Current status of cutaneous leishmaniasis in Aleppo, Syrian Arab Republic

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Cutaneous leishmaniasis has been endemic in Aleppo, Syria, for generations. Recently there has been a clear increase in the incidence of the disease, and more patients have shown a lack of response to antimonials. We report the results of a survey, undertaken over the period 2–17 January 1995, at a general hospital in Aleppo, of all patients presenting with cutaneous leishmaniasis. Patients were grouped according to the stage of their disease, and surgical biopsies were carried out for histopathological investigation.

Patients who were unresponsive to treatment and proceeded to chronicity were predominantly children aged under 15 years with facial lesions. Histopathological examination showed that the inflammatory changes had reached the upper layers of the subcutaneous tissues in 10 of the 25 chronic cases (40%) and three of the four acute cases (75%). These levels of the skin are not directly reached by the antimonials administered intralesionally.

The inadequacy of the intralesional method alone and technical errors in administration are discussed.

Introduction

Cutaneous leishmaniasis has been endemic in Aleppo, Syrian Arab Republic for generations; its occurence was documented as early as 1745 by Pocock (*1*). Common local names include "Aleppo boil" and "the one-year sore". The infective agent is *Leishmania tropica* (*2*). Oriental cutaneous leishmaniasis caused by *Leishmania tropica* is known to heal spontaneously within 1–2 years in about 90% of cases, with scar formation and subsequent life-long immunity against the disease in most cases (*3*).

In the mid-1950s, and after a campaign aimed at controlling malaria (*1*), cutaneous leishmaniasis declined considerably; however, before the end of the 1960s, it had regained momentum.

In the early 1970s, treatment with pentavalent antimonials was introduced, with meglumine antimoniate being used exclusively until sodium stibogluconate was introduced in the early 1980s. Substantial success in shortening the course of the disease and in reducing scarring to a minimum was achieved using these compounds. Intralesional administration of meglumine antimoniate alone was (and remains) the treatment of choice for cutaneous leishmaniasis in Aleppo; 3–5 intralesional doses at weekly intervals used to be sufficient for the complete healing of lesions (*4*, *5*). Occasionally, antimonials were given systemically when their intralesional use was not possible owing to the location, size or number of lesions. A few cases of acute cutaneous leishmaniasis did develop into the chronic or lupoid forms despite treatment, but these did not exceed 3–5% of the total (*5*, *6*).

Since 1992, there has been a clear but unexplained increase in the overall incidence of cutaneous leishmaniasis in Aleppo, despite repeated governmental insecticide spraying campaigns to combat the sandfly vector. This change was reported in 1993 (*7*), and has been noted subsequently in Ministry of Health reports. Moreover, patients began to require more intralesional doses of meglumine antimoniate before they responded. Gradually, however, even with the additional doses, the treatment became ineffective in a considerable proportion of cases, and more and more patients developed the chronic form of the disease.[a] Such patients were transferred from one clinic to another and were subjected to various treatments repeatedly without

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[a] In this study, a case was considered to have become chronic once the duration of a lesion had exceeded 1 year without healing, despite treatment. However, the term "chronic" was applied to patients whose lesions never healed (chronic cutaneous leishmaniasis) and to those who reported having had periods of healing that ranged from 3 months to 2 years (recurrent cutaneous leishmaniasis), since clinical and histopathological differentiation between these two categories is rather controversial (*3*), and depends mainly on case history, which is unreliable in most instances.

recovery (see Table 2). This increasing lack of response suggested that the parasite might be showing resistance to the antimonial compounds used in treatment.

As an initial step to verifying this hypothesis, we carried out a small study to obtain preliminary data and report our findings in this article.

Materials and methods

Design of the study

All patients presenting with cutaneous leishmaniasis at the outpatient clinic of Ibn-Rushd hospital, Aleppo, during the period 2–17 January 1995 were investigated. This hospital is one of 15 similar government centres that receive and offer free treatment to patients with this disease in Aleppo.

Detailed personal information was obtained for each patient, including the type, number, size, duration, and location of lesion(s), date of onset, age of patient at time of onset, earlier treatments received, and periods of healing (if any). The lesions were photographed, and skin biopsies were obtained from some patients.

New patients were diagnosed using a direct smear test in addition to clinical diagnosis; other patients would have been diagnosed earlier at the centre at which they presented initially. The Montenegro test could not be conducted as the necessary reagents were not available.

Biopsies were taken from 31 face lesions, 25 from chronic cases, four from acute cases and two from subacute cases (in which lesions showed a lack of response to treatment). The duration of the lesions biopsied lay in the range 1.5–8 years for chronic cases, 2–4 months for acute cases and 8–10 months for sub-acute cases. Samples were fixed in 10% formalin-saline and processed for light microscopy. Paraffin sections were stained with haematoxylin and eosin.

Study population

The 206 patients seen during the survey came from 70 different residential areas in Aleppo city and its surroundings. Patients were divided into four groups according to the course of disease (Table 1): 38 (18.4%) were new patients visiting the hospital for the first time to obtain treatment for acute cutaneous leishmaniasis; and 46 (22.3%) were patients coming to the hospital for their second to sixth weekly visit, and who were still considered to have a chance of recovery. The third group of patients included 58 (28.2%) who had received more than six intralesional doses of meglumine antimoniate with no clinical recovery. These patients were considered to be unresponsive to treatment (subacute cutaneous leishmaniasis). The lesions in this group were of less than 1 year old and appeared clinically and histopathologically similar to the acute lesions, while gradually developing into the chronic stage (Fig. 1). The fourth group consisted of 64 (31.1%) patients with chronic cutaneous leishmaniasis. The duration of lesions in this group lay in the range 1.5–8 years. These patients had been subjected to various methods of treatment repeatedly without clinical recovery (Table 2).

Description of lesions

The number of lesions per patient varied from 1 to 30. In acute cases, the lesions presented in two forms: dry (85%) and ulcerative (15%), which differed in their clinical appearance and development. Some patients had both forms of lesions at the same time. The dry forms were of two types: dry and smooth with no crust and dry with a crust. The smooth type mostly occurs on the face or neck, starting as a bright pink to violaceous papule, ranging from 3 mm to 1 cm in diameter. After 4 months, thin transluscent scales start to cover the lesion. This particular type is most resistant to treatment, especially with the intralesional method, and frequently becomes chronic, with new lesions sometimes appearing around the mother lesion at the sites of injections. In the dry crusted type, a moderately thin, silvery, adherent crust starts forming on the nodule very early. After about 4 months, if untreated, the crust thickens, and occasionally several small red papules (satellite lesions) appear around the mother lesion about 0.5–1 cm away from the margin. In the ulcerative form, lesions present as well-defined ulcers about 1–5 cm in diameter, with a thick brown firmly adhering crust at the centre. The skin around the ulcer (2 mm–2 cm) is inflamed, and assumes a dusky violet hue. This form of the disease responds very well to treatment, and rarely becomes chronic.

In chronic cases, some lesions are dull-red plaques, with healing centres, and raised, active, spreading borders leading to gyrate or annular structures; others take the form of soft papules ranging in colour from pink to brick red and are covered with thin whitish scales. Such papules appear at or near the border of a scar or even within the scar itself.

The intralesional method of treatment

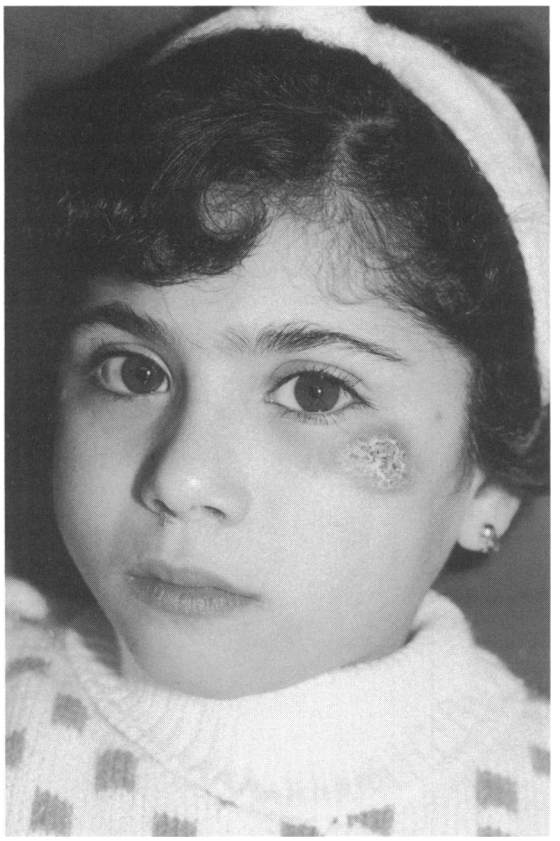
A 1-ml sterile, disposable syringe with a No. 26 needle was used. For a lesion 1 cm in diameter, 1–2 ml of meglumine antimoniate was injected into the upper-

Table 1: **Characteristics of the study patients with cutaneous leishmaniasis seen at Ibn-Rushd hospital, Aleppo, Syria, January 1995**

Patient group	No. of patients	Age of patients: Children (<15 years)	Age of patients: Adults (>16 years)	Location of lesion: Exclusively on the face	Location of lesion: On the face and extremities	Location of lesion: Exclusively on the extremities	Duration of lesion: 1–6 months	Duration of lesion: 7–12 months	Duration of lesion: 1–2 years	Duration of lesion: >2 years
1. New patients (1st visit)	38 (18.4)[a]	20 (52.6)	18 (47.4)	12 (31.6)	10 (26.3)	16 (42.1)	35 (92.1)	3 (7.9)	—	—
2. 2nd to 6th weekly visit	46 (22.3)	31 (67.4)	15 (32.6)	17 (37)	7 (15.2)	22 (47.8)	39 (84.8)	7 (15.2)	—	—
3. More than 6 weekly visits with poor response	58 (28.2)	37 (63.8)	21 (36.2)	28 (48.3)	6 (10.3)	24 (41.4)	32 (55.2)	26 (44.8)	—	—
4. Chronic cutaneous leishmaniasis	64 (31.1)	60 (93.8)	4 (6.3)	52 (81.3)	12 (18.8)	—	—	—	43 (67.2)	21 (32.8)
Total	206	148 (71.8)	58 (28.2)	109 (52.9)	35 (17)	62 (30)	106 (51.4)	36 (17.5)	43 (20.9)	21 (10.2)

[a] Figures in parentheses are percentages.

Fig. 1. **Leishmanial plaque of 1-year's duration, still active despite intralesional treatment, and showing development into chronic stage.**



and mid-dermis exclusively, at four points around the lesion, beyond the inflamed area. The lesion became swollen and white in colour. The treatment was repeated at weekly intervals for 6 consecutive weeks.

Results

The majority of patients (71.8%) were children under 15 years of age. The proportion was even higher (93.8%) in patients with chronic cutaneous leishmaniasis (Table 1).

The face was the most frequent location for lesions, with almost 70% of patients having at least one sore on the face and 81.3% of chronic patients having lesions exclusively on the face (Table 1).

Table 2 indicates the amounts of drugs administered to patients with chronic cutaneous leishmaniasis without success.

Histopathology

No sign of necrosis was detected in any of the biopsies. In four (16%) of the 25 biopsies from chronic lesions there was an ill-defined granulomatous infiltrate intermingled with lymphocytes and histiocytes. The duration of these lesions was 1.5–3 years. In 18 (72%) of the biopsies, the dermal infiltrate consisted of well-defined tuberculoid granulomas surrounded by a dense zone of lymphocytes and a few plasma cells. The duration of these lesions exceeded 3 years. In the remaining three (12%) biopsies, the dermal infiltrate was diffuse and composed of macrophages, lymphoid cells and some plasma cells. The duration of these lesions was less than 2 years. The inflammatory infiltrate was examined and in 10 cases (40%) inflammatory changes reached the upper layers of the subcutaneous tissues (Fig. 2), while in the remaining 15 (60%) the changes did not extend beyond the dermis. Amastigotes were detected in various proportions in 5 (20%) of the biopsies but there was no correlation between the presence of parasites and the duration of the lesion.

In biopsies from the two sub-acute cases, the inflammatory infiltrate was diffuse with ill-defined chronic granulomatous changes.

In biopsies from the four acute cases, the dermal infiltrate consisted predominantly of large macrophages filled with great numbers of *Leishmania* organisms in addition to lymphoid cells and a few plasma cells. In three of these cases (75%), the inflammatory changes had reached the upper layers of the subcutaneous tissues.

Discussion

The intralesional use of pentavalent antimonials as the sole treatment for cutaneous leishmaniasis has mainly been reported or recommended only for very small and localized lesions (*8*) and in cases where the infective species do not cause chronic or recurrent cutaneous leishmaniasis (*9*). Systemic therapy with antimonials for the treatment of primary cutaneous leishmaniasis has been specifically recommended if the infective agent is *L. tropica* (*3*), as in Aleppo, because of the potential risk of development of chronic infection.

The success achieved in Aleppo using intralesional meglumine antimoniate in speeding up recovery from acute cutaneous leishmaniasis, and its

Table 2: **Details of previous treatments received by the 64 study patients with chronic cutaneous leishmaniasis**

No. of patients	Type of treatment[a]	No. of sessions, treatment
18	Intralesional alone	3–50, intralesional
4	Systemic alone	10–20, systemic
22	Intralesional then systemic	2–68, intralesional 2–20, systemic
8	Intralesional then cryocautery[b]	1–50, intralesional 2–10, cryocautery
3	Intralesional then intralesional steroids	25–30, intralesional 1–2, intralesional steroids
2	Intralesional then systemic then cauterization	16–25, intralesional 10, systemic before cauterization
2	Intralesional then cryocautery then intralesional steroids	10, intralesional 5, cryocautery 3, intralesional steroids
5	Intralesional then systemic then cryocautery then intralesional steroids	15–20, intralesional 1–14, systemic 1–2, cryocautery 1–2, intralesional steroids

[a] Unless otherwise indicated, intralesional and systemic treatment was with pentavalent antimonials.
[b] Cryocautery was performed using CO_2 "snow".

superiority compared with other methods in terms of being less hazardous to the patients and much cheaper, has led to its widespread use in Aleppo over a prolonged period.

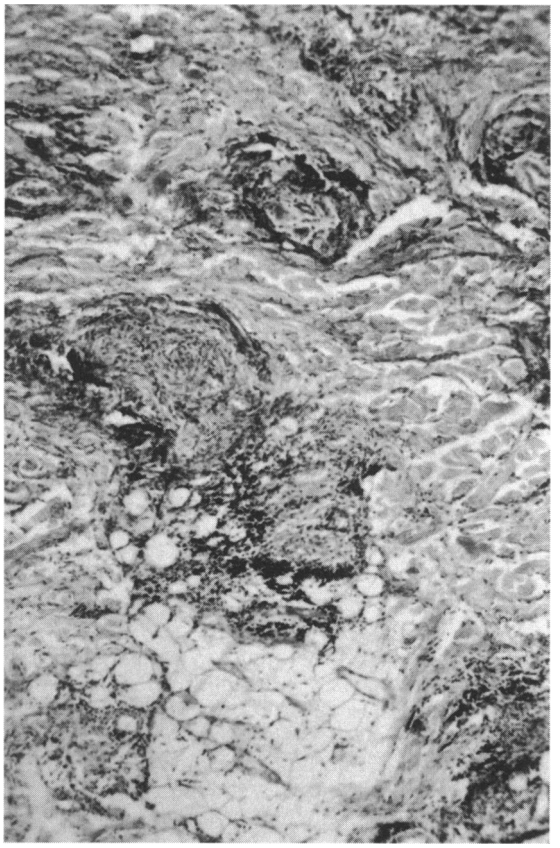
Systemic therapy alone using meglumine antimoniate or sodium stibogluconate gave results that were less satisfactory than those obtained with intralesional treatment alone using meglumine antimoniate (*5*). Even in instances when the use of systemic therapy was recommended owing to the size or number of lesions, we found that simultaneous use of the drug intralesionally and systemically (combined treatment) considerably enhanced its effectiveness (M. Douba, unpublished data, 1990). This situation continued in Aleppo until a few years ago, when response to treatment started to decline gradually.

Today, lack of response to treatment has become very common, and the rate of chronic cutaneous leishmaniasis has exceeded all previously reported levels. The increasing ineffectiveness of the method of treatment that had been successful for 25 years led us to suspect that the parasite had become resistant to pentavalent antimonials. To confirm this hypothesis, isolation of the parasite from resistant patients and *in-vitro* studies are recommended. We have been unable to conduct such studies owing to lack of facilities.

The rate of chronic and recurrent cutaneous leishmaniasis reported in the literature has never exceeded 10% (*3*). In this study, the rate of the chronic form was 31.1%. We consider that a substantial number of these cases are not exhibiting true chronicity but rather "treatment-induced chronicity". The use of the intralesional method of treatment alone and exclusion of systemic treatment might be the cause of this chronicity. Inadequate initial treatment interferes with the development of natural immunity, and can result in partial healing and partial immunity as well as in the development of a state that resembles chronicity. It appears that patients can remain in this phase for years before possible recovery.

Another phenomenon that is worth noting is the clear and unexplained increase in total incidence of cutaneous leishmaniasis in Aleppo (*7*). This could be a logical consequence of the increase in chronicity and hence growth of the human reservoir of the parasite. Infected individuals who move to newly inhabited residential areas could easily transfer the infection (the resistant strain in particular) to susceptible individuals, since their lesions are continuously active and generally located on exposed areas of the body. In Aleppo, the disease is no longer restricted to the poor, previously "endemic" areas; the 206 patients in this study came from 70 different residential areas.

Fig. 2. **Histopathological section of chronic leishmaniasis lesion (2-years' duration) showing the inflammatory changes in the subcutaneous tissues.**



If the intralesional method is responsible for the evolution of resistance to the drug, there are two points to consider: errors in carrying out the technique; and the inadequacy of the intralesional technique as the sole method of treatment.

The apparent simplicity of the intralesional technique permits persons who are not medically qualified to administer the drug to patients, especially in poor endemic areas where there is considerable overload of work. Errors in the application of the technique include administration of insufficient amounts of the drug per injection, an insufficient number of injections per lesion, wrong selection of sites for injections, harmful injections that penetrate deeper than the dermis into the subcutaneous tissues, and haphazard scheduling and early interruption of treatment. Such errors mean that the different parts of a lesion receive different concentrations of the drug. It is not uncommon to see a patient with two lesions, one responding well to treatment and ultimately recovering leaving a scar, and the other developing into chronicity. Treatment that is inadequate in dose or duration leads to relapse and drug resistance (*10*).

Use of the intralesional technique alone is not suitable for the treatment of the less common clinical expressions of cutaneous leishmaniasis, such as the pseudo-epitheliomatous forms (nose), psoriasiform plaques (elbows, knees) and verrucous forms (ankles). Intralesional treatment alone inevitably leads to chronicity of these lesions. Moreover, satellite lesions newly developing as papules around the mother lesion are often not covered by the treatment because they are not yet clearly visible. Consequently, certain foci of parasite clusters remain that are not reached by the drug, which could constitute the reservoir for the future nodules that are observed in cases of recurrent cutaneous leishmaniasis. Another drawback of the intralesional technique is that the drug is injected into the upper- and mid-dermis exclusively. However, in this study, in 10 of the 25 chronic patients (40%), and in three of the four acute cases (75%), the inflammatory changes had reached the upper layers of the subcutaneous tissues. This level of skin is not directly reached when the drug is injected intralesionally.

Recently, we have used combined intralesional and systemic treatment with antimonials for several acute cases and obtained much better results than with intralesional treatment alone (M. Douba, unpublished data, 1995). However, double-blind, randomized clinical trials with placebo are needed in order to prove the superiority of the combined method or of systemic treatment alone.

Investigations are also required to determine why the chronicity occurs mostly in children and in lesions located on the face, in particular. Anatomical characteristics specific to the skin of the face could be crucial, but in the meantime we recommend that children with lesions located on the face should be considered to be at high-risk of chronicity. Such patients should be given combined systemic and intralesional treatment, ensuring that the dose of antimonials conforms to that recommended by WHO.

In the long term, efforts should be made to find an alternative treatment for acute cutaneous leishmaniasis, which is both low in cost and easy to administer. There have been several reports promoting the use of paromomycin to treat cutaneous leishmaniasis, but our experience with this ointment has so far been disappointing, and it is also expensive.

In our opinion the real problem lies in the growing population of unresponsive chronic patients. As

long as their lesions are still active, control of cutaneous leishmaniasis is beyond reach.

Our results emphasize the need for further studies to try to control this disfiguring disease, which is becoming a threat to every family in Aleppo.

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Résumé

Situation actuelle de la leishmaniose cutanée à Alep (République arabe syrienne)

A Alep (République arabe syrienne), on a constaté une nette augmentation du nombre de patients atteints de leishmaniose cutanée qui ne répondent pas à l'administration intralésionnelle de dérivés pentavalents de l'antimoine, considérée depuis le début des années 70 comme le traitement de première intention de la maladie. Autrefois, l'injection intralésionnelle d'antimoniate de méglumine suffisait pour obtenir la guérison complète et l'on n'observait pas plus de 3 à 5% de cas chroniques ou récurrents. Il n'en est plus de même aujourd'hui. L'absence de réponse au traitement a entraîné une augmentation préoccupante des cas chroniques. On a donc soupçonné une résistance du parasite au médicament et une petite enquête a été entreprise.

Cette enquête a porté sur tous les patients qui se sont présentés avec une leishmaniose cutanée à l'hôpital Ibn-Rushd du 2 au 17 janvier 1995. Les patients ont été classés en fonction du stade de la maladie et des traitements qu'ils avaient suivis antérieurement. Des biopsies ont été pratiquées sur 31 d'entre eux pour analyse.

Sur les 206 sujets examinés, 38 (18,4%) étaient de nouveaux patients jamais traités auparavant (cas aigues), et 46 (22,3%) venaient pour la deuxième à la sixième fois recevoir leur injection intralésionnelle hebdomadaire de dérivé stibié pentavalent. En outre, 58 malades (28,2%), qui avaient reçu plus de six injections intralésionnelles sans amélioration clinique, ont été considérés comme réfractaires au traitement. Les 64 autres patients (31,1%) présentaient une leishmaniose cutanée chronique établie.

L'examen des biopsies a montré que la réaction inflammatoire atteignait la partie supérieure des tissus sous-cutanés dans 10 cas chroniques sur 25 (40%) et dans les trois quarts (75%) des cas aigus. L'administration d'antimoniate de méglumine dans les lésions est tenue pour responsable de la résistance de *Leishmania tropica* et du développement d'une "chronicité" iatrogène. En effet, le médicament n'atteint pas la même concentration aux différents niveaux du tissu cutané, ce qui entraîne une cicatrisation partielle ou temporaire des lésions. En outre, si le médicament est administré de façon incorrecte (quantité insuffisante, mauvais choix des sites d'injection, non respect du calendrier d'administration, interruption précoce du traitement), il peut arriver que des foyers parasitaires, notamment des lésions satellites, ne soient pas traités.

Il est recommandé de combiner le traitement général et les injections locales, notamment chez les patients qui présentent un risque élevé d'évolution chronique. Il faudrait également entreprendre des recherches pour trouver une autre méthode de traitement de la leishmaniose cutanée aiguë qui soit à la fois peu coûteuse et facile à appliquer.

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