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Treatment of cutaneous actinomycosis with amoxicillin/clavulanic acid

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Objective: To evaluate the efficacy and tolerability of amoxicillin/clavulanic (AMX–CLV) acid as treatment for cutaneous actinomycosis.

Methods: We present a long-term follow-up study of cutaneous actinomycosis patients. Cervicofacial (CFA) and abdominal (AA) were recruited during 6 years. Diagnoses were based on clinical and microbiological characteristics; presence of granules, isolation and identification of etiological agents were carried out in each case. Patients received AMX–CLV 875/125 mg BID PO at a maximum period of 12 weeks.

Results: Twenty-two cases were enrolled; the mean age was 45.2 years old. Twenty patients (91%) presented CFA and two AA (9%). All patients with CFA had dental caries, seven (35%) with periodontal disease and 10 (50%) had type-2 diabetes mellitus (T2DM). One case of AA had history of intrauterine device and other appendicitis. Granules were observed in all the cases, the main etiological agent was Actinomyces israelii 16/22 (72.7%). Clinical and microbiological cure was achieved in 19/22 cases (86.4%), the remaining patients presented clinical improvement. The average duration of the treatment was 6.6 weeks. Side effects were recorded in 4/19 cases (18.2%), three of them presented nausea and one diarrhea.

Conclusion: Treatment with AMX–CLV acid showed efficacy in the management of actinomycosis with cutaneous involvement.

Introduction

Actinomycosis is an uncommon, chronic, supplicative and inflammatory disease, caused by anaerobic branching Gram-positive bacteria, typically belonging to the genus Actinomyces. More than 40 species have been identified; Actinomyces israelii is the most prevalent species isolated, accounting 40–70%. Actinomyces viscosus, Actinomyces gerencseriae (previously A. israelii serovar 2), Actinomyces naeslundii, Actinomyces meyeri among others had also been reported (1–4). It is recognized as an endogenous infection because the low pathogenicity causative microorganisms are usually found as commensal flora at oropharynx, tonsillar crypts, intestinal and genitourinary tracts (1,5).

Actinomycosis can be classified according to the body site affected, the most common presentation is cervicofacial (CFA) accounting for 60% cases; in a smaller proportion, abdominal (AA), pelvic (PA) and thoracic (TA) actinomycosis are seen. Infrequent clinical forms include primary cutaneous, cerebral and disseminated actinomycosis (1,6).

Adults are frequently affected, the majority of cases are observed among adults from 20 to 60 years old. It usually affects immunocompetent patients and is also associated with predisposing factors such as dental caries, periodontitis, post-AA surgery or related IUD use (1,2,4,7,8).

Cutaneous involvement is very common in CFA and AA actinomycosis. In more than one third of cases, the skin is affected by direct invasion. CFA is characterized by an indurated mass, which rapidly evolves to one or more abscesses, fistulae and draining sinus tracts containing sulfur granules, commonly known as "lumpy jaw syndrome". When it comes to AA cases, fistulae and sulfur granules are usually located over the edges of surgical scars (1,4,9,10).

The gold standard for diagnosing actinomycosis is histological examination and bacterial culture with isolation of the agent on anaerobic enriched media (1,2,4). Penicillin has been the treatment of choice for many years; dosage and time of administration depend upon each case, however range between 12 and 50 million units (total dose), from two weeks to one year (1,2,5,11,12). The advantages of this regimen are the low cost of penicillin, accessibility, low resistance (in vitro) (5,13,14), although bacterial resistance appears after prolonged use (5); on the other hand, disadvantages comprise prolonged duration of therapy and route of administration (intramuscular) resulting in poor adherence to treatment (4). We sought to evaluate the efficacy and tolerability of amoxicillin/clavulanic acid (AMX–CLV) as a treatment choice for CFA and AA with cutaneous involvement.

Material and methods

A non-comparative, longitudinal, prospective study was carried out for 6 years (January 2009–December 2014) in a tertiary-referral center. All patients with confirmed ACF and AA were included. Diagnosis was based on clinical and microbiological criteria (presence of granules on direct examination (KOH 10%) and/or Giemsa stains, as isolation of the agent on thioglycollate broth and blood agar with 5% CO₂ atmosphere). Identification of isolated strains was completed using the automated system Vitek 2ANC-Card (Biomerux, Marcy-l’Étoile, France) (15).

Enrolled patients received AMX–CLV acid 875/125 mg BID PO. Clinical and microbiological follow-up was conducted biweekly (Figures 1–3). Blood tests comprising liver enzymes, complete blood count and blood chemistry were attained on baseline visit,
Figure 1. Cervicofacial actinomycosis (similar to scrofuloderma). Case 14. (A) Baseline. (B) After eight-week treatment with amoxicillin/clavulanic acid. (C) Orthopantography showing periodontitis. (D) Granule due to Actinomyces meyeri. (KOH, 10×).

Figure 2. Cervicofacial actinomycosis (similar to ulcerated basal cell carcinoma). Case 18. (A) Baseline. (B) After eight-week treatment with amoxicillin/clavulanic acid. (C) Orthopantography showing periodontitis. (D) Granule due to Actinomyces israelii. (Grocott, 10×).
monthly and at the end of treatment visit. Treatment was withdrawn when clinical and microbiological cure was achieved. Patients were observed for three months after the last dose. If cure was not achieved at a maximum period of 12 weeks, treatment regimen was changed. Once the infection was controlled, the predisposing factors were treated in each case, for example, treatment of dental caries, diabetes mellitus and IUD removed and replaced by another contraceptive method.

**Statistical analysis**

Data were entered and analyzed using SPSS version 20 for Windows (Chicago, IL). Means and standard errors were recorded for categorical variables.

**Results**

The study participants consisted of 22 patients, who fulfilled inclusion criteria. Twenty two were male (54.5%) and 10 female (45.5%); their ages were between 22 and 78 years with a mean of 45.25 ± 12.98 years; the duration of the disease before presentation ranged from 1 to 18 months (mean four months, median three months).

**Clinical assessment**

Clinical presentation corresponded to ACF in 20 cases (90.1%): the main anatomical sites were: neck (2), mandible (9), cheek (4), nasal groove (4) and nasal root or glabellas (1); whereas two cases were classified as AA (9.9%). Table 1 shows the patients’ demographics and clinical characteristics.

With regard to the predisposing factors, we found dental caries in 20 CFA cases, 16/20 cataloged as grade II and 4/20 as grade III; seven (35%) CFA patients showed underlying periodontal disease. The AA cases were related to appendicitis (one case) and IUD use (one case). Notably, in 10/22 cases (45.5%) an irregular treatment of T2DM was observed.

**Microbiological study**

Concerning microbiological data: granules were observed in 100% cases, the foremost causative agents were *A. israelii*: 16/22 (72.7%), *A. meyeri* 3/22 (13.6%), *A. naeslundii* 1/22 (4.6%) and *Actinomyces* sp. 2/22 (9.1%).

**Follow-up**

At the end of treatment visit, clinical and microbiological cure was attained in 19/22 cases (86%), the remaining patients (3 cases, 14%) presented clinical improvement. The average time required to accomplish cure was 6.6 weeks (range 4–12 weeks). Adverse events were registered in 4/22 cases (18.2%), from which three reported nausea and one patient informed diarrhea; the events were mild and did not require additional treatment or withdrawal. Blood test alterations were absent in all patients. During treatment 5/22 patients (22.8%) were diagnosed with oral candidiasis; all of these patients had T2DM, and received treatment with topical and systemic antifungals (topical miconazole and oral fluconazole).
Actinomycosis is a rare, chronic endogenous condition which is frequently misdiagnosed. Several case reports can be found, however case-series are limited. Pulvener et al. (16) described the clinical and microbiological data of 1997 CFA cases. CFA is the most common clinical presentation, accounting for 60% of the cases, followed by AA and PA (1,5,17–21).

There is a lack of data about cutaneous involvement of actinomycosis, however, we have observed that CFA and AA account for more than 70% actinomycosis cases (personal experience); therefore the index of suspicion is high. This highly differs from internal organ actinomycosis (e.g. digestive, genitourinary tracts) where more than 70% actinomycosis cases (personal experience); therefore the index of suspicion is high. This highly differs from internal organ actinomycosis (e.g. digestive, genitourinary tracts) where masses develop briskly and are often misdiagnosed as neoplastic conditions (2,4,7).

In our study, there was a mild predominance of male gender. Most patients were adults and presented with chronic evolution (six months), thus, correlating with previous reports (5,11,18). Actinomycosis is considered as an endogenous disorder, caused by low virulence pathogens requiring addition of predisposing factors for the condition development (1,5,10,22).

In the present study, all the CFA cases were concomitant with poor dental hygiene; cavities were observed in 100%, while periodontal disease was observed in 35% of the patients. Most of cases developed painless indurate mass and scant draining sinuses located over the mandible; moreover, a considerable number of patients presented the disease on the cheeks, neck, nasal groove and glabellas. Interestingly, 10/20 (50%) of CFA cases had T2DM, which was either under irregular management or uncontrolled. T2DM has been reported previously and represents a major predisposing factor because the latter is recognized as a virulent microorganism (1,4,21).

For some authors, penicillin is the treatment of choice, although trimethoprim sulfamethoxazole, erythromycin, clindamycin, tetracycline,ceftriaxone and imipenem are appropriate choices (1,2,5,11). Aminoglycosides and metronidazole are ineffective against A. israelii (12,14).

Amoxicillin is a semi-synthetic antibiotic, analog of ampicillin, with a broad-spectrum bactericidal activity against many Gram-positive and Gram-negative microorganisms. Clavulanic acid is a β-lactam drug that functions as a β-lactamase inhibitor; when combined with amoxicillin or other penicillin-group antibiotics can overcome resistance in β-lactamases-secreting bacteria (27–29).

AMX/CLV has shown efficacy in vitro against Actinomyces strains, Gomes et al. (30) proved that most of these strains were sensitive to AMX and resistant to clindamycin and penicillin. Actinomycosis treatment with AMX was reported since 1997 (31), recent studies report that the duration of treatment may range from 2 to 18 weeks (1,4,27,28,32). Some authors point that AMX as monotherapy is effective for the treatment of actinomycosis (1,3,4,9).
considering that *Actinomyces* spp is not able to produce β-lactamases; however, because many microorganisms are involved, we believe that the addition of CLV is essential (4,22).

All patients included in our study were immunocompetent and were classified according to the severity of the induration and the amount of fistulae in mild and moderate cases. Clinical and microbiological cure was achieved in 86% cases; those were followed during three months and did not developed signs of recurrence. Treatment failure, defined as presence of clinical manifestations after 12 weeks of therapy, was documented in three cases (two CFA and one AA), 2/3 were caused by *A. israelii* and one by *Actinomyces* sp; the causative agent was re-isolated after 12 weeks in two of them.

Adverse events of AMX/CLV are nausea and diarrhea which occurred in 18% of patients. These were transient and mild and did not require additional treatment of withdrawal (28,33,34). Oral candidiasis is a known phenomenon resulting from the microbial flora impairment that allows higher predominance of *Candida* spp. This is frequently observed in diabetic patients, in concordance with our results, where all 10 patients who developed oral candidiasis were also diabetics.

It is important to emphasize that in a current and large retrospective assessment of antimicrobial resistance patterns (392 Actinomyces spp), the authors conclude that β-lactam antimicrobial agents remain the first choice, whereas metronidazole should be avoided, in the treatment of actinomycosis. Reasonable alternatives for treatment are tetracyclines and carbapenems (35).

Limitations of our study are related to the study design. However, we were able to achieve clinical and microbiological cure in almost all patients treated with AMX/CLV. Furthermore, we conclude that AMX/CLV is a safe and effective option for treating mild to moderate CFA and AA with cutaneous impairment.

**Disclosure statement**

All authors declare no conflicts of interest and did not receive any financial support.

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