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Tropical medicine rounds

Clinical practice guidelines for the diagnosis and treatment of cutaneous leishmaniasis in Turkey

Soner Uzun[1], MD, Mehmet S. Gürel[2], MD, Murat Durdu[3], MD, Melih Akyol[4], MD, Bilge Fettahlıoğlu Karaman[5], MD, Mustafa Aksoy[6], MD, Sema Aytekin[7], MD, Murat Borlu[8], MD, Esra İnan Doğan[9], MD, Çiğdem Asena Doğramacı[10], MD, Yelda Kapıcıoğlu[11], MD, Ayşe Akman-Karakaş[1], MD, Tamer İ. Kaya[12], MD, Mehmet K. Mülayim[13], MD, Yusuf Özbel[14], PhD, Seray Özensoy Töz[14], MD, PhD, Orhan Özgöztaşı[15], MD, Yavuz Yeşilova[16], MD, and Mehmet Harman[17], MD

[1]Department of Dermatology, Faculty of Medicine, Akdeniz University, Antalya, Turkey, [2]Department of Dermatology, Faculty of Medicine, Medeniyet University, Istanbul, Turkey, [3]Department of Dermatology, Faculty of Medicine, Başkent University, Adana, Turkey, [4]Department of Dermatology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey, [5]Department of Dermatology, Faculty of Medicine, Çukurova University, Adana, Turkey, [6]Department of Dermatology, Faculty of Medicine, Harran University, Şanlıurfa, Turkey, [7]Department of Dermatology, Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkey, [8]Department of Dermatology, Faculty of Medicine, Erciyes University, Kayseri, Turkey, [9]Department of Dermatology, Faculty of Medicine, Adıyaman University, Adıyaman, Turkey, [10]Department of Dermatology, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey, [11]Department of Dermatology, Faculty of Medicine, İnönü University, Malatya, Turkey, [12]Department of Dermatology, Faculty of Medicine, Mersin University, Mersin, Turkey, [13]Department of Dermatology, Faculty of Medicine, Sütçü İmam University, KahramanmaraŞ, Turkey, [14]Department of Parasitology, Faculty of Medicine, Ege University, İzmir, Turkey, [15]Department of Dermatology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey, [16]Department of Dermatology, Lokman Hekim Hospital, Van, Turkey, and [17]Department of Dermatology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey

Correspondence
Soner Uzun, MD
Department of Dermatology
Faculty of Medicine, Akdeniz University
07059 Antalya
Turkey
E-mail: sonuzun@hotmail.com

Abstract

Background Cutaneous leishmaniasis (CL) is a vector-born parasitic disease characterized by various skin lesions that cause disfiguration if healed spontaneously. Although CL has been endemic for many years in the southern regions of Turkey, an increasing incidence in nonendemic regions is being observed due to returning travelers and, more recently, due to Syrian refugees. Thus far, a limited number of national guidelines have been proposed, but no common Turkish consensus has emerged.

Objectives The aim of this study was to develop diagnostic and therapeutic guidelines for the management of CL in Turkey.

Methods This guideline is a consensus text prepared by 18 experienced CL specialists who have been working for many years in areas where the disease is endemic. The Delphi method was used to determine expert group consensus. Initially, a comprehensive list of items about CL was identified, and consensus was built from feedback provided by expert participants from the preceding rounds.

Results Evidence-based and expert-based recommendations through diagnostic and therapeutic algorithms according to local availability and conditions are outlined.

Conclusion Because CL can mimic many other skin diseases, early diagnosis and early treatment are very important to prevent complications and spread of the disease. The fastest and easiest diagnostic method is the leishmanial smear. The most common treatment is the use of local or systemic pentavalent antimony compounds.

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Introduction

Leishmaniasis is a vector-born protozoan parasitic disease that includes three main clinical presentations (e.g., visceral, mucosal, and cutaneous) due to interaction between parasitic factors (e.g., tropisms, virulence, resistance, and species) and the host immune response.[1] The disease is caused by more than 20 *Leishmania* species found in many geographic regions of the world.[2,3]

Cutaneous leishmaniasis (CL), which is called "oriental sore" in Turkey, is a skin disease causing depressive cicatrices and disfiguration of the skin if healed spontaneously. There are two main clinical forms of CL, which are caused by different species of *Leishmania* parasites in different areas. The clinical form of CL that is observed in Central and South America is called "New World CL," whereas the clinical form mainly observed in Southern Europe, Middle East, Southwest Asia, and Africa is called "Old World CL."[4]

CL, a significant public health problem, has shown an increasing tendency in Turkey, as well as globally, due to the influence of various local and global factors.[5,6] In addition, many imported cases have been reported from the largest Syrian refugee community in the world, which have been hosted in many regions of Turkey in recent years, especially in metropolitan areas. For these reasons, the need to train clinicians, especially those working in nonendemic areas, regarding the diagnosis and treatment of the disease has arisen as has the urgency of developing diagnostic and therapeutic approaches for local conditions.

This guideline describes approaches to the diagnosis and treatment of CL in cases of various *Leishmania* species in Turkey. The clinical experience of the authors and previous guidelines from different endemic regions, as well as a limited number of randomized controlled trials to date, were used as the basis for developing these guidelines. The clinical practices and approaches for the diagnosis and treatment of CL are presented using the most simple and practical algorithms possible.

Methodology of Guideline Preparation

It is difficult to establish standard clinical practice guidelines for CL due to limitations in evidence-based and species-directed treatment options. This guideline is a consensus text prepared by experienced CL specialists who have been working for many years in areas where the disease is endemic. The Delphi method was used to determine expert group consensus.[7] Eighteen experts participated in the panel, all of whom were informed regarding the Delphi process. Initially, a comprehensive list of CL diagnosis and treatment suggestions was prepared, and the experts scored each item between 1 and 7 (1 = least agreement and 7 = highest agreement). According to Delphi statistical methodology, a consensus was built at the end of three separate rounds based on the feedback by the expert participants.

Epidemiology

According to the World Health Organization (WHO), leishmaniasis is currently endemic in 102 countries/areas, and more than 350 million people live in areas where active parasite transmission occurs.[5] More than 20 million patients have active leishmaniasis, and 1.5–2 million patients are added to this number each year, which is estimated to include 1–1.5 million individuals with cutaneous forms and 500,000 with visceral and mucocutaneous forms.[4] The mortality and morbidity due to leishmaniasis cause an estimated 2–4 million disability-adjusted life years worldwide.[8]

CL is a common skin infection, especially in the southern and eastern parts of Turkey. In 2016, the WHO identified 12 countries, including Turkey, Syria, and Iran, as being high-burden (>2500/year cases) countries for CL. These countries represent 90% of the CL cases that occurred globally in 2016.[5,9,10] In Iraq, and recently in Syria, CL has become much more prevalent due to the conflicts and civil wars in the region.[11,12]

Approximately 50 million people in Turkey are at risk of CL. The estimated annual number of new cases is approximately 5000, most of which are reported from nine endemic provinces, namely Sanliurfa, Diyarbakır, Mardin, Osmaniye, Adana, Hatay, Kahramanmaras, Icel, and Antalya.[13,14] However, the disease is not limited to these areas owing to increases in permanent or seasonal migrations to nonendemic areas, travel for trade and tourism, and individuals from nonendemic regions working in dams, oil fields, and agricultural and irrigation projects in endemic regions. In addition, with the number of Syrian refugees in the last few years reaching approximately 3 million, there has been a significant increase in the number of cases of CL. More than 2000 imported CL cases, distributed among the various regions of the country, were reported among these refugees in 2014,[15,16] and it is estimated that the actual number may be much higher. Therefore, both this and the factors mentioned above have made it a disease possibly encountered by clinicians in every region of the country (even in larger metropolises).[4]

Leishmania and Sand Fly Species in Turkey

Leishmania tropica is the predominant causative agent of CL in Turkey.[11] However, some CL cases in the Eastern Mediterranean region of Turkey are thought to be caused by *L. infantum*.[10,17] Recently, likely due to influx of Syrian refugees, *L. major* and *L. donovani* were identified in certain autochthonous patients with CL from the Mediterranean and southeastern Anatolia regions of Turkey.[9,18–20] In the Old World, CL lesions typically originate from the bite of sand fly vectors belonging to *Phlebotomus* spp. In Turkey, *P. sergenti, P. tobbi,* and

P. papatasi act as vectors for *L. tropica*, *L. infantum,* and *L. major* infections, respectively.[5,6,21] *P. alexandri*, a natural vector for *L. donovani* in China, is also present in many CL-endemic areas of Turkey, even though it is not a dominant species.[20,22]

Clinical Symptoms

People who have not previously had clinical or subclinical CL are susceptible. Spontaneous healing or treatment usually results in lifelong immunity, which protects from re-infections. Clinical lesions begin to appear following an incubation period that varies from weeks to months after inoculation of *Leishmania* parasites via the bite of a sand fly. Although the developing clinical lesion does not always exhibit specific features of the causative parasite species, the dry type of CL, which is generally caused by *L. tropica* and *L. infantum*, is the most common in Turkey and may appear in clinically different forms. The disease begins as a painless, brownish, erythematous papule after a 2- to 8-month incubation period in those who are bitten by an infected sand fly in the summer months (Fig. 1a). The lesion is located at the site of the sand fly bite, which is usually on an exposed area of the body. It gradually enlarges and deepens, becoming a nodule or plaque, which reaches a diameter of 1–2 cm within approximately 6 months (Fig. 1b). In time, this indurated nodule becomes ulcerated from its center and covered by a crust tightly adhered to the base (Fig. 1c). The sloping firm margins with a prominent central crater lend a "volcanic" appearance to the ulcer, which is the most distinctive feature of CL in differential diagnosis from other causes of chronic ulcer. This ulcer eventually heals by itself, leaving a depressive scar tissue (Fig. 1d) (acute CL). The time to self-cure varies and is related to the *Leishmania* species, with up to 2 years required in *L. tropica* and *L. infantum* infections. However, in 5–10% of patients, the lesions do not heal on their own and persist for years (chronic CL). New lesions occur around the scar tissue within 1–2 years following healing of the acute lesion (leishmaniasis recidivans) in <5% of patients.

Wet-type CL, which is caused by *L. major*, has a shorter incubation period (<2 months) and a shorter time to self-cure (<6 months) than the dry type. A large, furuncle-like inflammatory nodule appearing at the site of inoculation shows rapid progression and enlargement. This nodule rapidly ulcerates and heals spontaneously within 2–6 months, leaving a cribriform scar.

Although CL occurs at all ages, it is more common in children and young individuals in endemic areas. Occasionally, CL may be observed as a family infection due to the biting of more than one person by sand flies in the same environment. For those who live in nonendemic areas, there is frequently a history of travel to an endemic region in the summertime at least a few months before the lesion appears. CL typically develops as painless, chronic, single or multiple erythematous papules, nodules, plaques, ulcerated nodules, or plaques on uncovered body areas, especially on the head and extremities.

Clinical Differential Diagnosis

CL is called "the great imitator" because it can closely mimic many dermatoses. Sometimes, this similarity misleads diagnosis, resulting in treatment mistakes and morbidities. In particular, nodular or nodulo-ulcerative lesions can be confused with malignant tumors, frequently with basal or squamous cell carcinomas, when they are located around the mouth, nose, and eyes.[23–26] Apart from its usual appearance, CL may show

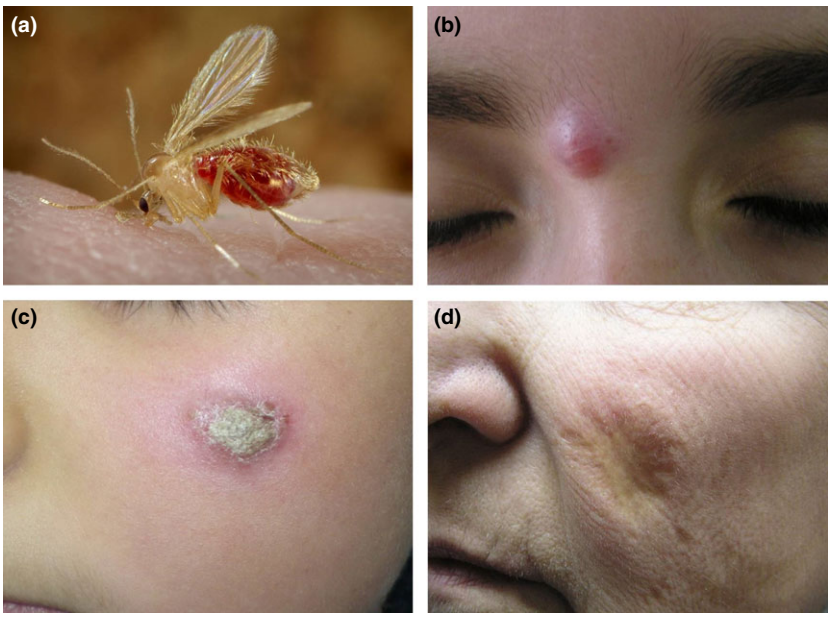

Figure 1 Natural course of CL in Turkey (a) *Phlebotomus papatasi*; content provider: CDC/Frank Collins, http://commons.wikimedia.org/wiki/, access date:23.01.2010

clinical manifestations such as erysipelas, eczema, sporotrichosis, lupus vulgaris, or psoriasis, which may lead to diagnostic difficulties. Indeed, clinical differentiation between leishmaniasis recidivans and lupus vulgaris can be almost impossible.[23,27,28]

Diagnosis

The most important step in the diagnosis of CL is to clinically consider the disease. Clinical diagnosis should then be confirmed by one of the laboratory methods listed in Table 1. Parasitological diagnosis is the gold standard because of its high specificity.

Leishmania smear

A smear, which is a simple, rapid, reliable, inexpensive method that directly reveals *Leishmania* amastigotes, is the most commonly used diagnostic tool.[29] Samples can be obtained by four different methods according to the lesion type: the slit-skin smear, the scraping smear, the touch (imprint) smear, and fine-needle aspiration. The first two methods are the most common.

The obtained materials can be stained with Romanowski-type dyes (Giemsa, May-Grünwald-Giemsa, Wright and Diff-Quick). *Leishmania* amastigotes (also known as "*Leishmania* bodies") are ellipsoid-shaped parasites that are 2–4 μm in length, with an eccentric nucleus and a paranuclear kinetoplast of a smaller size and darker color that are found in the cytoplasm of macrophages or extracellularly. A large number of parasites within the cytoplasm of macrophages may appear in a "swarm of bees" formation.

Recent studies have shown that four *Leishmania* species (*L. tropica*, *L. infantum*, *L. major*, and *L. donovani*) are present in Turkey and that molecular techniques have great advantages for rapidly identifying the species, allowing clinicians to initiate species-directed treatment.[20,30]

The algorithm provided in Figure 2 can be used for CL diagnosis. As CL is a notifiable disease in Turkey, every patient with a confirmed diagnosis should be reported to the Ministry of Health.

Treatment

Most CL lesions heal spontaneously, leaving scar tissue in their place, even when untreated (Fig. 1d). The duration of spontaneous healing from the onset of lesion appearance varies between 6 and 20 months for *L. tropica* and *L. infantum* and between 2 and 6 months for *L. major*, yet it is not possible to predict the duration for each case. Although lesions located outside the head and neck region that are less than 1 cm in diameter can be left untreated, there are many personal reasons, as well as social reasons, for choosing treatment because patients may also be a source of the disease. The indications for treatment of CL are shown in Table 2.[4,31]

Table 1 Summary of the laboratory diagnostic methods used for cutaneous leishmaniasis

- Dermal slit-skin and scraping smear (stained with Giemsa and subjected to direct microscopic examination)
- Culture (fine-needle aspiration or biopsy material is added to Novy-MacNeal-Nicolle medium)
- Incisional biopsy (stained with hematoxylin & eosin and Giemsa)
- PCR (in biopsy material or lesion aspirates)

As it may cause chronicity and parasite dissemination, all surgical procedures other than incisional biopsy with diagnostic and therapeutic purposes should be avoided.

In addition to accelerating healing, preventing complications, such as ugly scar formation at cosmetic sites, development of dysfunction, and spreading and recurrence of lesions, constitutes the main objectives of treatment.[32]

Despite effective treatments for CL, there is no single option that can be considered as the standard and ideal treatment (i.e., topically used, effective, inexpensive, and safe) for each clinical type and geographic region. Therefore, current CL treatment is unsatisfactory. Because the clinical severity of the disease and response to treatment varies according to the parasite species, the most important approach in recent years has been the introduction of species-directed therapies.[33] For example, polymerase chain reaction (PCR)-based typing as a diagnostic procedure is the recommended approach for effective treatment (Fig. 2).

Healing criteria

The decrease in elevated lesions (i.e., papules, plaques, nodules, or tumors) to the skin level and the closure of ulcerated lesions are considered complete healing. A reduction in lesion size by 2/3, a decrease in erythema and edema, and softening of the lesion can be considered partial healing. In these cases, the lesion should be re-evaluated after 1 month without treatment. If the lesion tends to heal, follow-up for complete healing should be continued, whereas the patient should be evaluated for a second cure treatment if there is no complete healing during the follow-up period. As relapses can occur even months after treatment, patients should be checked every 3 months over a span of 1 year.[31]

Depending on the species of the parasite and the treatment method used, a 2/3 reduction in lesion size is expected to be achieved after 6 weeks of therapy. If the reduction is between 1/3 and 2/3, an alternative treatment may be considered. However, if the lesion is reducing at less than 1/3 of the lesion, another treatment option must be sought.[3] Clinical and parasitological healing should be distinguished from each other. Despite clinical improvement, PCR results can remain positive for several years.[34]

If a destructive treatment is planned, which has an associated risk of cicatrix development, the expectation that "the cosmetic result obtained with the preferred method will be better than the cosmetic result with the spontaneous healing of the lesion" should be high. Otherwise, another treatment should be considered.[4,31]

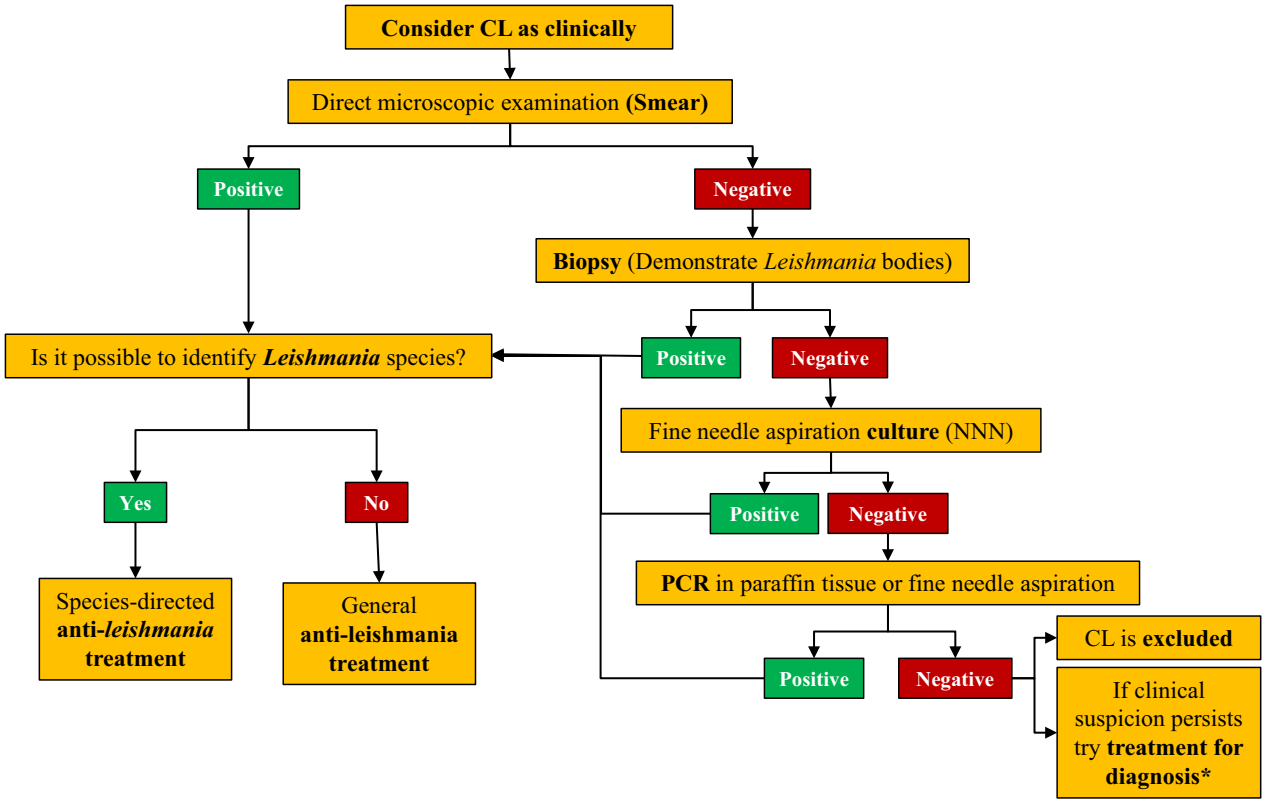

Figure 2 Algorithm proposed for cutaneous leishmaniasis diagnosis in Turkey. (*If strong clinical suspicion persists in cases where the causative parasites cannot be demonstrated, it can be diagnosed through treatment. According to this, intralesional antimony application is performed at a rate of one or two injections per week. If improvement is observed, the clinical diagnosis of cutaneous leishmaniasis is confirmed, and treatment is continued. If there is no improvement, cutaneous leishmaniasis is likely to be excluded.)

Table 2 Indications for the treatment of cutaneous leishmaniasis

• Cosmetically unacceptable lesions
• Persistent lesions (leishmaniasis recidivans and chronic cutaneous leishmaniasis)
• Large lesions
• Lesions on the joints or face
• Multiple lesions
• Lesions located in the mucosa or near the lips, eyelids, or intranasal areas
• Lesions accompanied by nodular lymphangitis
• Psychologically affected patients
• Patients with immunodeficiency

There are two basic approaches to the treatment of CL. These are anti-infective treatments and destructive physical methods.

Anti-infective treatment

In current CL treatment, anti-infective treatment employing agents that have direct toxic effects on *Leishmania* parasites is the most frequently used for each geographic region and parasite type. Table 3 lists the anti-infective agents used with different priorities and frequencies.[31]

Pentavalent antimony compounds (PACs)

These compounds, which are highly effective and the first-line treatment for most forms of leishmaniasis, are considered as the gold standard for investigations of the efficacy of new drugs.[33] There are two therapeutically equivalent PACs: meglumine antimoniate (Glucantime) and sodium stibogluconate (Pentostam). In Turkey, both drugs are provided free to endemic regions by the Provincial Health Directorates. Although primary resistance to PACs up to 15% has been reported in different geographic regions, they remain the most toxic drug to most *Leishmania* species.[3] Ineffectiveness of treatment is often associated with the use of these drugs below the therapeutic doses (<10 mg/kg per day or an insufficient dose due to obesity) and at an insufficient duration (<10 days).[34] These drugs are administered locally (intralesionally) or systemically (parenterally). Glucantime is administered intramuscularly (IM) or intralesionally, whereas Pentostam IM is administered intravenously (IV) or intralesionally. IM administration should be a deep injection; in contrast, IV should be a slow injection within 5 minutes.

Table 3 Summary of anti-infective agents used in the treatment of cutaneous leishmaniasis

Drug	Route of administration and dosage
First-line treatment	
Pentavalent antimony compounds (PACs)	IV or IM, 10–20 mg/kg per day for 15–20 days
	Intralesional (1 ml/cm^2 once or twice in a week; at least 5 injections in total)
Second-line treatments	
Amphotericin B (Liposomal)	IV, 3 mg/kg per day for 5 days and on the 10th day
Miltefosine	Oral, 2.5 mg/kg per day or 150 mg/day for 4 weeks
Pentamidine isethionate	IV or IM, 2–4 mg/kg on alternate days, 3 doses
Alternative treatments	
Paromomycin	Topical cream, twice daily application for 10–20 days
Ketoconazole	Oral, 400–600 mg/day for 6 weeks (*L. major*)
Itraconazole	Oral, 7 mg/kg per day, 400 mg/day for 3–4 weeks (*L. major*)
Fluconazole	Oral, 200 mg/day for 6 weeks (*L. major*)
Terbinafine	Oral, 250–500 mg/day for 4 weeks
Azithromycin	Oral, 500 mg/day for 10 days (per 1–2 months and 3–4 months cycles)
Allopurinol	Oral, 20 mg/kg per day for 15 days
Dapsone	Oral, 100 mg 2 × 1/day for 6 weeks
Zinc sulfate	Oral, 10 mg/kg per day for 6 weeks
Rifampicin	Oral, 1200 mg/day for 28 days (*L. tropica*)

The indications of intralesional and systemic PAC applications are shown in the treatment algorithm provided in Figure 3.

Intralesional PAC treatment has been used successfully in large series.[22,24] This application reduces the toxic effects of the drugs and the cost of treatment while maintaining the drug concentration in the lesion area at the highest level. Due to the limited toxic effects, it may be a suitable option for acute lesions that are noninflammatory and not very large (less than 4 cm in diameter) (Fig. 3).[4] In addition, in cases where systemic PAC therapy is contraindicated for several reasons (such as for cardiac problems), this treatment should be primarily considered.[33]

Hypersensitivity reactions to PACs are rarely observed. Therefore, intralesional PAC administration should be performed in a treatment room with the ability to intervene against a possible anaphylactic reaction. The drug is administered directly into the lesion with a fine-needle (27–30 gauges) syringe, such as an insulin syringe, without any dilution. However, due to the presence of particulates, Pentostam solution should be drawn up through a sterile filter with 5 microns or less pore size immediately prior to administration. The entire lesion must be blanched (optimal dose) for the drug to reach an effective dose in the lesion area. These injections are administered 1–2 times per week until the lesion heals. When the healing criteria described above are met, the treatment is discontinued. A minimum of five injections is generally required for this. After appropriate treatment, the recurrence rate is less than 2%.[22] Local (pain, a transient increase in inflammation, milia, and secondary bacterial infection) and systemic (urticaria, sneezing, and anaphylactic reaction) side effects may occur during or after intralesional PAC treatment. If there is evidence of secondary infection, such as temperature elevation, pain, and edema, in the CL lesion, intralesional PAC treatment should be discontinued until the infection is healed. In patients who had systemic treatment, intralesional PAC treatment can be combined with systemic PAC treatment to improve efficacy and shorten the healing period.[35,36]

Systemic PAC treatment is parenterally administered for the indications specified in the algorithm shown in Figure 3. Systemic PAC therapy is administered as a pentavalent antimony equivalent (Sb) at a dose of 10–20 mg/kg per day. PAC therapy has been shown to be more effective at daily doses of 20 mg/kg than at doses of 10 mg/kg and 15 mg/kg; however, most patients in Turkey respond to dosages below 20 mg/kg per day.[31] Systemic PAC treatment is administered for 15–20 days, but the treatment can be extended to 30 days according to the response. Nonetheless, it has been shown that longer periods such as 40 days do not increase the clinical recovery rate.[32] If the response is insufficient, the treatment may be repeated 4–6 weeks later.[33] Although some resistant cases have been observed in recent years, almost all CL forms in Turkey respond well to PACs. For this reason, the diagnosis of CL should be reviewed in all patients who do not respond to treatment (especially if parasites cannot be demonstrated and the diagnosis was based on clinical or histological findings alone). Considering the possible side effects of medications and the cost of treatment, confirmation of the diagnosis with a specific method is important. Although PACs are safe, nephrotoxic, hepatotoxic, and cardiotoxic effects of the drugs in clinical practice may be observed. In addition, pancreatitis and bone marrow suppression can develop. Therefore, systemic PAC treatment can be inconvenient for those with liver, kidney, and heart disease. It is useful to follow the protocol given in Table 4 in terms of the effects on the above-mentioned organs and systems in patients receiving PAC treatment. Such careful follow-up is usually possible when patients are hospitalized.

Laboratory abnormalities that are frequently encountered and concern the clinician are elevations in liver enzymes and asymptomatic hyperamylasemia. Our clinical experience suggests that increasing the normal limits of both liver enzyme and amylase levels to 4- to 5-fold does not pose a risk for the termination of treatment. The values are rapidly normalized if the therapy is discontinued or if the dosage is reduced when these levels are exceeded. In fact, according to experiences reported from both our center and other centers, the laboratory values do not exceed safe limits at this time, even when the old doses are applied.[33] The QT interval, the time between the beginning of the Q wave and the end of the T wave on electrocardiogram

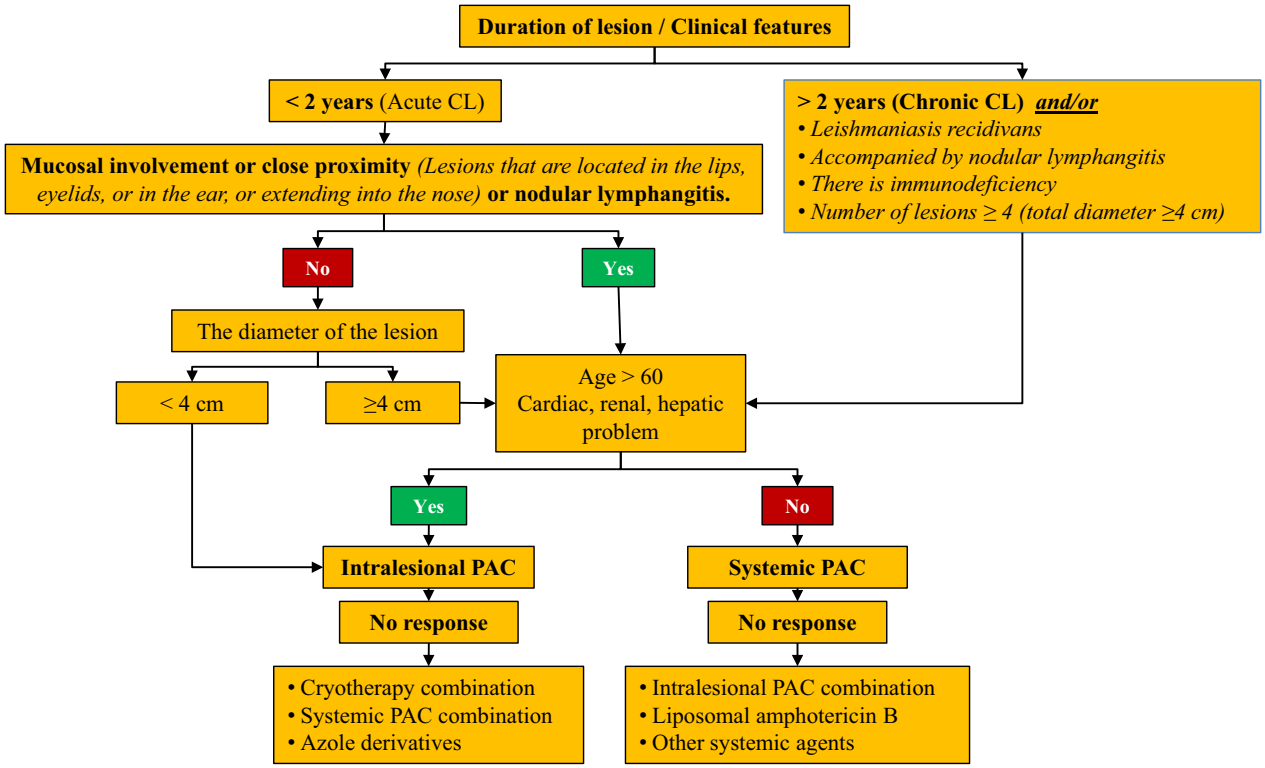

Figure 3 Algorithm proposed for cutaneous leishmaniasis treatment in Turkey

Table 4 Summary of the systemic pentavalent antimony compound treatment follow-up protocol

- ECG; checked before treatment and every 1–2 weeks during treatment. Treatment is interrupted in the following cases:
  - o Serious arrhythmia
  - o The QT interval is longer than 0.5 s (Corrected QT interval = QT/$\sqrt{RR}$)
  - o ST depression
- Transaminases are checked once a week; if 5 times higher than the upper limit of the normal value, treatment is interrupted.
- Hemoglobin, white blood cells, and thrombocytes; once a week
- Amylase is checked daily in the first week and then twice a week
  - o Treatment is interrupted if the serum amylase level is more than 4 times the normal upper limit (or more than 15 times for the lipase level).

(ECG), is normally short at 0.45 seconds. Prolongation in the QT interval is a cardiotoxicity marker that may develop in systemic PAC treatment and requires early detection; a corrected QT interval of 0.5 seconds is a sign that a serious and fatal arrhythmia may begin. For this reason, treatment should be interrupted when the corrected QT interval exceeds 0.5 seconds.[31] PACs should not be used with antiarrhythmic drugs that prolong the QT interval and tricyclic antidepressants with a risk for interaction. In addition, alcohol consumption during PAC treatment may increase the risk for hepatotoxicity. Although rare, PACs can cause hypokalemia, and continuous and close follow-up is required in situations that lead to electrolyte imbalance, such as diarrhea or the use of a diuretic. Fever, fatigue, myalgia, arthralgia, abdominal pain, and anorexia, which usually develop after the first 10 days during treatment, can be observed in a significant portion of patients. These side effects, which can be often tolerated, do not require treatment cessation. However, sometimes arthralgia and myalgia can be so disturbing that they can cause patients to want to discontinue treatment. In this case, an analgesic can be added to the treatment.

Liposomal amphotericin B

Amphotericin B, which is commonly used in patients with PAC resistance or in the case of PAC contraindication, is an antifungal agent that is also effective against *Leishmania* species. Amphotericin B is a second-line drug in the treatment of CL and the only anti-*Leishmania* drug in which clinical resistance is not observed.[37] Its serious side effect profile is a major disadvantage. However, the discovery of lipid formulations (liposomal amphotericin B) with a lower toxicity that directly target macrophages has increased its use for all forms of leishmaniasis, primarily the visceral form. The dosage used in CL is still controversial, but 3 mg/kg daily for 5 consecutive days and a 6th dose on day 10 were found to be effective (a cumulative dose not exceeding 18 mg/kg).[38] The drug should be given as

a slow infusion lasting 30–60 minutes. Renal function should be closely monitored throughout the application. The patient should also be awake in terms of a loss of potassium and associated cardiac arrhythmias. It can be used in elderly patients and in pregnant patients. Nonetheless, this drug is highly expensive, which is the most important factor that prevents it becoming the first choice in the treatment of CL.[3,39]

Pentamidine

Pentamidine is commonly used in New World CL and in mucocutaneous leishmaniasis, and it is even the first-line treatment in *L. guyanensis* infections.[3,33] This drug, which is produced as pentamidine isethionate (Pentacarinat®) and is not available in Turkey, is administered in dosages of 2–4 mg/kg per day, for a total of 4–7 doses (IM or IV) not exceeding 300 mg daily.

Miltefosine

Miltefosine (Impavido®), a phosphocholine analog, is a promising new agent for visceral leishmaniasis.[39] It has been found to be as effective as PACs in Old World CL, especially in *L. major* infections. The absence of serious side effects, except for nausea, diarrhea, and creatinine elevation, and its oral application are advantages over PACs.[3,39] There are limited data on its efficacy for *L. tropica* and *L. infantum* infections. Miltefosine may be an option for patients who are resistant to PACs or cross-resistant to amphotericin B.[3] However, a significant disadvantage is its cost and the severe nausea that sometimes limits its use. The recommended dosage of this drug, which is not available in Turkey, is 2.5 mg/kg per day for 28 days.

Paromomycin

Paromomycin is an aminoglycoside available in parenteral and 15% topical formulations (Leishcutan),[3,40] and the topical form has the potential to be an excellent option compared with parenteral and intralesional applications. However, the drug was found to be less effective or ineffective for some forms of CL.[41] Nevertheless, it has been reported that its administration with methylbenzethonium chloride, which increases percutaneous absorption of the drug, twice a day for 10–20 days may be an alternative to intralesional PAC treatment.[33] Regardless, it is not yet available in Turkey.

Intralesional hypertonic sodium chloride

Intralesional hypertonic (7%) sodium chloride is almost as effective as intralesional sodium stibogluconate but does not have systemic side effects.[42] However, this inexpensive treatment method should not be used at concentrations of 10% and higher because it may cause cutaneous necrosis.[43]

Fluconazole, itraconazole, ketoconazole, azithromycin, allopurinol

Antifungal imidazole derivatives also exert toxic effects against *Leishmania* parasites. The advantages are oral use and fewer side effects. Although there are reports that fluconazole is effective in *L. major* infections, some studies have reported no differences from placebo and ineffectiveness in *L. infantum* infections. There are also data regarding the limited efficacy of ketoconazole and itraconazole, particularly in *L. major* infections.[32,39] According to our experience, ketoconazole at a dosage of 600 mg/day for 6 weeks may be considered as an option in patients in whom PACs cannot be used due to risks of toxicity or allergic reaction or in patients who are resistant to PAC treatment. Although the effect of azithromycin is limited, it can be applied in children in whom other treatments were ineffective, in pregnant women, and in those with severe comorbidities.[39] Allopurinol is another option with limited efficacy that can be used in patients with PAC resistance.[44]

Physical treatment

Cryotherapy (liquid nitrogen or CO_2) is the most commonly used physical method for CL treatment in Turkey; it is used alone or in combination with intralesional or systemic PACs or paromomycin ointment. Such combined therapies are reportedly more effective than cryotherapy alone.[34] Weekly applications of a double freeze-thaw cycle of 10–25 seconds, including a 2 mm healthy area from the lesion border, have been effective.[45] However, this treatment can cause permanent hypopigmentation, especially in patients with darker skin, and it also has a high relapse rate (12%).[22,24] For these reasons, it should be considered only in selected patients and for lesions that do not exceed 3 cm in diameter or in cases in which intralesional PAC treatment is not possible.[22,24,46,47] Cryotherapy can also be combined with systemic PAC treatment in selected cases.[48,49]

Local heat treatments with infrared, ultrasound, and radio waves (thermotherapy: "burn the boil" at 50 °C for 30 seconds) are well-tolerated methods that are effectively used in the treatment of CL.[50] Local photodynamic therapy may be an option in those who do not respond to standard treatments in Old World CL.[40] Thermotherapy and photodynamic therapy are not available in Turkey.

Treatment during pregnancy and lactation

Systemic or intralesional anti-infective treatments are not recommended, as there is insufficient information on the safety of PACs and other drugs in pregnant or lactating women. A physical method, such as cryotherapy or thermotherapy, can be performed if the treatment is necessary during these periods.[50]

Prevention

The identification and treatment of all patients, the control of vector sand flies and reservoirs, informing health staff about the disease, and raising awareness are approaches that should be immediately put into practice. Hospital and health center staff in endemic regions should be trained in diagnostic and treatment algorithms and protocols and on the basic epidemiology of CL.

The most effective method of personal prevention is the use of long-lasting insecticide-treated nets (there are two products, PermaNet and Olyset generic, that are approved by the WHO). Additionally, indoor or outdoor residual insecticide spraying should be conducted regularly.[45,51] In endemic areas, dogs are domestic reservoirs of CL, and the use of topical insecticides with a proven efficacy against sand flies (deltamethrin-impregnated collars) can be effective for preventing infection and for reducing the incidence of CL in dogs.[45]

Conclusion

Although CL has been endemic for many years in the southern regions of Turkey, an increasing incidence is being observed in nonendemic regions due to the return of travelers and recently to the increase in Syrian refugees. Clinically, CL is usually characterized by self-healing noduloulcerative lesions on exposed parts of the body, but it can imitate many other skin diseases with its unusual manifestations and may cause misdiagnosis, major diagnostic delays, and morbidities. A timely diagnosis can avoid complications and help institute an early and effective treatment. Based on a consensus of experienced CL specialists, this guide provides approaches for the diagnosis and treatment of CL patients in Turkey. Direct microscopic examination and local or systemic PAC treatment are the first steps of the proposed algorithms for the diagnosis and treatment of CL, respectively.

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