

to be the first known in Israel. Convit et al. (5) and Convit & Kerdel-Vegas (6) described the characteristics of this type of cutaneous leishmaniasis. The most important characteristic in connection with the resistance to treatment, chronicity and recurrence of the disease, is the selective anergy condition of the patient against the leishmania parasite. The leishmanin (Montenegro) test is negative.

Unsuccessful attempts have been made in the past by the late Prof. Adler and Prof. Nelken (1) to induce delayed sensitivity to leishmania in normal individuals, by injecting subcutaneously peripheral leukocytes, 10^5 organisms, and by blood transfusions of 3×10^9 leukocytes from strongly sensitive donors. Bryceson succeeded in transferring sensitivity to leishmanin from strongly positive reactors, to leishmanin-negative patients and normal volunteers by injecting intradermally 5×10^6 organisms. This sensitivity lasted from some days up to 3 weeks but did not affect the course of the disease.

It seems therefore that heat-killed and lyophilized BCG bacilli and cord-factor in vaseline, on coming into contact with the leishmaniasis lesions, produce a strong inflammatory reaction, attract and activate macrophages, and induce sensitivity against the leishmania parasite, thus creating the prerequisite condition for the successful antibiotic and chemotherapeutic effect.

REFERENCES

1. Adler, S. & Nelken, D.: Attempts to transfer delayed hypersensitivity to leishmania tropica by leukocytes and whole blood. *Trans R Soc Trop Med Hyg* 59: 59-63, 1965.
2. Barrientos, L. P.: Un caso atipico de leishmaniose cutaneo-mucosis (espondia). *Mem Inst Oswaldo Cruz* 46: 417-418, 1948.
3. Bekierkunst, A.: Acute granulomatous response produced in mice by trehalose-6,6'-dimycolate. *J Bacteriol* 96: 958-961, 1968.
4. Bryceson, M. D. A.: Diffuse cutaneous leishmaniasis in Ethiopia. I. Clinical and histological features of the disease. *Trans R Soc Trop Med Hyg* 63: No. 1, 1969.
5. Convit, J., Kerdel-Vegas, F. & Gordon, B.: Disseminated anergic cutaneous leishmaniasis. *Br J Dermatol* 74: 132, 1962.
6. Convit, J. & Kerdel-Vegas, F.: Inoculation to laboratory animals, electron microscopy and fluorescent antibodies studies. *Arch Dermatol* 91: 439-447, 1965.
7. Convit, J. & Lapenta, P.: Sobre un caso de leishmaniasis diseminada. *Rev Pol XVII*, Caracas, 1948.
8. Kelly, M. T.: Activation of guinea-pig macrophages by cell walls of *Mycobacterium bovis*, strain BCG. *Cell Immunol* 26: 254-263, 1976.

9. Lederer, E.: Cord factor and related trehalose esters. *Chem Phys Lipids* 16: 11-21, 1975.
10. Ofek, I. & Bekierkunst, A.: Chemotactic response of leucocytes to cord factor (trehalose-6,6'-dimycolate). *J Natl Cancer Inst* 57: 1379-1380, 1976.

Treatment of Leishmaniasis Recidivens with Intralesional Injections of Emetine Hydrochloride: A Case Report

Haim A. Cohen and Asher Wahaba

Department of Dermatology and Venereology, Hadassah University Hospital, Jerusalem, Israel

Received June 16, 1979

Abstract. A patient, suffering for 42 years from the late tuberculoid-type of leishmaniasis located in his face, was successfully treated with intralesional injections of emetine hydrochloride. Previous treatments, which included intralesional injections of steroids and concomitant intramuscular injections of antimonials, flayyl, fluorocytosine, infusions of amphotericin B—with and without concomitant treatment by steroids systemically and/or intralesionally—and amphotericin B intralesionally, were altogether ineffective. In addition, the patient underwent five operations in a plastic surgery department.

Cutaneous leishmaniasis is a spectrum disease having in the center the primary nodular leishmaniasis lesion and two poles, which are the diffuse type and the tuberculoid or recidiva type (1). In Israel, the most common is the nodular type, while the recidiva is relatively rare, accounting for only about 10% of the cases observed (4). Recently on our country one case of the diffuse type was found and described (2). These three different variants of the disease are an expression of the underlying immunological mechanism (1). Whilst patients suffering from the nodosa type react to a dilution of leishmanin from 1:100 to 1:10000—with represents the "normergic zone"—those with the late tuberculoid type react to the dilution up to 1:10000000 (5). This is a hyperergic reaction characterizing the tuberculoid type of leishmaniasis.

Patients suffering from the diffuse type show a specific anergy against the parasite, have a negative

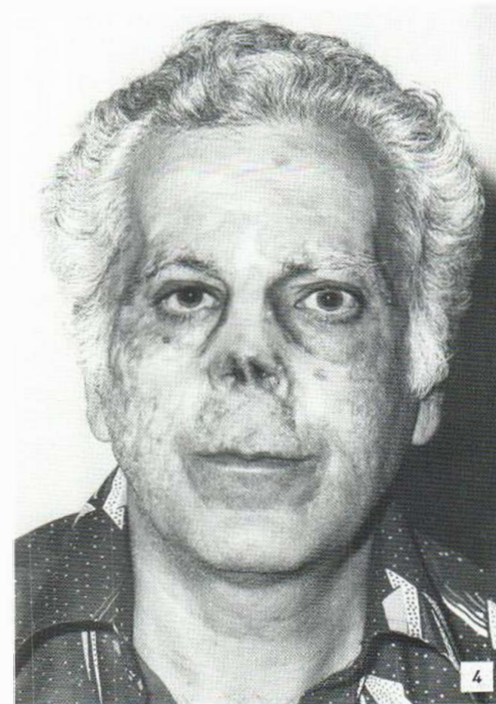


Fig. 1. Patient before treatment.

Fig. 2. Patient after treatment.

Fig. 3. Patient before treatment.

Fig. 4. Patient after treatment.

reaction to leishmanin, but have normal delayed reactions to other antigens (1). The prerequisite for the successful treatment of these patients is the induction of delayed reactivity against the parasite, thus shifting the patient's reactivity towards the center of the spectrum. The same therapy can be applied to the leishmaniasis recidivens sufferers, who display a hyperergic reaction to the parasite, also shifting their reactivity towards the "normergic zone" by the use of steroids. The steroids also destroy the tuberculoid structure of the lesions, thus helping chemical or antibiotic substances to penetrate and come in contact with the parasites. Cases of tuberculoid leishmaniasis have been treated successfully with steroids, with and without the concomitant use of antimonials (1). However, not all patients respond to these treatments, the case reported here being an example.

CASE REPORT

The patient, now 51 years old, immigrated from Iraq at the age of 10. He suffered from malaria when he was 7 years old and was treated with quinine, from asthma at 14–20 years, and from his 25th year from psoriasis. The first leishmaniasis lesion appeared at the age of 9 and was localized below the bridge of the nose. The lesion gradually enlarged, and later ulcerated. A plaque-like infiltration spread over the nose and to the cheeks, forehead, and later to the upper lip. There were also some isolated papules and nodules adjacent to the borders of the lesions.

This was the clinical picture in 1955 when he was first hospitalized at the age of 24 years. The microscopical examination was negative, but the culture revealed mastigotes and the Leishmanin test was strongly positive. The Mantoux test at 1:10000 dilution was negative. The patient was treated for 2 years, at first with systemic steroids (cortisone) and later with intralesional injections of hydrocortisone and intramuscular injections of stibophen or fanthorin (antimony salts) on an outpatient basis. In spite of this treatment, the lesions persisted and slowly but constantly multiplied, enlarged and ulcerated, covering the nose and cheeks in a 'butterfly' fashion. The lesions from the upper lip progressed into the mucous membranes of the nose. In 1968 the lesions deepened and produced distraction of the tip of the nose. At this stage, the patient was operated on at a plastic surgery department five times between 1968 and 1970.

In 1972 he was again hospitalized, in our department, and treated with 500 mg of fluorocytosine daily for 13 days, with no success. In 1973 he was again hospitalized. His face was swollen and the eyelids were almost entirely closed. He was treated with amphotericin B infusions, twice a week for 3 months; each infusion contained 25 mg of amphotericin B. This treatment achieved a resolution of the edema facialis, but without any effect on the nodular lesions of leishmaniasis. In 1975 he was again hospitalized. His face was again swollen and the eyelids of the

right eye were almost entirely closed. Ulcerative lesions were found in the forehead, cheeks and the distal portion of his nose was entirely destroyed and ulcerated (Fig. 1). His general health remained unaffected.

The patient was treated with amphotericin B infusions with mannitol, intramuscular injections of hydrocortisone, and intralesional injections of dexamethasone. This treatment was given twice a week during the 5-month period of hospitalization. The total amount of amphotericin B administered was 1414 mg, and the patient developed a duodenal ulcer due to the steroid treatment. No side effects appeared from the amphotericin B treatment. The swelling of the face and the ulcerative lesions subsided, but a biopsy taken 3 weeks before his discharge from the department revealed with Giemsa stain that LD bodies were present in the cytoplasm of histiocytes; no tuberculoid structures were found. The treatment was continued once a week on an ambulatory basis for 2½ years, in spite of which the culture for leishmaniasis remained positive. In 1978 the amphotericin B and steroid treatments were discontinued and instead intralesional injections of emetine hydrochloride (0.1–0.2 ml) were given once a week for 2 months into the scattered nodules in the atrophic scar tissue of nose and cheeks. For the first time the cultures, taken from samples of five treated nodules, became negative, and no apple-jelly-like lesions could be seen by diascopy (Fig. 2).

DISCUSSION

The therapeutic modalities effective for leishmaniasis nodosa are without effect when applied in cases of tuberculoid leishmaniasis. It seems that there are several reasons for this failure. The tuberculoid structure prevents the penetration of any therapeutic agent, thus protecting the parasites. The chronicity of the disease, which is the consequence of the aforementioned, results in the production of scar tissue which sometimes contains small islands of active tubercles. The scar tissue is also impenetrable, thus adding another impediment. From the so-well protected active tubercles, recurrences arise, thus perpetuating the disease.

It is also possible that the 'immunological status' of the scar tissue is an additional contributory reason for the resistance to treatment in this type of disease. It has been found that the scar of leishmaniasis is, in contrast to the reactivity of the normal skin of the patient, anergic or hypoallergic to leishmanin, whilst scars from other etiology (burns) are not (6). This local tissue reactivity might therefore resemble the general anergy found in cases of the diffuse type of leishmaniasis.

The therapeutic effect of infusions of amphotericin B, which was limited to the resolution of the edema facialis, was ineffective against the small,

isolated tubercles scattered in the scar tissue. Two years after the discontinuation of the treatment with amphotericin B, the patient was hospitalized again because of the reappearance of the edema facialis of the eyelids. The concomitant administration of amphotericin B with hydrocortisone intravenously and also of dexamethasone intralesionally in the isolated tubercles, was also without effect, producing only the resolution of the facial edema. The cultures remained positive.

Intramuscular injections of emetine hydrochloride have been used successfully in the treatment of amebic liver abscess. Since ameba and leishmania are both protozoa, and emetine hydrochloride was found to be highly effective against ameba, it was expected that it might also be effective against the leishmania parasite. For the first time we used, successfully, intralesional injections of emetine hydrochloride in some lesions of a patient suffering from leishmaniasis cutanea diffusa which had also proved resistant to amphotericin B treatment (2). The second patient is the case presented here. Interestingly, these 2 patients belong to the two poles of the leishmaniasis spectrum.

Emetine hydrochloride is a toxic substance causing nausea, vomiting and muscular weakness. Electrocardiographic changes and hypotension have also been reported (3). All these side effects can be avoided when small amounts of emetine hydrochloride are given intralesionally. There is, however, the possibility of inducing sensitivity and an anaphylactic reaction may appear. These side effects, not observed in our two patients, can be overcome if steroids are given simultaneously—systemically or intralesionally.

REFERENCES

1. Bryceson, M. D. A.: Immunological aspects of clinical leishmaniasis. *Proc R Soc Med* 63: 40-44, 1970.
2. Cohen, H. A.: Induction of delayed-type sensitivity to leishmania parasite in a case of leishmaniasis cutanea diffusa with BCG and cord factor (trehalose-6-6' dimycolate). *Acta Dermatovener (Stockholm)* 59: 547, 1979.
3. Data, D. V., Singh, S. A. K. & Chhuttani, P. N.: Treatment of amebic liver abscess with emetine hydrochloride, miridazole and metionidazole. A controlled clinical trial. *Am J Trop Med Hyg* 23: 586-589, 1974.
4. Dostrowsky, A. & Sagher, F.: Diagnostic significance of the culture method in cutaneous leishmaniasis (oriental sore). *Arch Dermatol Syphil* 54: 543-551, 1946.

5. Sagher, F.: Leishmania vaccine test in leishmaniasis of the skin (oriental sore). *Arch Dermatol Syphil* 59: 205-213, 1947.
6. Sagher, F.: The response of scars of cutaneous leishmaniasis (oriental sore) to the injection of leishmania tropica vaccine. *Br J Dermatol Syphil* 59: 205-213, 1947.

Antibiotic Sensitivity of Comedonal *Propionibacterium acnes*

Jere D. Guin, Deborah S. Huber
and Paul Lee Gielerak

Department of Dermatology, Indiana University School of Medicine, Indianapolis, and Department of Microbiology, St. Joseph Memorial Hospital, Kokomo, Indiana, USA

Received May 25, 1979

Abstract. Previous studies on antibiotic MIC levels for *P. acnes* and *P. granulosum* have shown them generally sensitive to therapeutic levels in both blood and surface lipids. The clinical response of acne vulgaris to antibiotic therapy is slower than one would anticipate from in vitro studies. It is also delayed well beyond the time tetracycline is known to appear in surface lipids. The concentration of antibiotics in comedonal material could be important, but it is not known. To determine the sensitivity level required for such an assay, MIC studies on *P. acnes* and *P. granulosum* from comedonal material were carried out from 0.05 to 25 µg/ml. The assay would need to detect 0.05 µg/ml or less in comedonal material. Interestingly, two organisms were found to be resistant to one or more antibiotics at the 25 µg/ml level and another had a MIC level of 12.5 µg/ml for tetracycline.

Key words: Acne; *P. acnes*; Ampicillin; Clindamycin; Erythromycin; Oxytetracycline; Tetracycline

Propionibacterium acnes has been associated with acne vulgaris for over 80 years. However, we still do not completely understand the part this organism plays in the pathogenesis of acne, or its response to antibiotic therapy. *P. acnes* is susceptible in vitro to a variety of antibiotics at modest concentrations (3, 7, 12). Such concentrations occur in surface lipids as well as in serum of patients on therapeutic dosage (9). However, the clinical response does not parallel in vitro sensitivity and this has not been adequately explained. It might be partly due to