Lymphatic Dissemination in Cutaneous Leishmaniasis Following Local Treatment

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Abstract. Cutaneous leishmaniasis (CL) is diverse in its clinical presentation but usually demonstrates an erythematous, infiltrated, ulcerated, and crusted papule or nodule in exposed areas of the body. Rare clinical features have been reported including lymphatic dissemination, usually with subcutaneous nodules along lymphatic channels. Herein, we present six patients suffering from Old World CL with lymphatic dissemination characterized by sporotrichoid subcutaneous nodules along the lymphatic channels draining the primary lesion. Patients' history, clinical and laboratory findings were collected and summarized. Lymphatic dissemination of CL in our patients manifested as subcutaneous nodules without epidermal involvement within the axis of lymphatic drainage toward the regional lymph node, at times accompanied by regional lymphadenopathy. In all patients, the lymphatic dissemination was not present at initial diagnosis of CL, appearing only after local (topical or intralesional) treatment was initiated. In three patients, the subcutaneous nodules resolved without systemic treatment. Lymphatic dissemination of Old World CL is not uncommon and may possibly be triggered by local treatment. It should be recognized by dermatologists, especially those working in endemic areas. Systemic treatment may be not necessary since spontaneous resolution may occur.

Old World cutaneous leishmaniasis (CL) is diverse in its clinical presentation and outcome. The disease spectrum is governed by an interplay between the parasite and the immunoinflammatory response of the host. The typical clinical presentation of CL is an erythematous, infiltrated, ulcerated, and crusted papule or nodule on any region of the body, with frequent involvement of exposed areas, especially the face and limbs. Lesions heal slowly over a period of months.¹ Although CL often resolves spontaneously, it can result in severe disfigurement. Treatment is usually initiated to hasten healing and prevent scarring.²

Old World CL is endemic in Israel and was attributed in the past almost exclusively to *Leishmania* (*Leishmania*) *major*, confined to rural areas of the Negev Desert in southern Israel. Over the last decade, CL due to *Leishmania tropica* has been increasingly reported in the Judean Desert in central Israel, as well as in northern Israel. *Leishmania tropica* is often more resistant to treatment and heals more slowly than *L. major* infections.³

Lymphatic dissemination of CL is uncommon but has been reported, usually with dermal or subcutaneous nodules along lymphatic vessels draining the region of the primary lesion.^{4–7} Herein, we present six cases of CL with subcutaneous sporotrichoid dissemination after local treatment of the primary lesion, probably caused by lymphatic spread of the parasites. The sporotrichoid dissemination was characterized by deep subcutaneous nodules without any sign of epidermal involvement.

The demographic, clinical, and laboratory data of the patients are summarized in Table 1. Patients 1 and 2 reside in areas endemic for *L. major*, whereas patients 3–6 live in an area endemic for *L. tropica*. All patients were treated locally with either topical Leshcutan® (TEVA Pharmaceutical Industries Ltd., Petach Tikva, Israel; 5% paromomycin + 12% methylbenzethonium) ointment (patients 1–3) or with

intralesional sodium stibogluconate. The nodules appeared during local treatment of the primary lesions, approximately 2–4 weeks after the initiation of the treatment, were painless and were either distributed in a linear pattern resembling a cord (patients 1 and 4) or as multiple separate lesions in the area proximal to the primary lesion (patients 2, 3, 5, and 6). Internal transcribed spacer 1 polymerase chain reaction (ITS1-PCR)⁸ performed on tissue obtained from primary lesions (patients 4 and 5) or from subcutaneous nodules (patient 6) confirmed *L. tropica* infection. Regional lymphadenopathy was noted in two patients (patients 2 and 3). In patients 3 and 6, a biopsy from the subcutaneous nodules established the presence of a deep granulomatous process with *Leishmania* bodies. After the occurrence of subcutaneous nodules, three patients were treated with intravenous sodium stibogluconate (patient 1, 3, and 4), or with sodium stibogluconate injected directly into the primary cutaneous lesion alone (patient 6) or into both the cutaneous lesion and the subcutaneous nodule (patient 5). The patients experienced total resolution of the primary lesions, the subcutaneous nodules, as well as regional lymphadenopathy. On the patients' request, intralesional injections of pentostam were terminated after a single treatment in patient 2. The primary lesion eventually healed with a scar and the subcutaneous nodules spontaneously regressed within a few weeks.

Sporotrichoid dissemination is characterized by the development of secondary lesions, often associated with lymphangitis that progresses along dermal and subcutaneous lymphatics.

The exact prevalence of Old World sporotrichoid CL is unknown but ranges between 10% and 19% of affected individuals in previous reports.^{6,7} The majority of reported sporotrichoid CL cases were shown to be caused by *L. major*,^{4,7} although *L. tropica* has also been implicated. The prevalence of this phenomenon may be species dependent but there are no data comparing rates of sporotrichoid CL among various species. Akilov and others⁹ in their classification of Old World CL also described this pattern of local spread of CL. They regard the sporotrichoid subcutaneous nodules as a form of lymphatic dissemination of the parasite and describe three clinical patterns: 1) subcutaneous nodules in

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TABLE 1
Demographic, clinical, and laboratory findings

Cases	Sex	Age (years)	Geographic region	Presenting symptoms	Initial treatment before appearance of subcutaneous nodules	Morphology and location of subcutaneous nodules	Regional lymphadenopathy	Investigations	Treatment with intravenous sodium stibogluconate	Response to treatment
1	M	16	Negev Desert	8-month history of an infiltrated and ulcerated erythematous plaque on right forearm	Paromomycin ointment	Subcutaneous painless cord extending proximally in a linear pattern from the right antecubital fossa toward the axilla (Figure 1A, B)	No	Smear: positive for amastigotes Doppler ultrasound: infiltration of lymphatic vessels	Yes	Flattening of the indurated plaque and disappearance of the subcutaneous cord
2	M	1.8	Negev Desert	6-month history of an ulcerated erythematous plaque on the right lower forehead	Paromomycin ointment and intralesional sodium stibogluconate	Two 5-mm soft and mobile subcutaneous nodules on the right cheek and right upper eyelid with overlying faint pink discoloration (Figure 1C), appeared a few weeks after the treatment with intralesional sodium stibogluconate	Yes (cervical)	Smear: positive for amastigotes Ultrasound: nondiagnostic	No	Subcutaneous nodules spontaneously regressed and the ulcerated plaque healed leaving a scar
3	F	16	Judean Desert	1-year history of two ulcerated erythematous plaques on right and left forearms	Paromomycin ointment and four treatment with intralesional sodium stibogluconate once weekly	Numerous 2-mm subcutaneous nodules above the primary lesions up to the armpit in both upper extremities	Yes (axillary)	Smear: positive for amastigotes Ultrasound: nondiagnostic. Biopsy (from a subcutaneous nodule on the left arm): normal epidermis and dermis, an epithelioid granuloma with plasma cells and abundance of <i>Leishmania</i> bodies was noted in the subcutaneous fat (Figure 2)	Yes	Flattening of the primary lesions and disappearance of the subcutaneous nodules
4	M	9	Judean Desert	10-month history of infiltrated erythematous, ulcerated plaques on the right cheek, right upper lip, angle of mouth, and left forearm	Two intralesional treatments with sodium stibogluconate	Subcutaneous cord extending from the right angle of the mouth to the right aspect of the jaw (Figure 3A)	No	Smear: positive for amastigotes ITS1-PCR: tissue from a primary lesion was positive for <i>Leishmania tropica</i>	Yes	Resolution of the subcutaneous cord and flattening of the plaques on face and forearm
5	F	7	Judean Desert	2 months history of erosive erythematous plaques at the tip of the nose, upper lip and five papules on right arm	Three intralesional treatments with sodium stibogluconate	Two subcutaneous nodules, without overlying erythema, proximal to the nose lesion	No	Smear: positive for amastigotes ITS1-PCR: tissue from a primary lesion was positive for <i>L. tropica</i>	No	Continued treatment with intralesional sodium stibogluconate with resolution of the lesions, as well as the subcutaneous nodules
6	M	17	Judean Desert	3 months history of an ulcerated plaque on the middle phalanx of the fourth finger and an erythematous erosive plaque on right upper arm	One intralesional treatment with sodium stibogluconate	Two subcutaneous nodules on the dorsal aspect of the right hand, proximal to the lesion on fourth finger (Figure 3C, D)	No	Biopsy (from a subcutaneous nodule): profound granulomatous process in the deep dermis with necrosis in the form of palisading granulomas. Suspicious <i>Leishmania</i> bodies were noticed within necrotic areas ITS1-PCR: tissue from a subcutaneous nodule was positive for <i>L. tropica</i>	No	Continued treatment with intralesional sodium stibogluconate with resolution of the lesions, as well as the subcutaneous nodules

F = female; M = male; ITS1-PCR = internal transcribed spacer 1 polymerase chain reaction.

FIGURE 1. (A) A 5-cm infiltrated and ulcerated erythematous plaque over the right forearm in patient 1. (B) Lymphatic dissemination without epidermal involvement in patient 1. (C) A 3-cm ulcerated erythematous plaque on the right lower forehead and two 5-mm soft and mobile subcutaneous nodules on the right cheek and right upper eyelid with overlying faint pink discoloration in patient 2.

proximity to the primary lesion, 2) dilated palpable lymphatic vessels in the form of a “beaded cord,” and 3) regional lymphadenitis,⁹ all seen in our case series.

Lymphatic dissemination in our patients manifested in the form of subcutaneous nodules without the typical surface changes noted in primary CL lesions (scaling, crusts, erosions, or ulcers). This was confirmed by the biopsy specimens taken from patients 3 and 6 showing the lack of epidermal and superficial dermal involvement. The nodules were either located within the axis of lymphatic drainage toward the regional lymph node or were accompanied by regional lymphadenopathy. The presence of numerous *Leishmania* bodies in biopsy specimens of patients 3 and 6 supports the notion that the subcutaneous nodules represent metastases of the parasitic infection.

In all our patients, the lymphatic dissemination was absent at initial diagnosis of CL and appeared only after local treatment was initiated. In the 261 patients who attended our *Leishmania* clinic over the last 2 years, sporotrichoid dissemina-

tion was observed only in the six herein reported cases (2.3%), suggesting that local treatment may trigger for this phenomenon, although a proof of cause and effect is currently lacking. Previous reports in the literature also suggest that lymphatic dissemination may be evoked by antiparasitic therapy, especially the use of local irritants and local injections.^{7,9} It has been shown that intralesional sodium stibogluconate induces an inflammatory response at the site of injection as well as tissue damage,¹⁰ which may activate lymphatic drainage and result in parasitic dissemination. Therefore, we hypothesize that the tissue damage caused by local treatment triggers the spread of the parasites into the subcutis and lymphatic vessels. Large prospective studies in endemic areas, where ITS1-PCR can be performed for parasite speciation using a large prospective randomized controlled trial, are needed to prove the causative relationship raised here between local treatment and lymphatic spread of CL.

Pentavalent antimonials such as sodium stibogluconate and meglumine antimoniate either systemically or intralesionally have been used to treat sporotrichoid CL.^{4,7} In three patients (patients 2, 5, and 6), we observed disappearance of the subcutaneous nodules following the resolution of the primary lesions, without initiating systemic treatment. Therefore, we suggest that initiation of systemic treatment in cases of lymphatic dissemination of Old World CL should be guided by the response of the primary lesion to the local treatment. Although no information is available, this may not be true for New World CL, where concern for mucosal disease exists.

Lymphatic dissemination of Old World CL is uncommon. This pattern of lymphatic and subcutaneous spread of CL, possibly triggered by local treatment, should be recognized by dermatologists, especially those working in endemic areas. Awareness to this phenomenon will prevent unnecessary workup to investigate the nature of the subcutaneous lesions.

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FIGURE 2. Histopathological findings from a subcutaneous nodule on the left forearm in patient 3: inflammatory infiltrate composed of lymphocytes, histiocytes, and abundant macrophages; round or oval basophilic structures can be seen consistent with *Leishmania* amastigotes (hematoxylin and eosin, original magnification $\times 600$).

FIGURE 3. (A) Infiltrated erythematous, ulcerated plaques on the right cheek, right upper lip, and angle of mouth with a painless subcutaneous cord extending from the right angle of the mouth to the right chin in patient 4. (B) A 2-cm erythematous ulcer on nose tip with subcutaneous nodes extending proximally in patient 5. (C) A 1.5-cm ulcer on the dorsal aspect of the middle phalanx of the fourth finger in patient 6. (D) Subcutaneous nodules on the dorsum of the right hand, proximal to the finger lesion in patient 6.

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REFERENCES

1. Bari AU, 2012. Clinical spectrum of cutaneous leishmaniasis: an overview from Pakistan. *Dermatol Online J* 18: 4.
2. Burden-Teh E, Wooton CI, Williams HC, 2015. Can a simple outpatient-based treatment be used to treat cutaneous leishmaniasis in young children? A critically appraised topic. *Br J Dermatol* 172: 861–866.
3. Solomon M, Pavlotsky F, Leshem E, Ephros M, Trau H, Schwartz E, 2011. Liposomal amphotericin B treatment of cutaneous leishmaniasis due to *Leishmania tropica*. *J Eur Acad Dermatol Venereol* 25: 973–977.
4. Bailey MS, Caddy AJ, McKinnon KA, Fogg LF, Roscoe M, Bailey JW, O'Dempsey TJ, Beeching NJ, 2012. Outbreak of zoonotic cutaneous leishmaniasis with local dissemination in Balkh, Afghanistan. *J R Army Med Corps* 158: 225–228.
5. Kibbi AG, Karam PG, Kurban AK, 1987. Sporotrichoid leishmaniasis in patients from Saudi Arabia: clinical and histologic features. *J Am Acad Dermatol* 17: 759–764.
6. Masmoudi A, Ayadi N, Khabir A, Bouzid L, Bouassida S, Meziou TJ, Akrouf F, Zahaf A, Boudawara T, Turki H, 2008. Sporotrichoid cutaneous leishmaniasis in Tunisia: a clinical and histological study. *Ann Dermatol Venereol* 135: 63–67.
7. Kubba R, El Hassan AM, Al Gindan Y, Omer AHS, Kutty MK, Saeed MBM, 1987. Dissemination in cutaneous leishmaniasis. I. Subcutaneous nodules. *Int J Dermatol* 26: 300–304.
8. Schonian G, Nasereddin A, Dinse N, Schweynoch C, Schallig HD, Presber W, Jaffe CL, 2003. PCR diagnosis and characterization of *Leishmania* in local and imported clinical samples. *Diagn Microbiol Infect Dis* 47: 349–358.
9. Akilov OE, Khachemoune A, Hasan T, 2007. Clinical manifestations and classification of Old World cutaneous leishmaniasis. *Int J Dermatol* 46: 132–142.
10. Najim RA, Sharquie KE, Al-Zubaidy SA, 2006. Possible mechanisms of action of the compounds injected intralesionally in the treatment of cutaneous leishmaniasis, in addition to their direct effects on the parasites. *Ann Trop Med Parasitol* 100: 33–38.