

CLINICAL REPORT

A Two-step Schedule for the Treatment of Actinomycotic Mycetomas

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Actinomycotic mycetomas usually respond slowly to treatment with antibiotics. In an attempt to hasten clinical resolution, we used a 2-step regimen consisting of an intensive phase of therapy with penicillin, gentamycin and co-trimoxazole for 5–7 weeks, followed by maintenance therapy with amoxicillin and co-trimoxazole. Seven patients were treated, all of whom showed significant reduction in discharge and swelling after the intensive phase. Maintenance therapy was continued for 2–5 months after the lesions became completely inactive. Five patients completed maintenance therapy, which was given for 6–16 months (mean 10.7 months), and remained free of disease during a mean post-treatment follow-up period of 6.4 months. The other 2 patients also responded satisfactorily and continue to receive maintenance therapy. Side-effects necessitating a modification of the treatment schedule occurred in 2 patients but reversed on discontinuation of the drugs responsible. This treatment schedule produces a rapid clinical response during the initial, intensive phase and promotes compliance with the longer maintenance phase of treatment necessary to achieve a complete cure. Key words: *maduromycosis*; *actinomycetales infections*; *dermatomycoses*; *therapy*.

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Mycetomas are chronic, subcutaneous infections characterized by the clinical triad of swelling, draining sinuses and discharge of granules. These granules are composed of colonies of the causative organism, which may be a fungus or an aerobic filamentous bacterium (1). The clinical appearance of mycetomas caused by fungi or bacteria is similar but they differ in their response to treatment. Eumycotic mycetoma, caused by fungi, respond poorly to therapy with antifungal drugs. Griseofulvin, amphotericin B, ketoconazole, fluconazole and itraconazole have been used in the treatment of eumycotic mycetomas with variable success. Surgical excision is the most effective treatment of localized lesions; longstanding, large lesions may require amputation of the affected part (2, 3). In contrast, actinomycotic mycetomas, caused by bacteria belonging to the genera *Nocardia*, *Actinomyces* and *Streptomyces*, show a better response to medical therapy. Sulfonamides and sulfones, tetracyclines, aminoglycosides, penicillins and other drugs have been used for treatment (1, 2, 4) and combinations of drugs are more effective than single agents (1, 5). However, response to

therapy is generally slow and treatment must be maintained for long periods (5).

In an attempt to produce a quicker clinical response, we treated patients in a two-step manner. The first phase consisted of intensive therapy with 3 drugs, administered in the hospital, followed by a maintenance phase of treatment with 2 drugs, taken at home. We report here the results achieved with this regime in 7 patients.

MATERIAL AND METHODS

Patients

Seven patients (5 men and 2 women; age range 17–52 years) with actinomycotic mycetomas were included in the study. The duration of the disease ranged from 7 to 40 years (mean 18 years). The sites affected were the foot and/or ankle in 4 patients, the ankle and leg in 1 patient, the ankle, leg and thigh in 1 patient and the hand, forearm and shoulder in 1 patient.

All patients had clinical features of swelling and discharging sinuses. Two patients reported the discharge of grains from the lesion. Biopsies from the lesion revealed histopathological features compatible with a mycetoma in 6 patients; 1 patient showed a non-specific dermatitis. Colonies of the causative organism consisting of filaments of bacterial width were demonstrated on biopsy in 4 patients and in a fine needle aspirate from the inguinal lymph node in 1 patient. Culture of the organism was attempted in all 7 patients on 9 occasions. *Nocardia* was isolated in 1 patient but the organism could not be grown in the other patients.

Previous treatments

Patients had received treatment for varying periods with a wide variety of drugs, including antibiotics, antifungals and anti-tubercular drugs. There had been some improvement for short periods with some of the medications but the overall response was poor in all patients. The lesions had been excised in 2 patients (twice in 1 of the patients) but recurred after surgery.

Two-step regime

All patients were admitted to the hospital during the intensive phase and received a combination of intravenous crystalline penicillin 1 MU every 6 h, intravenous gentamicin 80 mg twice daily and oral co-trimoxazole (80/400) 2 tablets twice a day. In 1 patient with associated multibacillary leprosy, co-trimoxazole was substituted by dapsone 100 mg twice daily. Initial therapy was given for 5–7 weeks depending upon the severity of disease and the response to treatment.

After the initial phase of therapy, patients were discharged from hospital and treatment was continued at home with amoxicillin 500 mg thrice daily and co-trimoxazole/dapsone at the same doses as before.



Fig. 1. Actinomycotic mycetoma of the hand: (a) before treatment; (b) 6 months after cessation of treatment.

Monitoring

None of the patients were known to be allergic to penicillin or sulfonamides. An intradermal sensitivity test for penicillin hypersensitivity was carried out before administering the first dose of penicillin. Serum levels of urea and creatinine were determined and urinalysis was carried out in all patients prior to therapy.

During the intensive phase, all patients were questioned daily for symptoms of ototoxicity. An evaluation by an otorhinolaryngologist, including audiometry and electronystagmography, was performed in patients who developed these symptoms. Urinalysis and monitoring of renal functions and other biochemical parameters was performed weekly. During the maintenance phase of treatment, patients were questioned for any evidence of toxicity and appropriate tests were conducted as indicated.

RESULTS

Six patients completed the therapy as advised. One patient requested discharge from hospital after 2 weeks of initial therapy because her daughter fell ill; she was consequently transferred to maintenance therapy early. However, because of financial constraints, she did not take treatment regularly and her mycetoma again became active. She was then readmitted and given the initial therapy again, this time for 6 weeks. The results of this second treatment schedule have been analysed with those of the other 6 patients.

The intradermal sensitivity test for penicillin allergy was negative in all patients. There was no abnormality in terms of renal functions as determined by urinalysis or serum levels of urea and creatinine in any patient at the start of therapy.

All patients showed a rapid response to treatment after the intensive phase of therapy. The sinuses stopped discharging pus 7–10 days after starting treatment and the swelling showed a perceptible diminution within 2 weeks. At the end of the first phase of treatment, the response defined by reduction of swelling and discharge was assessed to be around 50–60%.

Maintenance therapy was continued for 2–5 months after

the lesions became completely inactive. In the 5 patients who completed the treatment, the total duration of maintenance therapy ranged from 6 to 16 months (mean 10.7 months). These patients were followed up for up to 16 months (mean 6.4 months) after stopping therapy and continue to be well, with no re-activation of the mycetoma. Both the remaining patients are continuing maintenance therapy and have responded significantly.

Side-effects

Adverse effects ascribed to gentamicin developed in 2 patients; vertigo developed in 2 patients, 1 of whom also developed nephrotoxicity manifested by raised serum creatinine levels. Gentamicin was discontinued in these patients, with a reversal of these adverse effects. Thrombophlebitis at the site of intravenous injections developed in 1 patient. One patient developed urticaria during therapy, which was controlled with antihistamines. Therapy for mycetoma was continued in this patient, with no recurrence of urticaria.

DISCUSSION

We have demonstrated a rapid and favorable response to a 2-step treatment regime used for the treatment of actinomycotic mycetomas (Figs. 1a and 1b). The mycetomas in all our patients were longstanding and had been treated with various medical and surgical modalities with little lasting improvement. The rapidly perceptible improvement during the intensive phase of therapy was a strong motivating factor for these patients to continue maintenance therapy as advised. Side-effects due to the treatment regime occurred in 3 patients and required modifications to the treatment schedule in 2 patients. However, the adverse effects were reversed on discontinuation of the drug responsible. The side-effects were those expected with the drugs used; no new or unusual adverse effects were observed.

Several agents have been described to be effective in the

treatment of actinomycotic mycetomas. Mahgoub (5) found that co-trimoxazole, dapsone, streptomycin, sulfadoxine–pyrimethamine and rifampicin were all effective in different patients. However, the combination of streptomycin and co-trimoxazole was found to be the most efficacious. Magana & Magana-Garcia (1) found a combination of dapsone and co-trimoxazole to be very effective. Welsh (2) described the use of a combination of amikacin and co-trimoxazole given in cycles of 5 weeks each, with a cure rate of 95% after 1–3 cycles of treatment. Penicillin, parenteral or oral, is highly effective against *A. israelii*, which is a causative agent of mycetoma (6). In combination with sulfadiazine, penicillin was also effective in the treatment of mycetomas due to other organisms; the combination being more effective than sulfadiazine alone (7). Gomez et al. (8) described the use of amoxicillin–clavulanic acid in 2 cases. Other agents used include isoniazid (9) and tetracyclines (1, 10).

The choice of drugs for the regime that we used was based on considerations of availability and cost. We chose agents belonging to 3 groups of drugs with demonstrated efficacy in the treatment of actinomycotic mycetomas, namely penicillins, aminoglycosides and sulfonamides/sulfones.

In vitro (5) and *in vivo* (1, 5) studies have demonstrated that a combination of drugs is more effective than single drugs used alone. This may explain the uniformly good response to therapy in our patients, many of whom had previously been treated unsuccessfully with 1 or more of the drugs that we employed.

The duration of treatment for actinomycotic mycetomas is not clearly defined. Prolonged treatment (4–24 months) (5) is required and premature cessation of therapy usually results in reactivation of disease. Five of our patients have completed

therapy and remain free of disease during a mean follow-up period of 6.4 months after cessation of treatment.

Further studies on larger numbers of patients are planned in order to determine the optimal combination of drugs and the length of treatment necessary to cure the disease.

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