

Figure 1. Screening of the patients with invasive actinomycosis.

Table 1
Clinical presentation of 33 patients with invasive actinomycosis

Age, years, median (range)	47 (21–82)
Sex ratio, male/female	16/17
Underlying conditions, *n*	
Cancer	7
Immunosuppressive treatment	6
Diabetes mellitus	5
Hematological malignancy	5
Autoimmune disease	4
HIV infection	1
Bone marrow transplantation	2
Disease location, *n*	
Abdomen or pelvis	17
Central nervous system	2
Thorax	11
Oral and cervicofacial area	3
General symptoms, *n*	
Fever	26
Weight loss	15
Diagnostic procedure, *n*	
Surgical biopsy	20
Bronchoalveolar lavage	6
Pleural puncture	2
Fistulized abscess examination	2
Biopsy guided by radiology	3
Diagnostic method, *n*	
Microbiology alone	25
Pathology alone	7
Both	1

3.3. Presentation according to anatomical location

An abdomino-pelvic location was the most frequent ($n = 17$). Fifteen patients had peritonitis or abdominal abscesses: two had hepatic abscess, one had splenic abscess, two had postoperative collections, four had peritonitis (including two postoperative peritonitis, one hepatic abscess, and one pelvic abscess), three had appendicitis, one had retroperitoneal abscess, one had infected pancreatic necrosis after acute pancreatitis, and one had abscessed signoiditis. Two cases of pelvic infection in women presented as pseudotumor. Both cases had an IUD and no gynecological follow-up.

Thoracic actinomycosis was recorded in 11 patients. Most cases presented as organized pneumonia (8/11); the other patients had infection of a previous post-surgical cavity (1/11), sternal osteitis after radiotherapy (1/11), and pyopneumothorax (1/11). The two patients with central nervous system involvement had brain abscesses. Among three patients with cervical and oral actinomycosis, one had cervicofacial cellulitis, one had cervical postoperative abscess, and one had infected palatal necrosis.

3.4. Diagnosis

Microbiological examination of samples was performed in all but one patient. The samples grew Actinomyces in 26 cases (81%). Pathological examination of samples was performed in 18 patients. For eight of them (44%) the diagnosis of actinomycosis was retained. Both procedures were positive in only one patient.

3.5. Microbiology

Actinomyces identification was available in 26 patients (Table 2). *Actinomyces meyeri* and *A. odontolyticus* were the most frequent species. In three cases, identification to the species level was not done by standard methods. The results of susceptibility testing are shown in Table 2. All isolates were susceptible to amoxicillin, imipenem, vancomycin, rifampin, and tetracycline. Twenty-six (79%) patients had polymicrobial infections.

3.6. Treatment

All patients received effective empiric and definite antibiotic therapy with a beta-lactam (Table 3). Amoxicillin associated or not with clavulanic acid was administered in 91% of patients who received antibiotics for more than 48 h. The mean duration of antibiotic use was 105 days, with a median of 82 days. The range of antibiotic treatment duration was very wide, from 2 to 547 days. Three patients were treated for less than 10 days: the first died 2 days after the start of treatment due to cerebral hypertension, the second underwent a surgical resection of a thoracic actinomycosis revealed by a massive hemoptysis, and the third had appendicitis. At the other extreme, three patients were treated for more than 6 months: one had a liver abscess, one had pneumonia with leukemia, and one had hepatic and pelvic abscess with compression of the urinary tract.

Twenty (61%) patients underwent surgery (Table 4). Thirteen among 17 patients with abdominal actinomycosis (76%) had surgery: five had peritonitis at onset, two had an occlusive syndrome, one had compression of the urinary tract, one had a voluminous retroperitoneal abscess, one had septic shock, and three failed therapy despite adequate medical treatment combined in two cases with radiological drainage. All four patients with abdominal actinomycosis who did not undergo surgery received medical treatment combined with computed tomography-guided drainage.

The mean duration of antibiotic treatment was not significantly different in patients who underwent surgery compared to those who did not (84 days vs. 136 days, $p = 0.23$).

Table 2
Microbiological identification and susceptibility study of clinical isolates of Actinomyces

	Actinomyces susceptibility to different antibiotics[a]								
Species (number of isolates)	AMX	IPM	MTR	RIF	VA	ERY	CM	TE	FQ
Actinomyces spp ($n=3$)	3/3[a]	3/3	0/2	2/2	2/2	2/2	2/2	2/2	NT
Actinomyces odontolyticus ($n=8$)	8/8	8/8	0/8	7/7	7/7	4/4	5/6	3/3	0/5
Actinomyces meyeri ($n=9$)[b]	7/7	6/6	0/6	5/5	6/6	3 /4	4/4	1/1	0/5
Actinomyces israelii ($n=2$)	2/2	2/2	1/2	1/1	2/2	NT	2/2	1/1	0/1
Actinomyces naeslundii ($n=3$)	3/3	3/3	0/2	NT	2/2	1/1	2/2	2/2	1/2
Actinomyces neuii ($n=1$)	1/1	1/1	NT	1/1	1/1	1/1	0/1	1/1	NT
Total ($n=26$)	24/24	23/23	1/20	16/16	20/20	11/12	15/17	10/10	1/13

AMX, amoxicillin; IPM, imipenem; MTR, metronidazole; RIF, rifampin; VA, vancomycin; ERY, erythromycin; CM, clindamycin; TE, tetracycline; FQ, ofloxacin or levofloxacin; NT, not tested.

[a] Proportions are the number of susceptible isolates/number of isolates tested for a given antibiotic.

[b] Suceptibility testing was not available for two patients with *A. meyeri* infection.

Table 3
Antibiotic treatment in 33 study patients with invasive actinomycosis

Antibiotic regimens	Duration, days, median (range)
All antibiotics	82 (2–547)
Amoxicillin	168 (16–547)
Amoxicillin/clavulanic acid	22 (5–182)
Other beta-lactams	17 (2–133)
Others antibiotics	0

Table 5
Clinical outcome in 33 patients with invasive actinomycosis

	Cured of infection	Not cured of infection
Alive	26 (79%)	0 (0%)
Without relapse	26	
With relapse	0	
Dead	2 (6%)	5 (15%)
Cerebral hypertension	0	1
Evolution of underlying cancer or hematological malignancy	1	4
Chronic respiratory insufficiency	1	0

3.7. Outcome

The median follow-up was 199 days (range 2–3832 days). The overall mortality at hospital discharge was 21% (7/33). All deaths occurred among immunocompromised patients (7/20 deaths in immunocompromised vs. 0/13 in non-immunocompromised patients, $p = 0.027$) (Table 5). Twenty-eight patients (85%) were considered cured of infection by clinicians because of the absence of relapse after the end of antibiotic treatment. Two of these 28 patients died from their underlying diseases (chronic respiratory failure and lung cancer) after they had completed treatment. The five other patients died before the end of antibiotic treatment and were thus considered as failure. However, only one death (1/5) was directly related to actinomycosis, in a patient with a voluminous brain abscess with cerebral hypertension who died 2 days after the commencement of antibiotics. The last four (4/5) patients died from the evolution of underlying cancer or hematological malignancy. Overall, 26/33 (79%) patients were cured of infection and alive at hospital discharge.

4. Discussion

We have described 33 patients with different locations of invasive actinomycosis who were diagnosed and treated during a recent period. We excluded superficial actinomycosis, such as cutaneous abscess, for which the outcome was expected to be good with a short course of antibiotics associated or not with minimal surgery.

So far, the largest original clinical series reported at best 25 patients in 12 years (Table 6). Males have tended to be more affected than females,[1,4,6] a feature that was not confirmed in our study, in which the sex ratio was 1:1. This discordance may be explained by poor dental hygiene and more local trauma in males in earlier years. Poor dental hygiene was involved in only four of our patients. Improvements in oral and dental hygiene are also linked to the decrease in number of cervicofacial actinomycosis. Cervicofacial actinomycosis affected only 9% of our patients, whereas it represented up to 55% of cases in historic series.[3] This trend has already been noted by Pulverer et al.[2] The two German reference laboratories received 1218 clinical specimens responsible for cervicofacial actinomycosis between 1972 and 1984 (12 years) and only 778 between 1985 and 1998 (13 years). In addition, the majority of our patients were immunocompromised due to the extensive use of chemotherapy for cancer and hematological malignancy. Because of improved dental hygiene on the one hand and increased proportions of immunocompromised patients on the other, actinomycosis is becoming an opportunistic infection of the immunocompromised in our tertiary care setting.

Table 4
Surgical treatment in 20 patients with invasive actinomycosis

Sex	Age	Localization	Presentation	Type of surgery	Outcome
F	52	Abdominal	Obstructive syndrome with pelvic tumor	Colostomy and surgical biopsy	Cure
F	45	Abdominal	Septic shock 2 days after initiation of antibiotics for hepatic and pelvic abscess (with compression of the urinary tract)	Drainage of multiple abscesses, colostomy, suture of vesical fistula and hysterectomy, ovariectomy	Cure
F	63	Abdominal	Right pelvic abscess with acute abdomen	Ovariectomy and abscess drainage	Cure
F	35	Abdominal	Vesical tumor with compression of the urinary tract	Tumor ablation via coelioscopy	Cure
F	54	Abdominal	Hepatic abscess with signs of peritonitis/acute abdomen	Abscess drainage	Cure
M	28	Abdominal	Obstructive syndrome with pelvic abscess 5 days after cholecystectomy and removal of ileocolic anastomosis	Abscess drainage and colectomy	Cure
M	42	Abdominal	Appendicitis	Appendectomy	Cure
F	62	Abdominal	Septic shock 4 days after hysterectomy and ovariectomy for ovarian cancer	Douglas' abscess drainage and peritoneal cleaning	Progression of cancer; death
M	40	Abdominal	Voluminous perineal abscess	Abscess drainage	Cure
F	54	Abdominal	Septic shock 7 days after antimicrobial therapy for abscessed sigmoiditis	Left colectomy and Hartmann diversion	Cure
F	40	Abdominal	Torsion of teratoma	Appendectomy	
F	32	Abdominal	Appendicitis	Appendectomy	Cure
M	57	Abdominal	Persistent fever despite radiological drainage after 15 days of antimicrobial therapy in patient with pancreatic necrosis after acute pancreatitis	Necrosectomy and cholecystectomy	Cure
M	46	Thoracic	Empyema after pneumectomy in a patient with cancer	Surgical cleaning	Cure of infection; death 6 months later
M	51	Thoracic	Hemoptysis with pulmonary mass	Mass excision	Cure
F	82	Thoracic	Sternal osteoradionecrosis after radiotherapy for breast cancer	Sternum resection	Cure
F	72	Thoracic	Pneumopathy with mass blocking left stem bronchus	Lobectomy	Cure
F	32	Cerebral	Brain abscess	Puncture	Death due to engagement
M	29	Cervicofacial	Palatal necrosis in patient with acute leukemia	Necrotic tissue removal	Death on treatment due to acute leukemia

F, female; M, male.

Table 6
Review of the largest clinical series of actinomycosis in the literature

Authors [Ref.]	Description of the series	Sex ratio	Period	Treatment	Outcome
Pulverer et al. [2]	1997 cases of cervicofacial actinomycosis: microbiological description only	1376 M/574 F 47 NS	1972–1999	NS	NS
Baik et al. [3]	25 cases of thoracic actinomycosis	19 M/6 F	1985–1997	11 medical only 14 medical + surgical	11 alive 1 dead 13 NS
Kinnear and MacFarlane [4]	19 cases of thoracic actinomycosis	15 M/4 F	1974–1990	12 medical only 7 medical + surgical Median duration of ATB: 6 weeks (range 1–24 weeks)	19 alive
Choi et al. [11]	22 cases of abdominal actinomycosis	2 M/20 F	2000–2006	21 medical Duration of ATB: 1 to 6 months 1 NS	22 alive
Poey et al. [12]	9 cases of thoracic actinomycosis	6 M/3 F	NS	NS	NS
Hsieh et al. [13]	17 cases of thoracic actinomycosis	13 M/4 F	1984–1990	8 medical 9 medical + surgical Duration of ATB: at least 2–3 months	17 alive
Sung et al. [27]	23 cases of abdominal actinomycosis	5 M/18 F	1994–2010	23 medical Duration of ATB: 4.2 months (range 0.5–7 months)	23 alive

M, male; F, female; NS, not specified; ATB, antibiotic therapy.

The presentation in our study was also different from classical features. Most authors[7–10] have reported actinomycosis mimicking cancer with a slow evolution, while an infectious and more acute presentation has been less common.[5] In contrast, infectious presentations were most frequent in our study: most of our patients had fever regardless of the location of the actinomycosis. The study patients were therefore suspected of having an infectious process (pneumonia, abdominal abscess, etc.) according to the location of the process.

Abdominal involvement accounted for half of the cases. Previous descriptions have reported cases of women who had had an IUD for a long time and who developed an abdominal mass suggestive of gynecological cancer. Only two of our patients had such a pseudotumoral form; both had an IUD and none had attended gynecological follow-up. Peritonitis or peritoneal abscess was in fact the most frequent presentation in our patients with abdominal involvement. In a recent study Choi et al.[11] reported 22 cases with abdominal actinomycosis; 11 presented as an infectious process (two diverticulitis, five tubo-ovarian abscess, three appendicitis, and one pelvic abscess).

All our patients with thoracic involvement had infectious presentations. Various radiological features have been reported. All patients in the study by Poey et al.[12] had alveolar condensation, which was excavated in two of nine patients. Hsieh et al.[13] described a mass in five patients, pneumonia in four patients, abscess in four patients, and empyema in two patients. For Baik et al.,[3] a mass, nodules, and alveolar condensation were the most frequent features. Our results are similar, with alveolar condensation (with or without excavation) found in 73% of the patients. Complications of thoracic actinomycosis were less frequent in our series, with only one pyopneumothorax and one hemoptysis, which have previously been reported to be very frequent by Baik et al.[3] (72%) and Hsieh et al.[13] (43%).

In the majority of cases Actinomyces were isolated in combination with other bacteria (79% of our patients had polymicrobial infections). In our series, the first three species were *A. meyeri*, *A. odontolyticus*, and *A. naeslundii*. There was no link between species and anatomical location.

Susceptibility of Actinomyces to beta-lactams is the rule, with the exception of rare cases; Metgud et al.[14] reported a case of cutaneous actinomycosis due to *A. viscosus* that was resistant to penicillin and treated with co-trimoxazole. Smith et al.[15] described susceptibility of six different Actinomyces (*A. israelii*, *A. gerencseriae*, *A. turicensis*, *A. funkei*, *A. graevenitzii*, and *A. europaeus*) to 12 antibiotics. All were sensitive to penicillin and amoxicillin. A decreased susceptibility to piperacillin/tazobactam has been noted for some *A. turicensis*, *A. funkei*, and *A. europaeus*, and to erythromycin for some *A. europaeus* and *A. turicensis* strains. All isolates were resistant to ciprofloxacin. Our findings were similar: all isolates were fully susceptible to amoxicillin, piperacillin, and imipenem. Ninety-two percent of isolates were susceptible to erythromycin and the majority were resistant to fluoroquinolones. In spite of the fact that sulfonamides,[16] with penicillin, were the first effective treatment described for actinomycosis, co-trimoxazole has rarely been tested. Ninety-one percent of our patients were treated with amoxicillin alone or in combination with clavulanic acid.

Many authors including Russo[1] state that it is necessary to treat this disease with high doses of penicillin and for a prolonged period of time. Russo proposed 18–24 million units of penicillin intravenously for 2 to 6 weeks followed by oral therapy with amoxicillin (500 mg four times a day) for 6–12 months. This compliant treatment with high doses of antibiotic and for a long time was based on the description of relapse or failure in older studies.[6] In less extensive cases, less aggressive therapy might be required. Many authors have reported cases cured with a shorter duration of antibiotic therapy.[4,13,16–27] Choi et al.[26] reported a series of 28 thoracic actinomycosis patients: 27 of the 28 patients were cured with a median course of antibiotics of 2 days (range 0–18 days) intravenously and 167 days (range 76–412 days) orally in those treated with antibiotics alone, and of 8 days (range 3–17 days) intravenously and 150 days (range 0–534 days) orally in those treated with both antibiotics and surgery. Sudhakar and Ross[17] reported two cases of actinomycosis treated successfully with 9 days and 8 weeks, respectively, of antibiotics; the first patient had 9 days of antibiotics for cervicofacial cellulitis and the second had 8 weeks of penicillin for actinomycosis of the esophagus.

In our study, patients were treated for a median of 82 days and 28/33 (85%) patients were cured of their infection; 26 were cured and alive at hospital discharge. No relapse was observed. In fact, in only one case was clinical failure related to uncontrolled infection due to a brain abscess. Our results are in agreement with those reported by Choi et al.[26] and Sudhakar and Ross[17] and indicate that a shorter course of antibiotics is a possible option depending on the anatomical location, inoculum size, immunosuppression, and clinical evolution under therapy.

Despite heterogeneous clinical presentations, the prognosis was clearly related to underlying diseases, as six of seven deaths were not directly related to infection. However, the occurrence of an invasive actinomycosis in an immunocompromised patient should certainly be considered as a surrogate marker of a poor prognosis. Therefore, the severity of underlying disease rather than the duration of antibiotic therapy appears to be a key determinant of clinical cure.

Limitations of this series are the usual biases of retrospective studies. In particular, there was a selection bias towards more severe cases in the frailest patients due to the tertiary care recruitment. However, analysis of the outcome in this population can more easily be extrapolated than results obtained in less invasive cases and immunocompetent patients.

In conclusion, our study showed that immunosuppression was clearly associated with a more lethal outcome. This study also confirmed that surgery or drainage is part of the treatment and that a short course of antibiotic therapy, depending on the clinical presentation and outcome, might be considered. Amoxicillin remains the antibiotic of choice unless a polymicrobial infection is documented and requires a wider antibacterial spectrum.

Conflict of interest: All authors declare no conflict of interest.

References

1. Russo TA. Agents of actinomycosis. In: Mandell GL, Bennett JE, Dolin R, editors. *Principles and practice of infectious diseases*. 5th ed., Philadelphia: Churchill Livingston; 2000. p. 2645–54.
2. Pulverer G, Schutt-Gerowitt H, Schaal KP. Human cervicofacial actinomycoses: microbiological data for 1997 cases. *Clin Infect Dis* 2003;**37**:490–7.
3. Baik JJ, Lee GL, Yoo CG, Han SK, Shim YS, Kim YW. Pulmonary actinomycosis in Korea. *Respirology* 1999;**4**:31–5.
4. Kinnear WJ, MacFarlane JT. A survey of thoracic actinomycosis. *Respir Med* 1990;**84**:57–9.
5. Vyas JM, Kasmar A, Chang HR, Holden J, Hohmann E. Abdominal abscesses due to actinomycosis after laparoscopic cholecystectomy: case reports and review. *Clin Infect Dis* 2007;**44**:e1–4.
6. Harvey JC, Cantrell JR, Fisher AM. Actinomycosis: its recognition and treatment. *Ann Intern Med* 1957;**46**:868–85.
7. Benkhraba K, Benkabbou A, El Malki HO, Amahzoune M, Mohsine R, Ifrine L, et al. Digestive actinomycosis: three cases and review. *Gastroenterol Clin Biol* 2006;**30**:775–8.
8. Colmegna I, Rodriguez-Barradas M, Rauch R, Clarridge J, Young EJ. Disseminated *Actinomyces meyeri* infection resembling lung cancer with brain metastases. *Am J Med Sci* 2003;**326**:152–5.
9. Falchero L, Philit F, Berger F, Cordier JF. Pulmonary and musculo-cutaneous thigh actinomycosis. *Rev Mal Respir* 1997;**14**:141–3.
10. Louerat C, Depagne C, Nesme P, Biron F, Guerin JC. Disseminated actinomycosis. *Rev Mal Respir* 2005;**22**:473–6.
11. Choi MM, Baek JH, Lee JN, Park S, Lee WS. Clinical features of abdominopelvic actinomycosis: report of twenty cases and literature review. *Yonsei Med J* 2009;**50**:555–9.
12. Poey C, Giron J, Verhaegen F, Levenes H, Gruels S, Fajadet P, et al. X-ray computed tomographic and radiographic aspects of thoracic actinomycosis. *J Radiol* 1996;**77**:177–83.
13. Hsieh MJ, Liu HP, Chang JP, Chang CH. Thoracic actinomycosis. *Chest* 1993;**104**:366–70.
14. Metgud SC, Sumati H, Sheetal P. Cutaneous actinomycosis: a rare case. *Indian J Med Microbiol* 2007;**25**:413–5.
15. Smith AJ, Hall V, Thakker B, Gemmell CG. Antimicrobial susceptibility testing of *Actinomyces* species with 12 antimicrobial agents. *J Antimicrob Chemother* 2005;**56**:407–9.
16. Bates M, Cruickshank G. Thoracic actinomycosis. *Thorax* 1957;**12**:99–124.
17. Sudhakar SS, Ross JJ. Short-term treatment of actinomycosis: two cases and a review. *Clin Infect Dis* 2004;**38**:444–7.
18. Hirshberg A, Tsesis I, Metzger Z, Kaplan I. Periapical actinomycosis: a clinicopathologic study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;**95**:614–20.
19. Jamjoom AB, Jamjoom ZA, al-Hedaithy SS. Actinomycotic brain abscess successfully treated by burr hole aspiration and short course antimicrobial therapy. *Br J Neurosurg* 1994;**8**:545–50.
20. Martin MV. The use of oral amoxicillin for the treatment of actinomycosis. A clinical and in vitro study. *Br Dent J* 1984;**156**:252–4.
21. Nichols DR, Herrell WE. Penicillin in the treatment of actinomycosis. *J Lab Clin Med* 1948;**33**:521–5.
22. Nielsen PM, Novak A. Acute cervico-facial actinomycosis. *Int J Oral Maxillofac Surg* 1987;**16**:440–4.
23. Spilsbury BW, Johnstone FR. The clinical course of actinomycotic infections: a report of14 cases. *Can J Surg* 1962;**5**:33–48.
24. Walker JM, Hamilton JW. The treatment of actinomycosis with penicillin. *Ann Surg* 1945;**121**:373–84.
25. Yew WW, Wong PC, Wong CF, Chau CH. Use of imipenem in the treatment of thoracic actinomycosis. *Clin Infect Dis* 1994;**19**:983–4.
26. Choi J, Koh WJ, Kim TS, Lee KS, Han J, Kim H, et al. Optimal duration of IV and oral antibiotics in the treatment of thoracic actinomycosis. *Chest* 2005;**128**:2211–7.
27. Sung HY, Lee IS, Kim SI, Jung SE, Kim SW, Kim SY, et al. Clinical features of abdominal actinomycosis: a 15-year experience of a single institute. *J Korean Med Sci* 2011;**26**:932–7.