

Treatment of Cutaneous leishmaniasis with some Local Sudanese Plants (Neem, Garad & Garlic)

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SUMMARY: A total of 72 cutaneous leishmaniasis (CL) cases referred to the Wad Madani Teaching Hospital between September 1999 and December 2000 were included in the present study. The patients were from different parts of the Gezira State. The duration of lesions varied between several days and more than one year, with the duration of most of them ranging between 1-3 months (91.6%). Different types of lesions were observed such as ulcerative (63.9%), nodular (31.9%), nodular/ulcerative (2.8%), and fungal/ulcerative (1.4%). These lesions were found on different parts of the body including the limbs (87.5%), face (1.4%), and trunk (1.4%). The number of lesions varied between 1 and 16. The CL cases were treated using medicinal agents and plant methanol extracts. All agents showed good response (90.3%). The response ratio of medicinal agents to plant methanol extracts was 1.03:1. Garlic (*Allium sativa*) showed 100% response, with no significant difference from pentostam ($p=0.75$). Also neem (*Azadirachta indica*) showed an insignificant difference from pentostam ($P=0.09$). Leishmanol and garad (*Acacia nilotica*) showed significant difference from the control ($P=0.05$ & 0.04 respectively).

Key words: Cutaneous leishmaniasis, herbal therapy, Sudan

Sudan'da Yetişen Bazı Bitkilerle (neem, garad, sarımsak) Kutanöz Leishmaniasisin Tedavisi

ÖZET: Bu çalışmaya, Eylül 1999 ile Aralık 2000 tarihleri arasında Wad Madani Eğitim Hastanesi'ne başvuran ve Gezira Eyaleti'nin farklı bölgelerinden gelen 72 kutanöz leishmaniasisli (KL) hasta dahil edilmiştir. Hastalardaki lezyonların süresinin birkaç gün ile bir yıldan fazla, çoğunun -3 ay arasında (%91.6) olduğu saptanmıştır. Lezyonların, ülseratif (%63.9), nodular (%31.9), nodular/ülseratif (%2.8) ve mantar enfeksiyonlu/ülseratif (%1.4) gibi farklı tiplerde olduğu ve %87.5'inin kol ve bacaklarda, %1.4'ünün yüzde ve %1.4'ünün gövdede bulunduğu görülmüştür. Lezyon sayısının 1 ile 16 arasında değiştiği belirlenmiştir. Bu hastalar, konvansiyonel ilaçlar ve bitki etanol ekstratları kullanılarak tedavi edilmiş ve bütün ajanlarla %90.3 civarında olumlu sonuç alınarak, tedavide iyi oldukları görülmüştür. Konvansiyonel ajanlarla, bitki etanol ekstratlarına verilen cevap arasındaki oranın 1.03:1 olduğu saptanmıştır. *Allium sativa* (sarımsak) %100 olumlu sonuç verirken, pentostam ile arasında anlamlı bir fark olmadığı bulunmuştur ($p=0.75$). *Azadirachta indica* (Neem) da aynı şekilde yüksek etkili bulunmuş ve pentostam ile anlamlı fark saptanmamıştır ($p=0.09$). Leishmanol ($p=0.05$) ve *Acacia nilotica* (garad) ($p=0.04$) ise kontrol ile önemli derecede farklılık göstermiştir.

Anahtar kelimeler: Leishmaniasis, kutanöz, bitkisel tedavi, Sudan

GİRİŞ

Leishmaniasis are group of diseases with variable clinical presentations involving the viscera, mucosa and/or the skin. All these modalities are seen in Sudan beside the presence of a group of sub-clinical form (1-3).

Cutaneous leishmaniasis (CL) is skin involvement by *Leishmania* parasite in which the amastigote multiplication is

restricted to the skin macrophages. CL is caused by *L. tropica* complex in the Old World and *L. mexicana* complex in the New World.

In Sudan, CL was first reported in 1910 (19) and then the disease was reported in different parts of the country (6, 17). Abdalla & Sharif (5) reported the first outbreak of CL in the Shendi Atbra area, Sudan. The severe outbreak was reported by El Safi and Peter in 1991 (9). Abdalla *et al.* (4) studied on 21 cutaneous leishmaniasis cases, classified the lesions into three main types: (a) nodule-ulcerative and nodular, (b) ulcerative and (c) diffuse infiltrative types.

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Pentavalent antimonial compounds are the first line drugs in the treatment of CL and available in two forms as sodium stibogluconate (Pentostam[®]) and meglumine antimoniate (Glucantime[®]). On the other hand, different drugs and/or modes (chemicals, acids, antibiotics, cryotherapy and medicinal plants) for the treatment of CL are being used in the world (20). They are either showed a slight or highly effective on the parasites (8).

In the present study, we tried to efficacy of ethanol extracts of some plants growing in Sudan (neem, garad and garlic) in the treatment of cutaneous leishmaniasis. As a therapeutic agent, neem (*Azadirachta indica*) is one of the most popular trees in traditional medicinal systems and is increasingly becoming important in herbal alternative therapy. The tree itself is considered a “village pharmacy” because of the well-established fact that every part of the tree has an application in curing human diseases. *Acacia nilotica* grows in eastern Sudan and the local name of the plant is “Garad”.

MATERIALS AND METHODS

The study was carried out in Department of Dermatology of Wad Madani Teaching Hospital, Gezira State, Sudan. The study was carried out between September 1999 and December 2000. Specialized cutaneous leishmaniasis clinic was established and held for one day in a week. Seventy-two cases from different parts of Gezira State were included into the present study.

The objectives of the study were clearly explained to the patients. All cases gave a written agreement before their participation to the study. Each patient was interviewed and examined following a special designed questionnaire. This includes age, sex, locality, site, types, size, number of lesions and their duration and treatment, follow up and observation. Clinical examination was confirmed by a definitive laboratory diagnosis in which the amastigotes were examined microscopically.

Seventy-two patients were included into the study, and their ages ranged from 3 - 63 years old (mean = 28.2 years). Most of these cases (31.9%) their age ranged 21- 30 years old. Both sexes are included the study; male were 52.8% and female were 47.2%. They were from different parts of Gezira State (43.1% were from rural and 56.9% were from urban area). The study population had been divided into six categories (72 cases) equally in random manner.

The first one, which is a reference or control group, was admitted to hospital and treated with intravenous Pentostam. The starting dose was one ml., then one ml was added daily up to 5 ml (building dose), and then the patient was injected with 5 ml daily or alternatively for 10 days. In every case an electrocardiogram was done before the drug was administered.

The remaining groups were treated as out patients orally or topically as followed:

- The first group was subjected to metronidazole orally (750 mg/day) with co-trimoxazole (1 g/day).
- The second group used leishmanol topically twice a day.
- The third group was treated with neem methanol extract (100 mg/ml). It was being used topically twice a day.
- The fourth and fifth groups were treated in the same manner of the neem, by garad and garlic methanol extracts.

All patients were followed up weekly for two months.

Assessment of treatment: Criteria for the efficacy of the treatment were diminution or absence of parasites and macroscopic resolution of the lesion. The following definitions were used according to Abdalla (4):

1. Complete healing; smooth scar and parasite not detectable.
2. Partial healing; complete or almost epithelization and parasite not detectable.
3. Active lesion; the lesion with raised, reddish edges regardless the presence or absence of parasites.

RESULTS

The lesions were showed the morphological variations: 31.9% nodular, 63.9% ulcerative (most common type), 2.8% nodular and ulcerative and only 1.4% of the cases fungating/ulcerative.

These lesions were located in the different parts of the body but most of them were on the unclothed areas. Totally, 87.5% of the cases had at least one lesion on the lower or upper limbs.

The number of lesions was varied from one patient to another. Totally, 402 lesions were counted on the patients and the mean was 5.5. Multiple lesions were very common. The maximum number in one patient was 16 lesions. The 61.1% of CL cases had 1-5 lesions and the majority of this group had one lesion (22.2%). The 25% of CL cases had 6-10 lesions, 8.3% of CL cases had 11-15 lesions and only 5.6% of the patients had 15 lesions. The size of the lesions varied between few millimeters and more than 3 cm. Also their duration varied from few days to more than one year but the most of these cases (91.6%) ranged from few days to three months.

Treatment: The effect of agents used for the treatment of patients, 90.3% of cases showed good response while 9.7% could not show any improvement. 36.1% of cases showed complete healing while the rest (54.2%) showed partial healing of lesions. All cases treated with pentostam and garlic showed good response. Two cases showed complete failure of treatment with each of leishmanol, neem and garad. Only one case showed the failure in the treatment with metronidazole. The standard (pentostam) had mean 24.08 days. The shortest mean had been reported with garlic treatment (19.75 days). The longest one was seen in cases treated with metronidazole (27.4 days).

Table 1. The mean difference of pentostam (standard agent) with the other agents

Pentostam Vs	Mean diff.	Std dev.	Std. Err.	T value	Sig.
Leishmanol	0.005	0.7977	0.2303	2.171	0.05
Metronidazol	0.4167	0.9962	0.2876	1.449	0.19
Neem	0.4167	0.7933	0.2289	0.82	0.09
Garad	0.4176	0.9003	0.2599	2.244	0.04
Garlic	8.333	0.9003	0.2599	0.321	0.75

DISCUSSION

Our study showed that all age groups and both sexes were exposed to leishmanial infection. The highest infection was observed in a group of age 21 - 30 years (31.9%).

This fact was in agreement with El Safi *et al.* (10), Gaafar *et al.* (14) studies.

The infection was widely spread in the Gazira State covering the urban and rural citizens (Urban: rural=1.3:1). This may be due to the agricultural nature of the State and its situation along the bank of the Blue Nile in addition to the presence of canals in areas, which are remote to the river. The previous studies carried out by El-Safi&Peter (9) and Abdalla&Sharif (5) were confirmed this result.

The variation in morphology of lesions indicated that the majority of cases were reported late after ulceration (63.9%), this might be due to the fact that cutaneous leishmaniasis is painless. Patients seek for the treatment after ulceration and complication by secondary infection. El Safi (9) and Etoum (13) studies were confirmed this finding.

The study was proved that infection could involve all parts of the body. The most infected parts are the limbs (87.5%). This may be due to the fact that the limbs are the most exposed areas to sand flies bite particularly at night. El Safi *et al.* (11) and Gaafar *et al.* (14) reported the same results.

Duration of lesions varied from few days to more than one year. Most cases showed duration between 1-3 months (91.6%). This goes with El Safi *et al.* (11) and Etoum studies (13). The 2.8% of the cases in our study showed duration of lesions more than five months. This result indicates that cutaneous leishmaniasis lesion can remain up for more than one year if patients were not treated. According to Abdalla *et al.* (4), 4.7% of cases had duration of lesions up to 18 months.

The size of lesions varied from few millimeters to more than three cm. This is in accordance with El Safi (9) and Abdalla *et al.* (4) showed variations of the lesion size from 1 cm to 6 cm.

The number of lesions varied from one to sixteen lesions in one patient with mean (5.5). El Safi *et al.* (9) reported that multiple lesions were very common among patients (80%) of cases.

WHO (2000) reported that, the disease can produce a large number of lesions sometimes up to 200 lesions causing serious disability leaving the patient permanently scared, stigma which can cause serious social prejudice.

Because of the prognosis of CL infections varies according to the site, extent of the lesion and severity, different treatment regimes is required. In this study, we used different agents for the treatment.

The agents used for the treatment in our study showed response in 90.3% of the cases and only 9.7% of the cases showed no response or complete failure. The response varied from complete healing to partial healing in period ranged from 15 days to 45 days. The response ratio of medicinal agents to plant methanol extract was 1.03: 1 (approximately similar). This indicates the importance of consideration for folk Sudanese plants in the treatment of cutaneous leishmaniasis and other parasitic diseases. This was supported by the study of Khalid *et al.* (15, 16) showed that medicinal Sudanese plants are rich and diversified in the treatment of some diseases. However few studies investigated the potential usage of these plants.

Our study showed that the combination of metronidazole and co tri-moxazole caused to response in 91.6% (11/12) of CL cases, but only 16.6% (2/12) showed complete healing, while the rest just showed partial healing in period ranged from 15-37 days (mean 27.4 days). This result reflected that the combination of metronidazole and co-trimoxazole had an effectiveness of anti-leishmanial activity on cutaneous leishmaniasis with no significance difference with the control (P=0.195). This result showed agreement with Etoum (13), reported that the majority of the patients had responded to combination of metronidazole and co-trimoxazole (97%).

Leishmanol showed 83.3% (10/12) response of cases in period ranged from 15 to 37 days (mean 26 days). However, only 25% of cases showed complete healing. This result can be supported by the study, which was carried out in Department of Pharmaceutical chemistry (Khartoum University) Michigan Laboratory of National Health in July 1992- June 1993. The present study carried out with 72 cases. The 73.3% (52/72) of cases showed improvement within 7- 14 days (El Fatih, direct communication, University of Khartoum, Sudan).

One patient, who had already been treated with leishmanol and showed complete healing, he later showed a second leishmanial infection, which appeared at new sites after 5weeks. This may be due to new transmitting infection or due to the development of previously very small lesion, which had not been noticed early. Recurrent was noted in Elyzeragab tribe in Sudan, El-Kadaro *et al.* (7). Moreover another patient who had been treated with leishmanol showed dermatitis as a side effect.

The methanol extracts of all studied plants were used topically twice a day with the concentration equal 0.1 g/ml. Neem showed response in 83.3% (10/12) in period ranged from 15-37 days (mean 21.67 days). From the responded cases 33.33%

showed complete healing and 50% showed partial response. The failure of treatment had been shown in two cases this may be due to the location of the lesion (joint area). This result indicates that neem can be considered as anti-leishmanial agent. Neem was worldwide used traditionally, in both the maintenance of general health and skin care (18). It is clinically proven to be anti-parasitic, anti fungal, antiviral, anti bacterial, and anti-inflammatory. Also it is proven to be effective against some serious skin conditions like eczema. (18).

The extract of garad showed response in 83.3% of cases but only 16.6% of the cases showed complete healing. Garad showed significance with the standard (P= 0.04). However, it may be accepted as anti-parasitic according to El-Tahir *et al.* (12). Garad cannot be accepted as appropriate anti-leishmanial agent according to our study result.

All cases treated with garlic methanol extract showed response (100%). In 91.6% (11/12) of cases this response occurred within 15-22 days (mean 19.75 days) (see pictures). However one case showed response within 30 days. It showed no significance with pentostam. 66.67% of cases showed complete healing in case of garlic while pentostam showed complete healing in 58.3% of cases only. This result indicates that garlic can be considered as a powerful anti-leishmanial agent. It might be even better than pentostam in the treatment of cutaneous leishmaniasis. There is no published work in the field of usage of garlic *in vivo* against cutaneous leishmaniasis. However aqueous extract of garlic was tried in the treatment of 10 children infected with *Hymenolepis nana* and 26 infected with giardiasis lamblia. It was found to be efficient and safe and of short period of treatment. Also Venugopal and Venugopal (21) studied the ability of garlic to treat ringworm. They concluded that garlic could be used as effective anti-dermatophytic agent and even more it may be better than the standard anti-fungal drugs.

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