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Clinical Risk Factors of Systemic Antimony Treatment Failure in Patients with Acute Cutaneous leishmaniasis referred to the Dermatology Clinics of Mashhad University of Medical Sciences, Iran

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Abstract

Background: Systemic or topical forms of pentavalent antimony compounds such as meglumine antimoniate (MA) are used as standard treatment for cutaneous leishmaniasis (CL). However, an increasing number of studies demonstrate evidence of treatment failure with these drugs. The objective of this study was to determine the factors associated with systemic MA treatment failure in patients with acute CL.

Methods: In this case-control study, patients with urban cutaneous referred to leishmaniasis clinics in Mashhad from 2017 to 2018 were followed up 12 months after the start of treatment and were evaluated for improvement or failure according to the national leishmaniasis protocol.

Results: A total of 112 cases of CL (59 men and 53 women) with a mean age of 23.3±21.11 years were studied. The number of patients with clinical improvement was significantly higher in women ($P=0.005$). Age, body mass index (BMI), occupation and education, the possible infection and living location, past medical, drug and leishmaniasis recurrence history, lesion's characteristics and ulceration were also significantly different between the two groups of improved and unhealed patients.

Conclusion: The results of this study showed that the male sex, age less than 18 years, receiving pentostam, previous treatment history, lymphadenopathy, urban leishmaniasis, duration of illness more than 4 months, having a single lesion especially on the face, BMI less than 18 kg/m^2 and a lesion size of more than 3 cm is more common in patients with treatment failure.

Keywords: Cutaneous leishmaniasis, Antimony compounds, Systemic treatment, Treatment failure

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Introduction

Leishmaniasis is a parasitic infection caused by *Leishmania* protozoa, and despite significant progress in its control and treatment, the disease has remained a major public health concern in some countries, including Iran, and according to the World Health Organization (WHO), it is the sixth most important disease in the tropical and subtropical region (1). Cutaneous leishmaniasis (CL) begins as small nodules and often leads to ulcers on the skin. Although leishmaniasis is a self-healing disease, the healing takes a very long time, and in some cases, it may take more than two years until recovery (2).

Early treatment of leishmaniasis can prevent scarring and lesion progression (3). It is worth noting that 10% of untreated lesions might be developed into chronic disease. Therefore, effective and timely treatment is highly recommended for patients suffering from leishmaniasis. For the past 60 years, pentavalent antimony compounds such as meglumine antimoniate (MA), glucantime and pentostam have been the first line of treatment for all forms of leishmaniasis. Antimony compounds are administered intramuscularly and intralesionally (4,5).

Standard treatment for CL is available with systemic or local injections of pentavalent antimony compounds such as MA (6,7), which can be accompanied with several limitations such as systemic side effects of the drug, painful injections, lack of patient compliance for accurate follow-up of the disease and even drug resistance (8).

Over the past decades, the continued use of antimicrobial agents in the treatment of infections has led to the development of resistance among different types of microorganisms. Leishmania species are no exception to this rule and have been greatly resisted to antibiotics. Different responses to treatment with these agents and

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numerous cases of treatment failure and resistance to treatment in various endemic areas have been reported by researchers (9,10).

Various factors contribute to resistance to this treatment (11), including the type of parasite and its genetic characteristics (12). However, when considering cases of comorbid leishmaniasis of parasite species within families, different treatment responses were observed among families, suggesting that in addition to parasite characteristics, clinical factors may also be effective in resistance to MA treatment (8).

CL is one of the most important health problems in Iran. Due to glucantime resistance and treatment challenges, the disease burden and treatment costs have increased. Although CL is a self-healing disease, the recovery time is long and in some cases even the treatment fails. In the present study we aimed to investigate the factors associated with systemic MA treatment failure in patients with acute CL.

Material and Methods

Study population

This case-control study included 56 CL patients with failure of systemic MA therapy as the case group and 56 patients whose lesions improved with systemic MA therapy as the control group. The required data was extracted from the patient's medical records. After obtaining the informed consent through telephone call, the patients were invited for an interview. Next, they were asked to complete a consent form (for children, this was done by a parent or guardian). Checklists prepared for this purpose were completed afterwards. All patients with confirmed urban CL (cases of CL confirmed by parasitology laboratory that had clinical and epidemiological evidence of urban areas) referred to clinics of the CL research center of Mashhad University of Medical Sciences in Imam Reza and Ghaem educational and medical centers and Ab-O-Bargh Health Center during 2017 to 2018 were eligible to enter the study.

Inclusion and exclusion criteria

Inclusion criteria were: 1) Being diagnosed with CL that has indications for systemic treatment (lesions on the face, ears, genitals, 5 or more in number, more than 3 cm in diameter, sporotrichoid, on the joint or fingers, cases of recurrence or treatment failure). 2) Confirmation of diagnosis by direct smear or in some cases by histopathological examination. 3) Receiving a full course of systemic antimony based on the individual's ideal weight (at a dose of 20 mg/kg of body weight for 20 days) with treatment control tests at the beginning and during the treatment.

4) Completion of the informed consent form by the patient (in the case of children by his legal guardian).

The exclusion criteria were: 1) Incomplete treatment course, 2) Incomplete file information, 3) Pregnant and lactating women, 4) History of internal disease that prevented the administration of MA compounds, 5) History of allergy to MA compounds, 6) Problems with skin mucosal involvement and immunodeficiency.

Data collection

Simple checklists were used to collect demographic information. Clinical and demographic information included age, sex, occupation of the patient, economic and social status, level of education, time between the onset of the lesion to the start of treatment, concomitant lymphadenopathy, lesion diameter, number of lesions, anatomical location of the lesion, type of lesion (ulcerated or without ulcer), clinical signs of bacterial infection, previous history of receiving treatment for leishmaniasis, history of chronic internal disease, history of drug use, dose of the received antimony in the prescribed drug, other treatments with anti-histamines, history of previous leishmaniasis and history of previous skin disease.

Patients were followed for 12 months after the initiation of treatment and reassessed for improvement or lack of improvement. During this period, 56 patients were collected as the case group according to the treatment failure criteria, and 56 of those who improved were included in the control group. At patient follow-up, the number of treatment sessions and adherence to the treatment were also recorded by completing a questionnaire. The patient was being excluded from the study if the treatment was not completed for any reason.

Complete and definite improvement in the form of ulcer healing was defined by re-epithelialization and loss of induration in red and inflamed areas and incomplete re-epithelialization or the presence of induration, protruding or red margins in any of the lesions and recurrence at any time after the course of treatment with systemic antimony was considered as treatment failure.

Statistical analysis

SPSS version 22 software was used for statistical analysis. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to check the normal distribution in the data. Mean and standard deviation were used to describe quantitative data. Tables and graphs were used to describe qualitative data. Independent samples t-test or Mann-Whitney and chi-square or Fisher's exact tests were used to compare the variables between the two groups. In all tests, a significant level of 0.05 was considered.

Sample size calculation

The sample size was calculated using the data of a previous study (13) in which the history of chronic disease was 30% in people with resistant systemic leishmaniasis and 9% in non-resistant people, equivalent to 56 people in each group (Considering alpha equal to 0.05 and beta equal to 0.2). The sample size was also calculated using other

variables such as lesion diversion and lesion location, which were calculated as 31 and 52 people in each group, respectively. This study was conducted as a census for 2 years .According to the sample size, 56 people were collected in the case group during this period. The same number of patients were included in the control group.

Results

A total of 112 patients were included in the study. The mean age of patients was 23.3 ± 21.11 years, and 59 (52%) were male. A total of 57 patients (51%) lived in Mashhad, about half of them in the suburbs of the city. Twenty-five patients (22%) lived in the southwest of Mashhad and 13 (11%) in the northeast of the city (Table 1).

The patient's basic clinical features, as revealed by history and initial clinical examination, are summarized in Table 2. According to the table, only 6 patients (5%) had a history of leishmaniasis and 52 patients (46%) had received prior treatment. Lymphadenopathy was also observed in 9 (8%) patients.

After 12 months of follow-up, 56 patients were included in the treatment failure group according to the inclusion criteria and 56 improved cases were included in the control group for comparison based on the sample size. Baseline, clinical, and treatment related variables were compared between patients who had been fully recovered and those who did not. According to the table, age (P value = 0.057) and previous history of treatment (P value = 0.05) showed nearly significant differences between the two groups. The injection site, history of skin disease, previous history of leishmaniasis and treatment with antimony did not show significant difference between the two groups, but the rest of the variables were significantly different (Table 3).

Table 4 compares the underlying quantitative, basic clinical, and therapeutic variables between patients who had fully recovered and those who did not. According to the table, all the quantitative variables studied showed a significant difference between the two groups of improved and unimproved patients.

Considering that some patients had more than one lesion and outcomes were different for each lesion, we also performed a separate statistical analysis for the lesions. In total, 112 patients in this study had 196 lesions. Characteristics of patients' lesions are presented in Table 5. The location of the lesions and their size and the fact whether or not they were ulcerated, showed a significant difference between the improved lesions and the non-improved lesions. The location of most unhealed lesions was on the face, while among the improved ones, the most common site was the upper limb, followed by the face.

Discussion

In total, 112 patients with leishmaniasis were studied in this study, of whom 52.6% were male and the rest were female. About half of the patients lived in the suburbs of Mashhad. Most patients had undergraduate education.

Table 1. Demographic characteristics of patients (N = 112)

Variable		
Age (year)		23.3 ± 21.11
Gender	Male	59 (52%)
	Female	53 (47.3%)
Weight (kg)		45 ± 26
Height (m)		140.8 ± 34.2
BMI (kg/m^2)		20 ± 5
Education	Illiterate and elementary school	62 (55%)
	High school diploma	36 (32%)
	College and post grad	14 (12%)
Location (in the city of Mashhad)	North West	10 (8%)
	Northeast	13 (11%)
	Southeast	2 (1.7%)
	Southwest	25 (22%)
	Middle	7 (6%)
	the suburbs	55 (49%)
Type of housing	Rental	36 (32%)
	Owner	76 (67%)
Patient's occupation	Unemployed	35 (31%)
	Student	30 (26%)
	Retired and employed	14 (12%)
	Freelance	18 (16%)
	Housewife	15 (13%)
Guardian's occupation	Unemployed	10 (8%)
	Student	2 (1.7%)
	Retired and employed	23 (20%)
	Freelance	77 (68%)

Table 2. Basic clinical characteristics of patients

Properties	
History of previous leishmaniasis	6 (5%)
Previous treatment history	52 (46%)
Lymphadenopathy	9 (8%)
History of skin disease	3 (2%)
History of drug use	8 (7%)
History of underlying disease	10 (8%)
Smoking	7 (6%)
Infection in the lesion	25 (22%)
History of leishmaniasis recurrence	10 (8%)
Skin reaction to the drug	11 (9%)
Treatment with antimony	8 (7%)
Duration of lesions (months)	4.96 ± 3.25
Number of lesions in each patient	1.12 ± 1.63
Dosage of antimony received (mg/kg)	17.53 ± 5.32
Ulcerative lesion	31 (27%)

Table 3. Comparison of the qualitative variables of improved and unimproved patients

Variable		Improved (n=56)	No improvement (n=56)	*P* value
Gender	Male	(39%) 22	(66%) 37	0.005*
	Female	(60%) 34	(33%) 19	
Age	Children (under 18 years)	(46%) 26	(64%) 36	0.057*
	Adults (over 18 years old)	(53%) 30	(35%) 20	
Probable location where the patient got infected	Living Location	(78%) 44	(76%) 43	0.001*
	out of town	(21%) 12	(23%)13	
Injection site	Home	(0%) 0	(7%) 4	0.07*
	Health center	(83%) 47	(83%) 47	
	Other centers	(16%) 9	(8%)5	
living area in Mashhad city	North West	(10%) 6	(7%) 4	0.001*
	northeast	(10%) 6	(12%) 7	
	Southeast	(28%) 16	(0.8%) 1	
	Southwest	(0.8%) 1	(7%) 4	
	Middle	(5%) 3	(55%) 31	
	the suburbs	(42%) 24	(35%) 20	
Type of housing	Rental	(28%) 16	(64%) 36	0.001*
	Owner	(71%) 40	(32%) 18	
Patient's occupation	Unemployed	(30%) 17	(32%) 18	0.001*
	Student	(19%) 11	(33%)19	
	Retired and employed	(14%) 8	(10%) 6	
	Freelance	(17%) 10	(14%) 8	
	housewife	(17%) 10	(8%) 5	
Guardian's occupation	Unemployed	(7%) 4	(10%) 6	0.001*
	Student	(0.8%) 1	(0.8%) 1	
	Retired and employed	(26%) 15	(14%) 8	
	Freelance	(64%) 36	(73%)41	
Level of education	Illiterate and elementary school	(60%) 34	(50%)28	0.001***
	High school diploma	(25%) 14	(39%) 22	
	College and post grad	(15%) 8	(11%) 6	
Weight-based antimony dose (mg/kg)	<10	(4%) 2	(2%) 1	0.001***
	20-10	(57%) 32	(53%) 30	
	≥20	(39%) 22	(45%) 25	
History of skin disease	+	(5%) 3	(0%) 0	0.07*
	-	(94%) 53	(56%) 56	
History of drug use	+	(8%) 5	(5%)3	0.001*
	-	(91%) 51	(94) 53	
History of chronic disease	+	(12%) 7	(5%)3	0.001*
	-	(87%) 49	(94%) 53	
Smoking	+	(7%) 4	(5%)3	0.001*
	-	(92%) 52	(94%) 53	
Infection in leishmaniasis lesion	+	(30%) 17	(14%)8	0.04*
	-	(69%) 39	(85%)48	
History of leishmaniasis recurrence	+	(7%) 4	(10%) 6	0.001*
	-	(92%) 52	(89%) 50	
The name of the antimony received	Glucantime	(98%) 55	(94%)53	0.001**
	Pentostam	(0.8%) 1	(5%)3	

Table 3. Continued.

Variable		Improved (n=56)	No improvement (n=56)	*P* value
Skin reaction to antimony	+	(12%) 7	(7%) 4	0.001*
	-	(87%) 49	(92%)52	
Previous history of leishmaniasis	+	(5%) 3	(5%) 3	0.99**
	-	(94%) 53	(94%) 53	
Previous history of treatment	+	(37%) 21	(55%) 31	0.05**
	-	(62%) 35	(44%) 25	
Simultaneous treatment with other drugs	+	(7%) 4	(7%) 4	0.99**
	-	(92%) 52	(92%)52	
Lymphadenopathy	+	(5%) 3	(10%)6	0.001**
	-	(94%) 53	(89%) 50	
Type of lesion	Urban	(89%) 50	(96%) 54	0.001**
	Rural	(10%) 6	(3%) 2	
Weight (kg)	>68	(30%) 17	(17%) 10	0.001*
	≤68	(69%) 39	(82%) 46	
underweight (BMI≤18)	+	(42%) 24	(48%) 27	0.001*
	-	(57%) 32	(51%) 29	
Overweight (BMI≥25)	+	(28%) 16	(17%) 10	0.001*
	-	(71%) 40	(39%) 46	
Duration of the lesion (months)	≤4	(71%) 40	(37%) 21	0.001*
	>4	(28%) 16	(62%) 35	
More than 1 lesion	+	(59%) 33	(41%) 23	0.059*
	-	(41%) 23	(59%) 33	
More than 2 lesions	+	(36%) 20	(20%) 11	0.057*
	-	(64%) 36	(80%) 45	
More than 3 lesions	+	(18%) 10	(11%) 6	0.001*
	-	(82%) 46	(89%) 50	
3 cm or less lesion	+	(77%) 43	(57%) 32	0.018*
	-	(33%) 13	(43%) 24	

*Chi-square test was used to compare the two groups. ** Fisher test was used to compare the two groups. *** The Mann-Whitney test was used to compare the two groups.

Table 4. Comparison of quantitative variables between improved and unimproved patients

Variable	Improved (n=56)	No improvement (n=56)	*P* value
Age (y)	26±23	19±5	0.001*
Weight (kg)	48±28	42±24	0.001*
BMI (kg/m^2)	20.9±6.19	19.6±5	0.001*
Duration of lesion (months)	3±2	5±3	0.001*
Number of lesions	2±1	1±1	0.038*
Dosage of antimony received (mg/kg)	17±5	18±5	0.001**

*Chi-square test was used to compare the two groups. ** The Mann-Whitney test was used to compare the two groups.

Table 5. Characteristics of patients' lesions at the beginning of the study

Variable		Improved (n=138)	No improvement (n=58)	*P* value*
Ulcer	+	(45%) 63	(25%) 15	0.01
	-	(55%) 75	(75%) 43	
Site of lesion	Face	(38%)52	(68%) 40	0.001
	Upper limb	(46%) 64	(7%) 4	
	Lower limb	(15%) 20	(20%) 11	
	trunk	(1%) 2	(5%) 3	
Size of lesion (14)		2.5±2.1	3.2±2.2	0.009

*Chi-square test was used to compare the two groups.

Most patients were infected in the city of Mashhad. A previous history of leishmaniasis was 5% and a history of underlying disease and lymphadenopathy was seen in about 8% of patients. Previous treatment of leishmaniasis and infection with leishmaniasis lesions were 46% and 22%, respectively.

After 1 year follow-up, 56 patients were in the treatment failure group and 56 patients with improved lesions were included as the control group. In recovered patients, the percentage of women was significantly higher than men, and other parameters such as age, body mass index,

location in which the patients lived in and got infected, lymphadenopathy, duration of lesions, number of lesions, site of lesions, showed a significant difference between the two groups of improved and unimproved patients. Mean age and body mass index in treatment failure subjects were lower than those in the control group. Lymphadenopathy was seen more in the treatment failure group. The mean duration of illness until the start of treatment was shorter in recovered individuals. The average number of lesions in recovered individuals was also higher. Most of the unhealed lesions were on the face, while among the improved lesions, the most common site was the upper limb. The unimproved group got infected with the parasite outside the city of Mashhad. Furthermore, this group mostly lived in the suburbs of Mashhad and in rental houses, and the financial supporters of the families in this group were also reported to be unemployed. Symptoms of infection and skin reaction to the received antimony drug were more common in the improved group. History of leishmaniasis recurrence, use of pentostam, previous history of treatment, and urban type of lesions were seen more in the treatment failure group.

In a large cohort study conducted by Aflatoonian et al in the southern part of Iran in 2019, 1391 patients with leishmaniasis who were treated with Meglumine antimony topically, systemically, or via a combination of the two were studied and a 3-month follow-up was performed. Multivariate regression identified the risk factors for treatment failure in the mentioned study. The risk factors included male gender, the presence of facial lesions, multiple lesions, poor adherence to treatment, and duration of illness greater than 4 months (15).

In terms of the risk factors for treatment failure, including male gender and the presence of lesions on the face and the duration of the disease, the mentioned 2019 cohort study are very similar to our study, but according to our results numbers of lesions were seen more frequently in the group who recovered from the disease.

In a study published by Del Mar Castro et al in 2017, the extent and the factors influencing the failure of systemic leishmaniasis treatment were evaluated among 118 patients treated with meglumine antimony and 112 patients treated with miltefosine in Colombia. Adherence to treatment was calculated based on the ratio of the dose received to the total dose of meglumine antimony. The results showed that factors such as age of 8 years or less, duration of disease of 1 month or less, regional lymphadenopathy, treatment with meglumine antimony and adherence to treatment below 90% were associated with treatment failure (16).

In the present study, being younger than 18 years of age and the duration of the disease of more than 4 months were considered as risk factors for treatment failure. Lymphadenopathy was also significantly different between the two groups. The difference in these risk factors can be attributed to the fact that the nature of leishmaniasis and the causative agents of the disease in our region are different from the mentioned study conducted in Colombia. Moreover, it can be due to the difference in the inclusion and exclusion criteria of the two studies.

In another study published in 2006, Rodrigues et al examined the factors associated with failure of treatment in CL patients treated with systemic MA. This retrospective cohort was performed on 151 patients and the patients were followed up for an average of 2.5 months. Meglumine antimony dose of less than 10 mg per kg, a previous history of leishmaniasis treatment, 3 or more lesions, incomplete treatment and a body weight less than 68 kg were recognized as effective factors in treatment failure. This study, like ours, reported treatment history and lower weight to be associated with treatment failure (17). In the present study, more than 2 lesions had higher frequency in the recovered individuals. Regarding the dose of drug based on weight, the difference of the two groups is statistically significant. These differences can be related to different sample sizes, racial differences, retrospective study design, and lack of the same follow-up duration.

In a study by Mohammadzadeh et al in 2013, the efficacy of glucantime for the treatment of CL was investigated in 164 patients with leishmaniasis in Yazd. Patients who had lesions less than 3 cm or a maximum of 3 lesions (with the condition of having no lesions on the face, neck and joints, no signs of sporotrichoid lesions and secondary infection) received intra-lesional topical glucantime and others were treated with intramuscular form of this drug. There was no significant relationship between treatment failure and variables of age, sex, weight, number and size of lesions, how glucantime was administered, intramuscular injection dose and number of topical injection sessions and only a previous history of glucantime intake was significantly associated with treatment failure (18).

In contrast to the work of Mohammadzadeh and his team (18), in our study there was a significant relationship between treatment failure and variables of age, weight, number and size of lesions. In our study, the history of previous treatment (cryotherapy, oral treatment, intracellular glucantime) as in the above study, was significantly associated with treatment failure and the number of injection sessions could not be evaluated. Mohammadzadeh et al examined both topical and systemic treatments, which may be one of the reasons for the differences between its results and ours. In addition, Mohammadzadeh et al excluded patients with facial lesions. Their exclusion criteria were different from ours. It is important to note that the number of patients with a history of previous treatment of leishmaniasis in our study was 52, while in the above study it was 10, but in both studies, it had a significant relationship with treatment failure.

In a retrospective study by Jaffary et al, 1216 patients

with leishmaniasis who had been referred to the leishmaniasis center in Tehran for two years and had been treated with antimony compounds were studied. Male gender and a previous history of leishmaniasis were significantly associated with treatment failure. Also, the rate of treatment failure in the group treated systemically was higher than the groups treated topically and in combination, but this difference was not statistically significant. According to their results, site, type, size and number of lesions, wound infection, patient age, living location, education and occupation of the patient had no significant effect on treatment failure rate (19).

In a case-control study published by Llanos-Cuentas et al in 2008, risk factors for treatment failure were age, duration of illness less than 5 weeks, number of lesions and the disease-causing species (20).

In a study conducted by Unger et al In Brazil, 136 patients aged between 13 to 60 years with American CL received systemic treatment with antimony compounds for 20 days and were evaluated after 90 days. The results of this study showed that the presence of ulcers in leishmaniasis lesions is associated with a much lower treatment failure rate in patients (21).

Conclusion

Our results showed that the factors associated with the failure of treatment in male patients were the age of under 18 years, getting infected at a location outside of Mashhad, living in the suburbs of this city, living in a rental house, the patient being unemployed or student himself and the financial supporter of the household being Unemployed, lack of proper education, no infection in primary lesion, history of leishmaniasis recurrence, receiving pentostam (compared to glucantime), previous history of treatment, lymphadenopathy, urban type of lesion, weight of 68 kg and less, lesion duration more than 4 months, site of lesion being on the Face, having a single lesion, the size of the lesion being more than 3 cm.

Authors' Contribution

Conceptualization: Yalda Nahidi.
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Writing–original draft: Yasaman Rastgar.
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Competing Interests

None of the authors have a conflict of interest to declare in relation to this work.

Ethical Approval

This study was approved by Mashhad University of Medical Sciences (Code: IR.MUMS.MEDICAL.REC.1397.664).

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