Predictive factors associated with antimony treatment failure in anthroponotic cutaneous leishmaniasis in Kerman: a case-control study

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Received: 4 October 2021
Accepted: 22 February 2022

Background: Treatment failure of antimony drugs for anthroponotic cutaneous leishmaniasis (ACL) is rising. Recognizing predictive factors of unresponsiveness to treatment can substantially influence better ACL management. The goal of this study was to investigate predictive factors associated with treatment failure in ACL in Kerman, southeast Iran.

Methods: This case-control study was conducted retrospectively on 2,128 ACL cases in Kerman over ten years from 2011 to 2020. The case group included patients whose lesions failed to resolve after one treatment course. The control group included those whose lesions were cured after one treatment course.

Results: Treatment failure was observed in 13.5% of cases (10.7% of systemic therapy and 16.7% of local therapy). No significant difference was reported between the type of treatment and treatment failure. The association of treatment failure with winter-onset (P = 0.001, OR = 1.39, CI = 1.23–1.56), face (P = 0.001, OR = 1.86, CI = 1.38–2.49), ulceration (P = 0.01, OR = 0.51, CI = 0.30–0.85), small diameter (P = 0.005, OR = 0.57, CI = 0.38-0.84) and long duration of lesions (P = 0.01, OR = 1.57, CI = 1.11–2.21) was validated by multivariate logistic regression analysis.

Conclusion: Efficient detection and timely management of ACL cases are essential to reduce resistant cases, as lesions lasting longer than four months show poor response to treatment. Furthermore, early treatment of facial lesions with systemic therapy is suggested to optimize results and reduce the risk of disfiguring scars. Further surveys are required to determine the reason behind more treatment failure in winter-onset lesions.

Keywords: leishmaniasis, treatment failure, glucantime

Iran J Dermatol 2022; 25: 328-335

DOI: 10.22034/IJD.2022.308945.1441

INTRODUCTION

Leishmaniasis is one of the most neglected infectious diseases with widespread clinical spectrums from the fatal type, visceral leishmaniasis (VL), to the less threatening type, cutaneous leishmaniasis (CL). CL is the most prevalent type of leishmaniasis, accounting for three-quarters of cases. Although CL is not a life-threatening disease, permanent disfiguring scars may lead to lower quality of life [1-4]. Iran is one of the endemic regions of CL, with an estimated annual incidence of approximately 20,000 cases [4,5].

Two main types of CL are recognized:

anthroponotic CL (ACL) and zoonotic CL (ZCL), caused by *Leishmania tropica* and *Leishmania major*, respectively. In old-world CL, ACL or urban type and ZCL or rural type are transmitted to the host by the bite of the female sandfly (*Phlebotomus sergenti* and *Phlebotomus papatasi*, respectively) [6,7].

Based on a previous survey, Kerman is an endemic region for ACL [8]. According to the World Health Organization (WHO) and national leishmaniasis treatment guidelines, early detection and efficient treatment are recommended to prevent the spread of ACL. First-line therapy for ACL is pentavalent antimonials, including meglumine antimonate (Glucantime) and sodium stibogluconate (Pentostam) administered intralesionally (IL) or parenterally as intravenous (IV) or intramuscular (IM) depending upon the *Leishmania* species, clinical features of the lesions (site, size, and the number of lesions), and host's immune system status. Both methods of drug administration can result in noticeable adverse effects. Local administration is painful and can lead to erythema, edema, and swelling. Parenteral administration can have toxic effects on the heart, pancreas, kidney, and liver, leading to elevated pancreas and liver enzyme levels, cardiac arrhythmia, leukopenia, thrombocytopenia, myalgia, and abdominal pain [8-10].

Considerable numbers of recalcitrant cases have been reported in recent years. Several factors, such as the type of *Leishmania* species, demographic features of patients, clinical features of lesions, and host's immune system status, can influence treatment failure or success [11]. In this study, we investigated predictive factors associated with treatment failure in ACL in Kerman, southeast Iran.

PARTICIPANTS AND METHODS

Study design

This case-control study was conducted retrospectively at Shahid Davari Health Center in Kerman, Iran, for ten years (2011 to 2020). This study was approved by the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.AH.REC.1399.173).

Study population

Inclusion criteria were patients suffering from ACL referred to this center from 2011 to 2020, those who have completed records of demographic characteristics and clinical features of lesions, received a complete treatment course, and were followed for three months afterward. Only patients who lived in Kerman city and presented with new leishmaniasis lesions were enrolled. Exclusion criteria were patients with either an incomplete treatment course or incomplete data.

The case group included patients whose lesions failed to resolve after one treatment course. The control group included those whose lesions were cured after one treatment course. Complete cure was described as complete re-epithelialization of the lesion and absence of any induration or inflammation. The treatment course consisted of weekly IL administration of meglumine antimonate (0.1 ml/cm^2, maximum 5 ml) and biweekly cryotherapy with liquid nitrogen for a maximum of 12 weeks or until complete healing of the lesions. A 21-day treatment course of IM administration of meglumine antimonate (20 mg/kg/day, maximum 3 ampoules) with biweekly cryotherapy was prescribed for those with lesions on the face, digits, genitalia, and joints, > 4 lesions, or ≥3 cm lesion diameter. Demographic characteristics (age, sex, nationality, job, and history of chronic disease), clinical features of lesions (date of onset, site, number, diameter, duration, and type of lesion), type of treatment, and response to therapy were recorded and statistically analyzed with SPSS.

Statistical analysis

Data were analyzed by SPSS 16 (IBM, Armonk, NY, USA). Quantitative and qualitative data were described by mean ± standard deviation and frequency, respectively. Initially, univariate logistic regression analysis was used to assess the correlation of lesions' diameter or number as well as treatment response with the patients' demographic characteristics and clinical features. Subsequently, multivariate logistic regression analysis was performed to omit confounding factors and confirm the results. P-values of less than 0.05 were regarded as significant.

RESULTS

From 3,765 cases, 2,128 ACL cases were enrolled in the study. The highest rates of infection occurred in 2015 (20.3%), March (12.3%), and the autumn season (28.4%) (Table 1).

Demographic features

The mean age of patients was 27 ± 20.7 years (range 8 months to 92 years). The mean age of females was higher than that of males (30.06 ± 21 and 24.61 ± 18.7 years, respectively). Male and female cases were roughly equal (49.8% and 50.2%, respectively). Children and adolescents (19 years old or younger) constituted 43.9% of cases. Most patients had Iranian nationality (87.6%), and the remaining were Afghan. Most patients were students (26.7%) (Table 1).

Clinical features of the lesions

The mean number of lesions was 1.81 ± 0.73 (range 1–30), and most were single (63.5%). The mean diameter of lesions was 13.06 ± 9.40 mm, and most lesions had a diameter of 10 mm or less (82.8%). The vast majority of the lesions were ulcerated (95.7%) and located on body areas other than the face (71%, Table 1).

Association between clinical features of lesions and the number of lesions

Univariate analysis revealed that most of the single lesions were spring-onset, while the majority of multiple lesions occurred in the autumn season (*P* = 0.031, OR = 1.09, CI = 1–1.8). Most face lesions were single (*P* = 0.001, OR = 0.644, CI = -0.52–0.78). Moreover, most of the multiple lesions were ulcerated (*P* = 0.014, OR = 0.737, CI = -0.57–0.94), had a duration longer than four months (*P* = 0.001, OR = 1.69, CI = 1.34–2.14), and were 1 cm or less in diameter (*P* = 0.001, OR = 1.55, CI = -1.23–1.95). Multiple lesions were observed most frequently in patients younger than nine years old (*P* = 0.001, OR = 1.13, CI = -1.08–1.18) (Table 2).

Multivariate analysis confirmed that single lesions were mostly spring-onset (*P* = 0.018, OR = 1.10, CI = 1.01–1.19) and in the face area (*P* = 0.018, OR = 0.77, CI = 0.62–0.95). Predictive factors of multiple lesions included age of younger than nine years (*P* = 0.001, OR = 1.08, CI = 1.03–1.14), autumn-onset (*P* = 0.018, OR = 1.10, CI = 1.01–1.19),

Table 1. Demographic and clinical features of patients with anthroponotic cutaneous leishmaniasis

Variables	Number	Percentage
Sex		
Female	1068	50.2
Male	1060	49.8
Age (years)		
0-4	193	9.1
5-9	345	16.2
10-19	398	18.7
20-29	270	12.7
30-39	343	16.1
40-49	210	9.9
50-59	188	8.8
60-69	116	5.5
70-79	45	2.1
≥80	20	0.9
Nationality		
Iranian	1864	87.6
Afghan	267	12.4
Occupation		
Student	564	26.7
Others	555	26.3
Housewife	532	25.2
Child	355	16.8
Worker	62	2.9
Employee	32	1.3
Farmer	11	0.5
History of chronic disease		
Yes	70	3.3
No	2058	96.7
Season of onset		
Spring	579	27.2
Summer	448	21.1
Autumn	604	28.4
Winter	497	23.4
Type of treatment		
IL (meglumine antimonate) + cryotherapy	1969	92.5
IM (meglumine antimonate) + cryotherapy	159	7.5
Site		
Face	614	28.9
Body	1511	71.1
Type of lesion		
Ulcerated	2033	95.7
Non-ulcerated	91	4.3
Treatment response		
Cure	1841	86.5
Failure	287	13.5
Duration (months)		
≤ 4	440	20.7
> 4	1688	79.3
Size of lesion (mm)		
≤ 10	1761	82.8
> 10	367	17.2

Abbreviations: IL, intralesional; IM, intramuscular

Table 2. Association of demographic and clinical features of patients with the number of lesions

Variables	Single lesion	Multiple lesions	*P*-value	Univariate OR (CI)	Multivariate OR (CI)	*P*-value
Sex						
Male	670 (49.4)	390 (50.2)	0.79	0.976 (-0.81-1.16)		
Female	681 (50.4)	387 (49.8)				
Age (years)						
0-9	385 (28.5)	153 (19.7)	0.001	1.71 (-1.42-2.05)	1.08 (1.03-1.14)	0.001
10-19	277 (20.5)	121 (15.6)				
20-29	144 (10.7)	126 (16.2)				
30-39	219 (16.2)	124 (16)				
40-49	133 (9.8)	77 (9.9)				
50-59	107 (7.9)	81 (10.4)				
60-69	51 (3.8)	65 (8.4)				
70-79	23 (1.7)	22 (2.8)				
≥ 80	12 (0.9)	8 (1)				
Season of onset						
Spring	401 (29.7)	178 (22.9)	0.031	1.09 (1-1.18)	1.10 (1.01-1.19)	0.018
Summer	277 (20.5)	171 (22)				
Autumn	352 (26.1)	252 (32.4)				
Winter	321 (23.8)	176 (22.7)				
Face lesions	433 (70.5)	181 (29.5)	0.001	0.644 (-0.52-0.78)	0.77 (0.62-0.95)	0.018
Type of lesion						
Ulcerated	1281 (94.9)	752 (97.2)	0.014	0.737 (-0.57-0.94)	0.75 (0.58-0.96)	0.024
Non-ulcerated	69 (5.1)	22 (2.8)				
Duration of disease (months)						
≤ 4	320 (23.7)	120 (15.4)	0.001	1.69 (1.34-2.14)	1.66 (1.31-2.11)	0.001
> 4	1031 (76.3)	657 (84.6)				
Size of lesion (mm)						
≤ 10	1150 (85.1)	611 (78.6)	0.001	1.55 (-1.23-1.95)	1.30 (1.03-1.65)	0.027
> 10	201 (14.9)	166 (21.4)				

ulceration (P = 0.024, OR = 0.75, CI = 0.58–0.96), longer duration (P = 0.001, OR = 1.66, CI = 1.31–2.11), 1 cm or less in diameter (P = 0.027, OR = 1.30, CI = 1.03–1.65) (Table 2).

Association between demographics and clinical features of lesions

Univariate analysis revealed that larger lesions (diameter > 1 cm) were observed more commonly in men (P = 0.011, OR = 0.746, CI = -0.59–0.93) and had a longer duration (P = 0.008, OR = 1.51, CI = -1.11–2.04). Furthermore, larger lesions were frequently ulcerated (P = 0.003, OR = 0.46, CI = -0.27–0.76), single (P = 0.001, OR = 1.55, CI = -1.23–1.95), and located most commonly in body areas other than the face (P = 0.001, OR = 0.62, CI = -0.49-0.78). Patients younger than nine had a significantly higher number of smaller lesions (P = 0.001, OR = 2.03, CI = -1.59–2.59) (Table 3).

Multivariate analysis confirmed the association of larger lesions with the male gender (P = 0.021, OR = 0.73, CI = 0.57–0.95), longer duration of lesions (P = 0.013, OR = 1.49, CI = 1.08–2.05), ulcerated lesions (P = 0.003, OR = 0.46, CI = 0.27–0.76), single lesions (P = 0.018, OR = 1.33, CI = 1.05–1.69), and body lesions (P = 0.008, OR = 0.69, CI = 0.53–0.91). Patients younger than nine years old demonstrated a significantly higher number of smaller lesions (P = 0.001, OR = 1.12, CI = 1.04–1.2) (Table 3).

Type of treatment

Most patients received IL Glucantime combined with cryotherapy (92.5%), and the remaining received IM Glucantime combined with cryotherapy. Treatment was mostly initiated treatment after four months of lesion onset (79.3%). Most patients were cured after one treatment course (86.5%), and treatment failure was observed in 13.5% of cases (Table 1). Treatment failure was observed in 10.7% and 16.7% of cases treated with IM or IL Glucantime

Table 3. Association of demographic and clinical features of patients with the size of the lesion

Variables	≤ 10 mm	> 10 mm	*P*-value	Univariate OR (CI)	Multivariate OR (CI)	*P*-value
Sex						
Male	855 (48.6)	205 (55.9)	0.011	0.746 (-0.59-0.93)	0.73 (0.57-0.95)	0.021
Female	906 (51.4)	162 (44.1)				
Age (years)						
0-9	486 (27.6)	52 (14.2)				
10-19	340 (19.3)	58 (15.8)				
20-29	223 (12.7)	47 (12.8)				
30-39	276 (15.7)	67 (18.3)				
40-49	163 (9.3)	47 (12.8)	0.001	2.03 (-1.59-2.59)	1.12 (1.04-1.2)	0.001
50-59	139 (7.9)	49 (13.4)				
60-69	89 (5.1)	27 (7.4)				
70-79	32 (1.8)	13 (3.5)				
≥ 80	13 (0.7)	7 (1.9)				
Duration of disease (months)						
≤ 4	383 (21.7)	57 (15.5)	0.008	1.51 (-1.11-2.04)	1.49 (1.08-2.05)	0.013
> 4	1378 (78.3)	310 (84.5)				
Site of the lesion						
Face	540 (87.9)	74 (12.1)	0.001	0.571 (-0.43-0.75)	0.92 (0.67-1.27)	0.630
Body	1282 (84.8)	229 (15.2)	0.001	0.62 (-0.49-0.78)	0.69 (0.53-0.91)	0.008
Type of lesion						
Ulcerated	1670 (95)	363 (98.9)	0.003	0.46 (-0.27-0.76)	0.46 (0.27-0.76)	0.003
Non-ulcerated	87 (5)	4 (1.1)				
Number of lesions						
Single	1150 (65.3)	201 (54.8)				
Multiple	611 (34.7)	166 (45.2)	0.0001	1.55 (-1.23-1.95)	1.33 (1.05-1.69)	0.018
Failure	254 (14.4)	33 (9)				

combined with cryotherapy, respectively. No significant difference was reported between the type of treatment and treatment failure (*P* = 0.09) (Table 4).

Association between clinical features of the lesions and treatment failure

Univariate analysis revealed that treatment failure was most common in winter-onset (*P* = 0.001, OR = 1.37, CI = -1.22–1.54), face (*P* = 0.001, OR = 1.89, CI = -1.46–2.44), ulcerated (*P* = 0.015, OR = 0.533, CI = -0.32–0.88), smaller (*P* = 0.006, OR = 0.586, CI = 0.4–0.85), and long-lasting lesions (*P* = 0.037, OR = 1.42, CI = -1.02–1.99) (Table 4).

The association of treatment failure with winter-onset (*P* = 0.001, OR = 1.39, CI = 1.23–1.56), face (*P* = 0.001, OR = 1.86, CI = 1.38–2.49), ulceration (*P* = 0.01, OR = 0.51, CI = 0.30–0.85), small diameter (*P* = 0.005, OR = 0.57, CI = 0.38–0.84) and long-lasting lesions (*P* = 0.01, OR = 1.57, CI = 1.11–2.21) were validated by multivariate logistic regression analysis (Table 4).

DISCUSSION

This study revealed that overall treatment success and failure percentages were 86.5% and 13.5%, respectively. Furthermore, there was no significant difference between the type of treatment (IL or IM) and treatment failure, somewhat similar to the previous study in Kerman and dissimilar to a study in Yazd [12,13]. The treatment failure rate in different regions of Iran varies from 7% to 59% [14]. Two studies in Pakistan demonstrated treatment failure of 19% and 45% [15,16].

In this study, most spring-onset lesions were solitary and responded better to treatment. In contrast, winter and autumn lesions demonstrated the highest percentage of treatment failure. These lesions usually are caused by sandflies at the highest levels of their activities in late spring or summer. Thus, they may be associated with the highest parasite load levels and greater diversity in *Leishmania* species, leading to less response to treatment [12].

In the current study, face lesions had a significantly

Table 4. Demographic and clinical features of patients associated with treatment failure

Variables	Cure	Failure	*P*-value	Univariate OR (CI)	Multivariate OR (CI)	*P*-value
Sex						
Male	911 (49.5)	149 (51.9)	0.443	0.907 (-0.70-1.16)		
Female	930 (50.5)	138 (48.1)				
Age (year)						
0-9	444 (24.2)	94 (32.8)	0.418	0.902 (-0.70-1.15)		
10-19	355 (19.3)	43 (15)				
20-29	226 (12.3)	44 (15.3)				
30-39	305 (16.6)	38 (13.2)				
40-49	191 (10.4)	19 (6.6)				
50-59	163 (8.9)	25 (8.7)				
60-69	101 (5.5)	15 (5.2)				
70-79	39 (2.1)	6 (2.1)				
≥ 80	17 (0.9)	3 (1)				
Season of onset						
Spring	529 (28.7)	50 (17.4)	0.001	1.37 (-1.22-1.54)	1.39 (1.23-1.56)	0.001
Summer	392 (21.3)	56 (19.5)				
Autumn	526 (28.6)	78 (27.2)				
Winter	394 (21.4)	103 (35.9)				
Site of the lesion						
Face	496 (80.8)	118 (19.2)	0.001	1.89 (-1.46-2.44)	1.86 (1.38-2.49)	0.001
Body	1293 (85.6)	218 (14.4)	0.047	1.33 (1-1.78)	0.95 (0.68-1.32)	0.77
Type of lesion						
Ulcerated	1750 (95.3)	283 (98.6)	0.015	0.533 (-0.32-0.88)	0.51 (0.30-0.85)	0.01
Non-ulcerated	87 (4.7)	4 (1.4)				
Size of the lesion (mm)						
≤ 10	1507 (81.9)	254 (88.5)	0.0006	0.586 (0.4-0.85)	0.57 (0.38-0.84)	0.005
> 10	1334 (18.1)	33 (11.5)				
Duration of disease (months)						
≤ 4	394 (21.4)	46 (16)	0.037	1.42 (-1.02-1.99)	1.57 (1.11-2.21)	0.01
> 4	1447 (78.6)	241 (84)				
Number of lesions						
Single	1178 (64)	173 (60.3)	0.22	1.17 (-0.90-1.15)		
Multiple	663 (36)	114 (39.7)				
Type of treatment						
Local treatment	270 (92.3)	1699 (94.1)	0.09	0.837 (-0.68-1.02)		
Systemic treatment	142 (7.7)	17 (5.9)				

higher rate of treatment failure than body lesions, similar to other studies [12]. Previous studies revealed that most lupoid leishmaniasis cases were located in the face area. Regarding the chronic course of this type of leishmaniasis and higher resistance to therapy, less response of facial lesions can be expected [12]. On the other hand, this study shows a higher percentage of larger lesions in the body area than in the face area.

In the present study, a higher percentage of treatment failure was observed in smaller lesions, probably due to early treatment of these lesions [12]. Previous surveys hypothesized a positive correlation between lesions' diameter and immune response activation. As a result, larger lesions are associated with more release of pro-inflammatory cytokines related to the T-helper 1 (Th1) immune pathway [tumor necrosis factor (TNF)-α, interferon (IFN)-gamma, and interleukin (IL)-2], resulting in phagocytosis and killing of *Leishmania* parasites. In contrast, smaller lesions may relate to less activation of the immune system and inflammatory cytokines; thus, a higher percentage of treatment failure can be expected with smaller lesions and facial lesions [17].

Studies indicated higher treatment failure in early ulcerated lesions than in classic ulcerative ones. Furthermore, they showed less activation of the immune system and production of inflammatory cytokines in early ulcerative lesions [17,18]. The present study showed a higher percentage of treatment failure in ulcerated lesions than in non-ulcerated ones. On the other hand, most of the multiple lesions were ulcerated, which can lead to a higher percentage of treatment resistance.

The current study indicated that longer durations of lesions (> 4 months) had a significant association with treatment failure. Previous studies showed a higher percentage of resistance to therapy in patients who had delayed treatment [7,12,18,19]. On the other hand, evidence shows a higher percentage of treatment resistance with early treatment of lesions (duration of less than 5 weeks) [20]. It is assumed that early lesions are accompanied by less activation of the immune system against the parasite and less production of cytokines associated with Th1; therefore, early-developed lesions result in more resistance to treatment [20]. This emphasizes the importance of choosing the right time to commence therapy post-lesion onset, probably after five weeks and definitely before four months.

Research revealed patients of younger age are associated with a significantly higher percentage of treatment failure [17,21,22]. The current study demonstrated no significant difference between the age of the patients and treatment failure; however, patients younger than nine years old had a higher percentage of treatment failure than other age groups. Factors including less exposure to the parasite, lower serum concentration of antimony drug, administration of an inadequate amount of drug, and low compliance and adherence to treatment in children might contribute to more treatment failure in this age group [20,23,24].

Our study showed no significant difference between males and females in treatment response. Treatment failure was only slightly higher in males compared to females. Few studies indicated a higher rate of treatment failure in the male gender, probably due to differences in pharmacokinetics, hormonal issues, immune system response, and treatment adherence [12].

Although our study was performed retrospectively, it included many patients with ACL and attempted to determine factors leading to poor response to antimony treatment. The results of this study emphasize the importance of commencing therapy at an appropriate time. Furthermore, growing numbers of ACL cases resistant to antimony therapy warrants seeking alternative treatments for recalcitrant cases.

CONCLUSION

Our study indicates that factors including winter onset, facial lesions, ulceration, small size, and long duration of leishmaniasis may predict poor treatment response. Multivariate logistic regression analysis confirmed predictive risk factors of large lesions including the male gender, longer duration of disease, ulcerated lesions, single lesions, and body lesions. Smaller lesions were observed more prevalently in patients younger than nine years old. Single lesions were observed mostly in spring-onset lesions and in the face. Multivariate logistic regression analysis confirmed predictive risk factors of multiple lesions as an age of younger than nine years, autumn onset, ulcerated lesions, longer duration of disease, and smaller lesions.

Conflict of interest: None declared.

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