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Cutaneous leishmaniasis

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Abstract

Background: Leishmaniasis is a disease caused by parasites of the *Leishmania* type. Cutaneous leishmaniasis is a neglected worldwide, zoonotic, vector-borne, tropical disease. The clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to a mutilating mucocutaneous disease and even to a lethal systemic illness. People who recover from cutaneous leishmaniasis are protected against future infections. The risk of infection is for people of all ages if they live or travel where leishmaniasis is found. Leishmaniasis usually is more common in rural than in urban areas, but it is found in the outskirts of some cities. The transmission risk is highest from dusk to dawn because this is when sand flies generally are the most active. Cutaneous leishmaniasis causes skin lesions, which can persist for months, sometimes years. The skin lesions usually develop within several weeks or months after the exposure but occasionally first appear years later. Presented here is a clinical case of leishmaniasis of the cutaneous form, diagnosed by the microscopic method. The patient was diagnosed, monitored and treated in Clinical Hospital of Infectious Diseases "Toma Ciorbă" from 10.01.2018-09.02.2018. The progression of the disease was favorable following the etiotropic treatment with antimony meglumine (Glucantime), requiring careful monitoring due to adverse reactions.

Conclusions: Clinical symptomatology was characteristic for cutaneous leishmaniasis: skin lesions of various pink-cherry sizes, some with ulcers on the body. The first etiotropic treatment with antimony meglumine was effective. Antimonate Meglumine treatment at a dose of 15 ml resulted in adverse reactions: asthenia, fever, myalgia and arthralgia.

Key words: cutaneous leishmaniasis, diagnosis, treatment, adverse reactions.

Introduction

Leishmaniasis owes its name to Sir William Leishman, a British army medical officer, who discovered the disease in 1901 and published his findings in 1903 [28]. Leishmaniasis is a polymorphic disease produced by several protozoa species of Leishmania genus that can affect the skin, mucous or internal organelle. Infections in humans are caused by more than 20 species of *Leishmania* [27, 28]. Cutaneous leishmaniasis can be caused by several *Leishmania* spp and is transmitted to human beings and animals by sandflies [19, 20, 24, 27]. Other modes of transmission of leishmaniasis to humans, though less common, include blood transfusion, sharing of contaminated needles, and mother-to-child transmission during pregnancy [16, 17]. Risk factors include poverty, malnutrition, deforestation, and urbanization [3, 27]. Some people have a silent infection, without any symptoms or signs. People who develop clinical evidence of infection have one or more sores on their skin. The sores can change in size and appearance over time [9]. Leishmaniasis has three principal clinical forms: cutaneous (CL), mucocutaneous (ML) and visceral (VL). The distributions are: ≈1.5 million cases of CL and ≈50 000 cases of VL occur annually [11]. Cutaneous leishmaniasis (CL) is a neglected worldwide, zoonotic, vector-borne, tropical disease that is a threat to public health. This threat may spread from endemic to non-endemic areas, is endemic in the tropics and neotropics [13, 20]. The World Health Organisation (WHO) estimates that 350 million people are at risk of contracting leishmaniasis and an estimated 1.6 million new cases occur annually [23]. The morbidity associated with human CL is 0.7-1.2 million cases distributed worldwide resulting in extensive integumentary lesions [1]. Since 2002, there has been a dramatic increase in the cases of cutaneous leishmaniasis: from 1 case per 100,000 in 2002 to 4.5 cases per 100,000 in 2012. Since 2012, the incidence rates have decreased (2.7 cases per 100,000 in 2015) [6].

There are two groups of CL, New World and Old World leishmaniasis, with only the latter group identified in the Middle East and it includes three main species; *L. major*, *L. tropica* and *L. infantum* [22]. The majority of cutaneous Leishmaniasis cases occur in Afghanistan, Algeria, Brazil, Colombia, the Islamic Republic of Iran, Pakistan, Peru, Saudi Arabia and the Syrian Arab Republic [1, 28]. Recent studies showed a high prevalence of CL in Iran [7, 8], Turkey and Syria [12]. Although Iraq shares long borders with these countries and leishmaniasis is endemic, the World Health Organization has not classified it as a country with a high burden profile [26]. CL has long been endemic in Israel. More recently, illness caused by *L. tropica* parasites

has been reported in several semi-arid hilly areas in Israel's more densely populated, and less dispersed, central and northern population centers [10, 21].

It is often referred to as a group of diseases because of the varied spectrum of clinical manifestations, which range from small cutaneous nodules to gross mucosal tissue destruction. Cutaneous leishmaniasis is the most common form of the disease. It usually produces ulcers on the exposed parts of the body, such as the face, arms and legs [2, 28]. The lesions typically evolve from papules to nodular plaques to ulcerative lesions, with a raised border and central depression, which can be covered by scab or crust; some lesions persist as nodules. The lesions usually are painless but can be painful, especially if ulcerative lesions become infected with bacteria or if the lesions are near a joint. The healing process typically results in atrophic scarring [9]. The gold standard for confirmation of Leishmania infection is visualisation of parasites by microscopy and scrapings or fluid from cutaneous sores in the case of CL [23]. In cutaneous and mucocutaneous leishmaniasis, clinical manifestations with parasitological tests confirm the diagnosis but serological tests have limited value [28]. The risk factors: poverty and malnutrition play a major role in the increased susceptibility to leishmaniasis. Another risk factor is the movement of susceptible populations into endemic areas, including large-scale migration of populations for economic reasons [3].

Leishmania may live quietly for years in the body and then begin to multiply (reactivate) if the person's immune system becomes suppressed. Thus, people who were born in a country with leishmaniasis and those who have had travel-related exposure are at risk if they become immunosuppressed by conditions such as chemotherapy, use of steroids, or infection with HIV. Patients who have previously had cutaneous leishmaniasis acquired in certain parts of the New World are at risk for mucocutaneous leishmaniasis [14]. Meglumine antimoniate (Glucantime) is a pentavalent antimony (Sb^V) recommended by the World Health Organization as the first-choice drug for the treatment of all types of leishmaniasis; the maximum dose recommended is 20 mg/kg of body weight/day via the intramuscular route [4, 5, 15, 25]. Some of the side-effects may be rare but serious: fever, irregular heartbeat, nausea, back pain, upper abdominal pain, vomiting, chills, cough, skin rash, drowsiness [18,].

Results and discussion

Patient U.V., aged 44 years, from Chisinau, was hospitalized in the IMSP Clinical Hospital of Infectious Diseases "Toma Ciorba" on 10.01.2018. At the time of admission there were the following complaints: physical asthenia, rash all over the body, skin pruritus - more pronounced in the eruption region. The patient is considered ill from mid-September 2017, when moderate skin pruritus appeared in the large joints, and then on the entire body surface, increasing in intensity until it became unbearable. On October 9-10, 2017, there appeared skin rashes (papules) in the joints region, which then spread throughout the body. In November, he contacted a dermatologist who prescribed treatment with Betaden, Erolin, Flosteron, Ung. Dermovate, Maxitrol, Central -B. The indicated treatment improved the pruritus, but the rash continued to progress to ulceration.

On 27.12.17, the patient came to the Diagnostic Advisory Center of Parasitic and Tropical Diseases of the Toma Ciorbă Infectious Diseases Clinical Hospital, and was suspected to have Leishmanioza, of skin form, which was later confirmed parasitologically, by detecting leishmanias in the smear taken from the ulcer of the left leg region (fig. 1) [23].

From the epidemiological history, it was found that during May-June 2017 the patient was in Denmark, where he was bitten by mosquitoes, and from August to October 2017 (45 days) he was in Israel, where he worked in construction, and had satisfactory living conditions in the first three weeks; however, afterwards, he lived in precarious conditions, where there were many vagabond cats. In his spare time he sunbathed and swam in the sea. The patient was often pricked by insects, but without consequences. He also worked in Israel in the years 2013-2014, when he had an episode of hives that ceased after treatment.

At the first examination, the general condition of the patient was of average severity. He had usual skin color and several moist skin lesions of various sizes (1-8 cm) of pink-burgundy color, some of which were covered with ulcerations, while others were covered with crusts surrounded by an indented, pointed, and well-defined by a wave of edema and hyperemia, edge. There were also rashes characteristic of the first clinical manifestations of leishmaniasis and 4 papules located on the chest and abdomen. The largest lesions were found in the forearm and right leg 5 × 7-8 cm, on the face and head – rashes absented [2, 28]. In total there were 24 eruptive outbreaks, and 3 more appeared in the first days of staying.

The exam on the systems did not show any special changes.

On 11.01.18, treatment with Meglumine antimonate (Glucantime) 1.5 g/5 ml – 60 mg/kg /day was initiated according to the scheme: 1st day – 1/3 of the total dose / day (5 ml); day 2 – ½ of total dose / day (7.5 ml); 3rd day – ¾ – of total dose / day (12.5ml); 4th day total dose (15.0 ml). Sol. Clemastin 2.0 ml i / m. Sol.Dexamethasone 4mg i / m (for 3 days after initiation of treatment), group B vitamins.

Beginning from 21.01.18 (on the 11th day of the treatment), the patient started having fever, up to 38.5 ° C, that became pronounced in the second half of the day. Initially, the fever did not significantly affect the patient's general condition, but, after one week, the condition gradually worsened: pronounced asthenia, muscle and bones pain, suffocation, pronounced palpitations. Data from additional investigations have excluded the association with other pathological conditions, including sepsis, pneumonia, urinary infections, endocarditis, etc. On 29.01.18 (on the 19th day of the treatment), the general condition of the patient continued to worsen, as the signs of general intoxication have intensified, manifesting themselves through pronounced physical

asthenia, muscle pain, arthralgia, fever over 39.0 ° C, and insomnia. These symptoms were considered to be caused by the adverse reaction to treatment with Meglumine antimonate [18, 25]. Following the occurrence of these side effects, the dose of antimony meglumine was reduced to 5 ml/day. On 30.01.18 the condition of the patient improved, the fever decreased, the signs of intoxication disappeared, and physical asthenia was decreasing. The patient continued treatment with Meglumine antimonate 5 ml / day until 06.02.18. He was discharged on 09.02.18 in satisfactory condition. 1 month after the discharge, the general condition was satisfactory, and no serious consequences surfaced. Some crusts of very small size were present.

In fig. 2, tab. 1 and tab. 2 we present the evolution of cutaneous lesions and laboratory investigations during the treatment period:

Specific clinical data

The smear of the eruptive element from the right leg region (27.12.17) - gen. Leishmania was found.

The smear of the eruptive element from the right forearm region (15.01.18) - gen. Leishmania was not found.

The smear of the eruptive element from the right lateral abdominal region (18.01.18) - gen. Leishmania was not found.

Non-specific clinical data

11.01.2018 – FCC - 86 b / min; AEC – normal; sinusoidal rhythm.

29.01.2018 – FCC – 110 b / min. Sinusoidal rhythm, tachycardia. Moderate deregulations of the ventricular repolarization processes in the anterolateral, apical VS region. Signs of overloading VS.

USG abdominal organs (11.01.2018): Liver: LD – 153 mm; LS – 73 mm; V. Portae – 10 mm;

V. splenic – 6 mm; Gallbladder – deformed; walls – 2 mm; calculus – absent. Pancreas – Regular contour; Structure – poorly homogeneous. Splint – 116x41mm; Ecogeneity – slightly increased. Kidney: Nephroptoza of grade I-II on the right. In the calcification system – micro-calculus with d = 1- 3 mm.

Conclusion USG: Hepatomegaly. The slightly increased ecogeneity of the liver and spleen. Deformed collector. Chronic pancreatitis. Renal microlithiasis, more pronounced on the left, uric diathesis. Nephroptotic grade I-II on the right.

Flora hemoculture at sample I (31.01.18) – Aerobic flora – negative; Anaerobic flora – negative.

Flora Hemoculture on Sample II (05.02.18) – Aerobic Flora – Negative; Anaerobic flora – negative.

Table 1

Hemoleucogram in dynamics

Indicators / Data	**11.01.18**	**15.01.18**	**22.01.18**	**27.01.18**	**29.01.18**	**30.01.18**	**07.02.18**
Hemoglobin (g / l)	148	157	-	129	126	-	-
Erythrocytes (10^{12}/l)	4,9	5,2↑	-	4,2	4,2	-	-
Color Index	0,9	0,9	-	0,92	0,9	-	-
Platelet count (10^9/l)	248,0	288,0	-	264,0	-	-	-
Leukocytes (10^9 / l)	6,1	12,3↑	10,8	8,6	12,0↑	9,8	9,8
Unsegmented (%)	15↑	11↑	21↑	22↑	7	7	8
Segmented (%)	41↓	63	52	47	56	72	49
Eosinophils (%)	5	-	4	3	2	2	9
Lymphocytes (%)	29	19	20	25	27	15	23
Monocytes (%)	10	7	3	3	8	4	11
RSH (mm / h)	13↑	8	-	47↑	61↑	49↑	22↑

Table 2

Biochemical analysis of blood in dynamics

Indicators / Data	**11.01.18**	**15.01.18**	**16.01.18**	**27.01.18**	**30.01.18**
Bilirubin mcmol / l	10,8	-	-	7,6	-
ALT U/l	22,1	-	-	50,7↑	39,4
AST U/l	17,5	-	-	31,6	-
Total cholesterol mmol/l	6,6	-	-	-	-
Urea mmol/l	4,0	5,2	-	5,7	5,9
Creatinine mcmol/l	88,0	84,0	-	72,0	82,0
Glucose mmol/l	-	-	4,8	4,8	-
GGT U/l	-	38,5	-	77,5	74,8
Amylase U/l	28,0	-	-	58,0	-
Total protein g/l	68,9	-	-	-	-
Prothrombin Index %	90,0	-	-	-	-
Alkaline phosphatase U/l	163,0	-	-	-	-

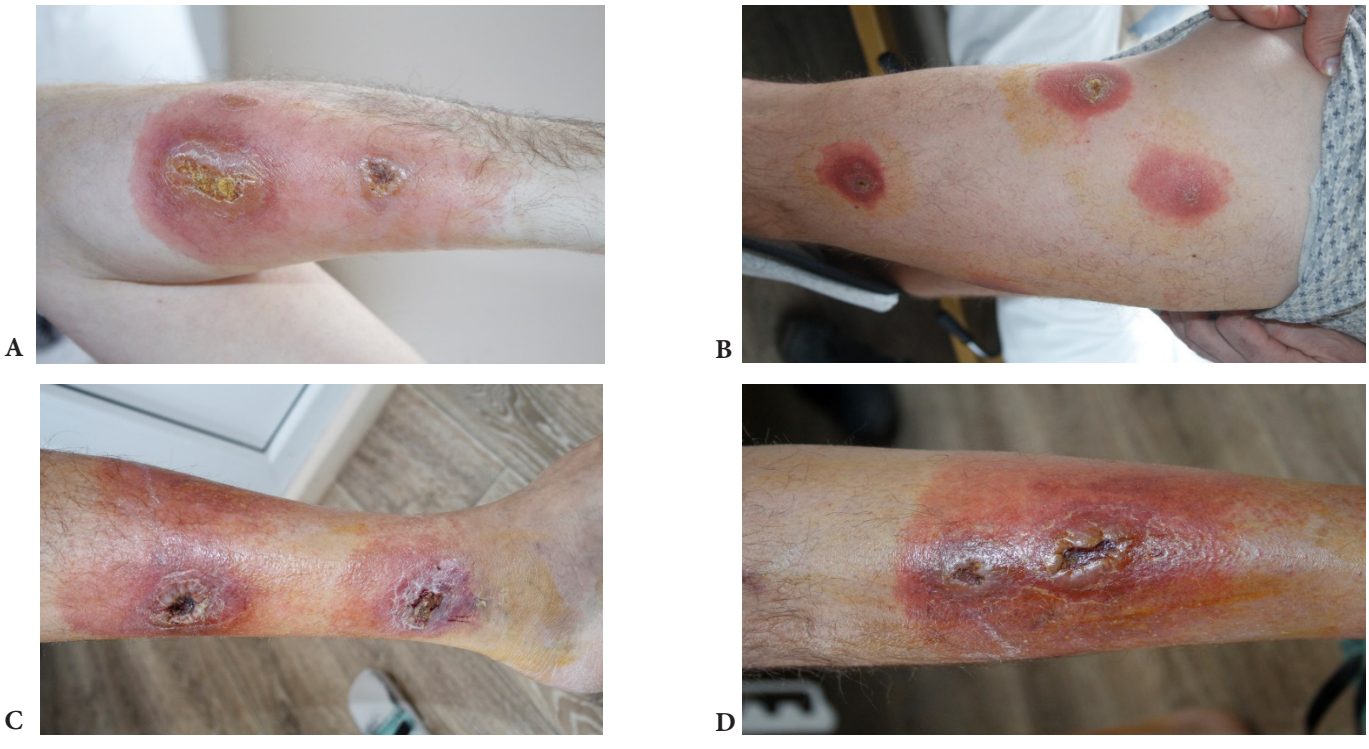

Fig. 1. Skin lesions before admission on the 08.01.2018.

A – Right forearm, **B** – Right leg anterior surface, **C** – Left leg, **D** – Right leg posterior surface.

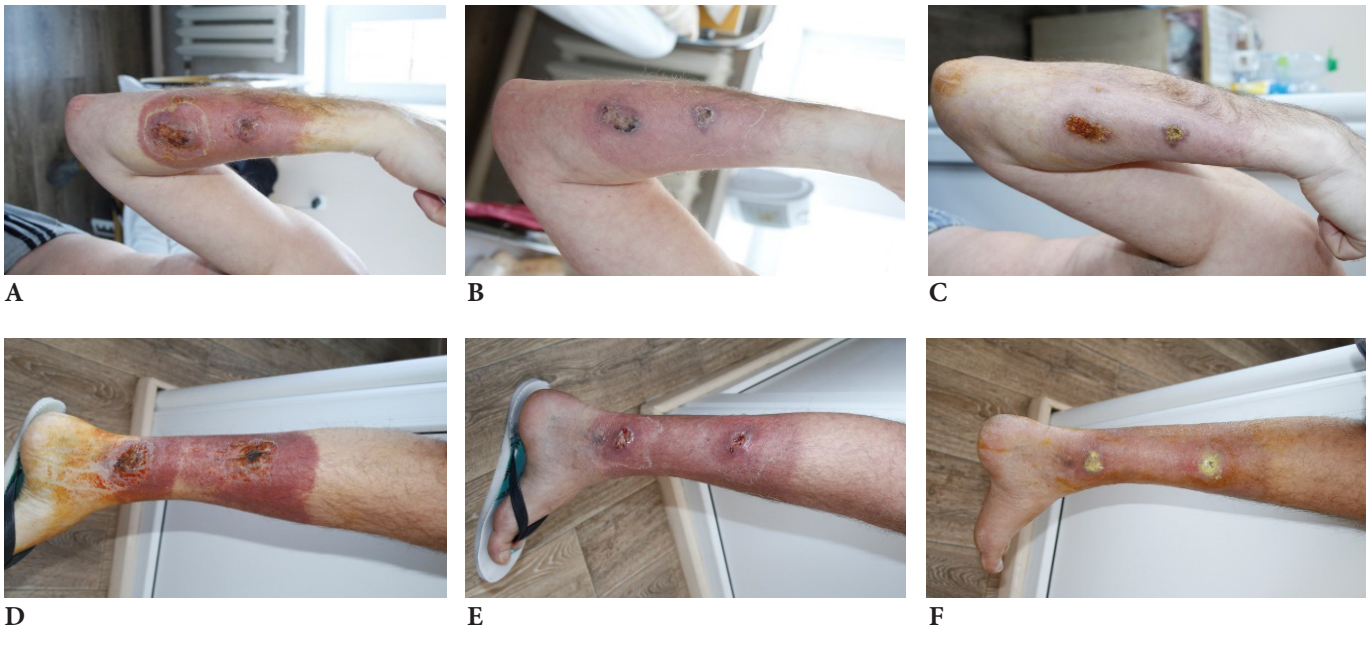

Fig. 2. Evolution of cutaneous lesions during the treatment period.

The right forearm region on the: **A** – 5th day of treatment, **B** – 12th day of treatment, **C** – 23rd day of treatment.

The left leg region on the: **D** – 5th day of treatment, **E** – 12th day of treatment, **F** – 23rd day of treatment.

Conclusions

1. This case of Cutaneous Leishmaniasis is the first of this form registered with a national citizen returned from a region where the morbidity through this parasitosis varies from 2.7-4.5 cases in 100.000 according to literature data.

2. It is necessary to raise the level of knowledge among practitioners, because, due to global warming, these infections may spread through new areas linked by the presence of transmission vectors.

3. A thorough management is needed to highlight the adverse events caused by etiotropic treatment with those of other clinical syndromes of other origins.

4. The emergence of similar cases requires the familiarization of the local medical community with the modern methods of diagnosis and treatment of this disease through continuous medical education.

References

1. Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One. 2012;7(5):e35671. doi: 10.1371/journal.pone.0035671[PMC free article] [PubMed].
2. Barrett MP, Croft SL. Management of trypanosomiasis and leishmaniasis. Br Med Bull. 2012;104:175–96. doi:10.1093/bmb/lds031. PMC 3 530408. PMID 23137768.
3. Stark CG, Conjivaram V. Leshmaniasis [Internet] [cited 2018 March 28]. Available from: http://emedicine.medscape.com/article/220298-overview.
4. Heymann David L. Manual de management al bolilor transmisibile [Manual of communicable diseases management]. Bucuresti: Amaltea; 2012. p. 227-233. ISBN 978-973-162-105-0. Romanian.
5. Leishmanioses. In: E. Pilly: Maladies infectieuses. [place unknown]: Association des Professeurs de Pathologie Infectieuse et Tropicale; 1993. p.552-554. ISBN 2-909710-02-5. French.
6. Epidemiology Department, Israel Ministry of Health. Position paper for case definition, diagnosis and treatment of cutaneous Leishmaniasis (Hebrew) (2016) [cited 2017 November 20]. Available from: https://www.health.gov.il/Publications Files/17647316A.pdf.
7. Eslami G, Salehi R, Khosravi S, Doudi M. Genetic analysis of clinical isolates of *Leishmania major* from Isfahan, Iran. J Vector Borne Dis. 2012;49(3):168–74. [PubMed].
8. Hajjaran H, Mohebali M, Teimouri A, Oshaghi MA, Mirjalali H, Kazemi-Rad E, et al. Identification and phylogenetic relationship of Iranian strains of various *Leishmania* species isolated from cutaneous and visceral cases of leishmaniasis based on N-acetylglucosamine-1-phosphate transferase gene. Infect Genet Evol. 2014;26:203-12. doi: 10.1016/j.meegid.2014.05.026 [PubMed].
9. Centers for Disease Control and Prevention. Parasites: Leishmaniasis. Atlanta: CDCP. [cited 2017 Nov 20]. Available from: https://www.cdc.gov/parasites/leishmaniasis.
10. Jaffe CL, Baneth G, Abdeen ZA, Schlein Y, Warburg A. Leishmaniasis in Israel and the Palestinian Authority. Trends Parasitol. 2004;20:328–32. doi: 10.1016/j.pt.2004.05.001.
11. Cohen J, Powderly WG, Opal SM. Infectious Diseases. Amsterdam: Elsevier; 2017. 1059 p. ISBN: 978-0-7020-6285-8.
12. Karakus M, Nasereddin A, Onay H, Karaca E, Ozkeklikci A, Jaffe CL, et al. Epidemiological analysis of *Leishmania tropica* strains and Giemsa-stained smears from Syrian and Turkish leishmaniasis patients using multilocus microsatellite typing (MLMT). PLoS Negl Trop Dis. 2017;11(4):e0005538. doi: 10.1371/journal.pntd.0005538 [PMC free article] [PubMed].
13. Al-Bajalan MMM, Al-Jaf SMA, Niranji SS, Abdulkareem DR, Al-Kayali KK, Kato H. An outbreak of Leishmania major from an endemic to a non-endemic region posed a public health threat in Iraq from 2014-2017: Epidemiological, molecular and phylogenetic studies. PLoS Negl Trop Dis. 2018;12(3):e0006255. doi: 10.1371/journal.pntd.0006255.
14. Nettleman MD, Davis CP. Leishmaniasis. [cited 2017 Nov 29]. Available from: https://www.medicinenet.com/leishmaniasis/article.htm
15. Mohammadzadeh M, Behnaz F, Golshan Z. Efficacy of glucantime for treatment of cutaneous leishmaniasis in Central Iran. J Infect Public Health. 2013 Apr;6(2):120-4. doi: 10.1016/j.jiph.2012.11.003. Epub 2013 Feb 1.
16. Nettleman MD, Davis CP. Leishmaniasis Symptoms, Causes, Treatment – 717 What are the Different Types of Leishmaniasis?, MedicineNet, Inc., 2013.
17. Siewe N, Yakubu AA, Satoskar AR, Friedman A. Immune response to infection by leishmania: a mathematical model. Math Biosci. 2016 Jun;276:28-43. doi: 10.1016/j.mbs.2016.02.015.
18. PubMed Health. Meglumine Antimoniate (Intravenous route, Injection route) [cited 2016 October 12]. Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0011067/
19. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. Lancet. Infect Dis. 2007;7(9):581-96. doi: 10.1016/S1473-3099(07)70209-8.
20. Schwarz NG, Loderstaedt U, Hahn A, Hinz R, Zautner AE, Eibach D, et al. Microbiological laboratory diagnostics of neglected zoonotic diseases (NZDs). Acta Trop. 2017;165:40–65. doi: 10.1016/j.actatropica.2015.09.003 [PubMed].
21. Shani-Adir A, Kamil S, Rozenman D, Schwartz E, Ramon M, Zalman L, *Leishmania tropica* in northern Israel: a clinical overview of an emerging focus. J Am Acad Dermatol. 2005;53:810-5. doi: 10.1016/j.jaad.2005.07.026.
22. Steverding D. The history of leishmaniasis. Parasit Vectors. 2017;10(1):82 doi: 10.1186/s13071-017-2028-5 [PMC free article] [PubMed].
23. Stockdale L, Newton R. A review of preventive methods against human leishmaniasis infection. PLoS Negl Trop Dis. 2013;7(6):e2278. doi: 10.1371/journal.pntd.0002278 [PMC free article] [PubMed].
24. González U, Pinart M, Sinclair D, Firooz A, Enk C, Vélez ID, Esterhuizen TM, Tristan M, Alvar J. Vector and reservoir control for preventing leishmaniasis. Cochrane Database Syst Rev. 2015 Aug 5;(8):CD008736. doi: 10.1002/14651858.CD008736.pub2.
25. Moreira VR, de Jesus LCL, Soares RP, Silva LDM, Pinto BAS, Melo MN, Paes AMA, Pereira SRF. Meglumine antimoniate (Glucantime) causes oxidative stress-derived DNA damage in BALB/c mice infected by Leishmania(Leishmania) infantum. Antimicrob Agents Chemother. 2017;61(6). doi: 10.1128/AAC.02360-16.
26. World Health Organization. Leishmaniasis: Country profiles 2014. [cited 2017 June 22]. Available from: http://www.who.int/leishmaniasis/burden/Country_profiles/en/.
27. World Health Organization. Leishmaniasis Fact sheet N°375 January 2014. Archived from the original on 21 February 2014. Retrieved 2014 February 17.
28. World Health Organization. Leishmaniasis. Geneva: WHO. [cited 2017 Oct 23]. Available from: http://www.who.int/leishmaniasis/en/mics