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Delayed diagnosis among patients with cutaneous and mucocutaneous leishmaniasis

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Dear Editor,

Leishmaniasis is a vector-borne protozoan disease included by the World Health Organization in the list of neglected tropical diseases which is endemic in the Mediterranean basin. Cutaneous and mucocutaneous leishmaniasis (CL and MCL) have a broad spectrum of clinical manifestations [1] and represents a diagnostic challenge also in endemic regions. The aim of our study was to estimate the time of diagnostic latency of patients finally diagnosed with CL and MCL and characterize the medical encounters with a missed diagnostic opportunity before the correct diagnosis of leishmaniasis was reached.

We performed a monocentric retrospective observational study including all subjects with a diagnosis of CL and MCL managed at the Infectious Diseases Department of Luigi Sacco Hospital (Milan, Italy) from January 2005 to March 2022. All patients with suggestive skin or mucosal lesions, a compatible epidemiological history and parasitological confirmation (direct histological demonstration of *Leishmania* spp. amastigotes, culture positivity or PCR positivity on skin or mucosal samples) were included in the study. The diagnostic latency was defined as the number of days elapsed between the first contact with a health care provider for signs and/or symptoms referable to CL and MCL and the laboratory diagnosis of leishmaniasis. A wrong treatment for leishmaniasis before the diagnosis was defined as a treatment not recommended for the disease in accordance with the current Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) [2]. The study was approved by our Comitato Etico Interaziendale Area 1 (Protocol N° 0037058).

We observed 21 patients with CL (Fig. 1), mostly men (57.1%), with a median age of 51 years (IQR 42–64) (Table 1). Only one was a people living with HIV, and another one was on immunosuppressive therapy (infliximab). In 15 cases CL was acquired in Italy and in 6 cases CL was acquired abroad: Costa Rica (2), Bolivia (1), Ecuador (1), Chad (1) and Afghanistan (1). We observed 5 cases of MCL all but one without an history of travel outside Italy (Brazil). Two of them were on systemic immunosuppressive therapy (methylprednisolone + azathioprine and methotrexate + infliximab) and another one, with a laryngeal localization of MCL, under inhaled steroids.

For CL the median diagnostic delay was 189 days (IQR 84–300) with 13 patients (61.9%) reporting at least one medical encounter before the definite diagnosis: in 12 cases a dermatologist was consulted, in 3 cases an infectious diseases specialist, in one case a gastroenterologist and in another case a paediatrician. In 2 cases the medical encounter was with a physician in charge for the management of a chronic underlying condition (1 infectious diseases specialist and 1 gastroenterologist). For 11 patients (52.3%) a wrong treatment (antibiotics plus topic steroids in most of cases) was prescribed before the diagnosis. For patients with MCL the diagnostic time latency ranged from 151 to 648 days; one patient received an erroneous treatment with a systemic antibiotic and one with topic steroids.

The diagnostic delay observed in our study was in line with what has been observed in another Italian study (median 6 months) conducted in the north-eastern regions not endemic for the disease [3] but longer when compared to the 143 days reported by Vandeputte et al. for CL and MCL cases in Belgium [4]. Slight longer diagnostic delay was reported in Valencia (Spain) for CL and MCL cases with a mean of 7.36 ± 6.72 months in immunocompetent patients and 8.79 ± 6.9 months in immunosuppressed patients [5]. A significant delay was also reported in a study conducted in Germany on Syrian refuges in which the authors described several barriers faced by the patients to reach access to diagnosis and care during and after the migration [6]. The long diagnostic latency observed in our study in patients with MCL is compatible with the rarity of the disease in the Mediterranean basin and in line with other European studies providing pooled data for CL and MCL (4, 5); moreover, the mucosal localization observed in 4 cases in our study has to be considered an atypical presentation, because *L. infantum* specie seldom causes MCL in Mediterranean Basin. In our study one patient with CL was on treatment with infliximab, while 3 patients with MCL were on an immunotherapy. Immunomodulatory and/or immunosuppressant therapy has to be considered an emerging risk factor for developing CL and MCL leishmaniasis [7].

Our findings highlight the importance of increasing the awareness of the disease to a wide range of medical providers and specialists, also in countries considered endemic for this neglected tropical disease, with particular attention to patients under iatrogenic immunosuppression.

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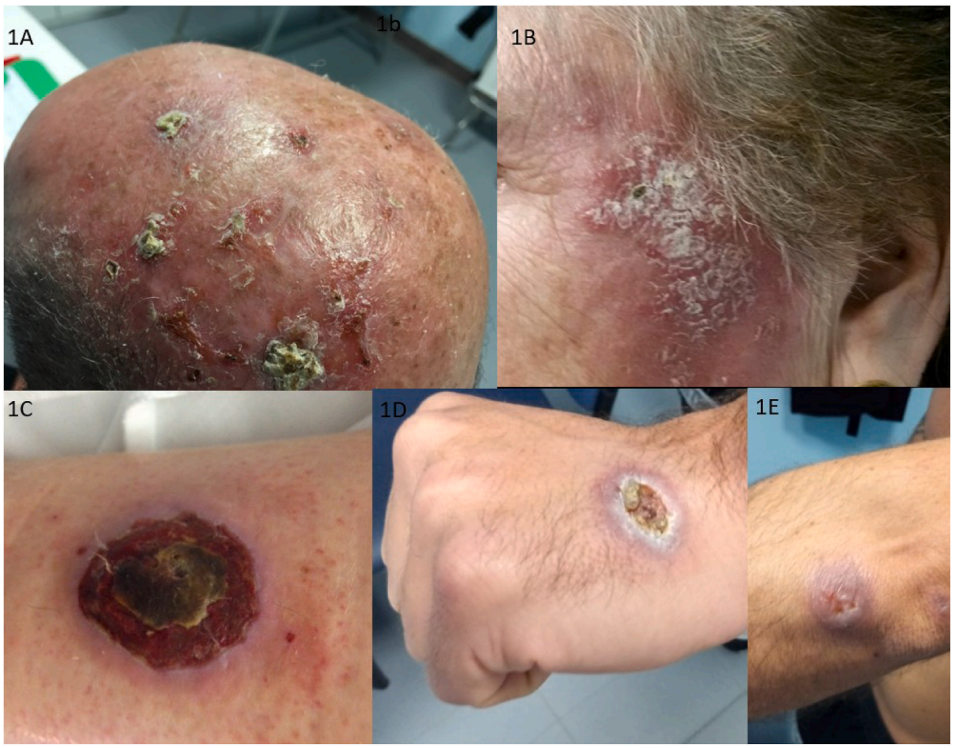

Fig. 1. 1A, cutaneous leishmaniasis of the scalp acquired in Tuscany. 1B, cutaneous leishmaniasis of the face acquired in Calabria. 1C, cutaneous leishmaniasis of the right inferior limb acquired in Liguria in a man affected by Chron disease under immunosuppressive treatment with infliximab. 1D, cutaneous leishmaniasis of the left hand and, 1E of the left elbow acquired in Tuscany.

Table 1
Epidemiological, clinical and laboratory features of patients with cutaneous and mucocutaneous leishmaniasis.

Characteristics	CL n = 21	MCL n = 5
Male gender, n (%)	12 (57.1)	4
Age, median (IQR) and range	51 (42–64)	55–76
Italian nationality, n (%)	18 (85.7)	4
Probable autochthonous infection, n (%)	15 (71.4)	4
Regions of residence in Italy, n (%)		
Liguria	1 (6.7)	2
Tuscany	3 (20)	0
Calabria	2 (13.3)	1
Sicily	5 (33.3)	0
Sardinia and Tuscany	1 (6.7)	1
Sicily and Liguria	2 (13.3)	0
Lombardy	1 (6.7)	0
People living with HIV, n (%)	1 (4.7)	0
Patients with iatrogenic immunosuppression, n (%)	1 (4.7)	3
Multiple lesions, n (%)	10 (47)	1
Lesions localization, n (%)		
Head/face	7 (33.3)	4
Superior limbs	10 (47.7)	0
Inferior limbs	7 (33.3)	0
Trunk	2 (9.5)	0
Other	0 (0)	1[a]
Characteristics of the lesion, n (%)		
Erythematosus	12 (57.1)	0
Papular	2 (9.5)	0
Nodular	8 (38.1)	2
Ulcerous	9 (48.2)	2
Crusted	4 (19)	0
Other	0 (0)	2[b]
Diagnostic analysis performed, n (%)		
Serology positive	6/17 (35.3)	4/5
Culture positive	2/8 (25)	0/0
PCR on cutaneous sample	10/12 (83.3)	4/4
Histology positive	16/16 (100)	5/5
Days of diagnostic latency, median (IQR) and range	189 (84–300)	151–648
***Leishmania* species**		

(*continued on next page*)

Table 1 (*continued*)

Characteristics	CL n = 21	MCL n = 5
L. major	1 (4.8)	0
L. panamensis	1 (4.8)	0
L. infantum	14 (66.6)	4
L. aethiopica/tropica	1 (4.8)	0
Unknown	4 (19)	1

List of abbreviations: CL, cutaneous leishmaniasis; MCL, mucocutaneous leishmaniasis; n, number; IQR, inter quartile range; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

[a] Larynx.

[b] Mucosal hyperaemia of the nasal nostril and scarring and widespread dyschromia of the labial commissure.

Ethical approval

The study was approved by our Comitato Etico Interaziendale Area 1 (Protocol N° 0037058).

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None.

CRediT authorship contribution statement

Andrea Poloni: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Andrea Giacomelli: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Romualdo Grande: Data curation, Formal analysis, Writing – review & editing. Mario Corbellino: Data curation, Formal analysis, Writing – review & editing. Manuela Nebuloni: Data curation, Formal analysis, Writing – review & editing. Giuliano Rizzardini: Data curation, Formal analysis – review & editing. Anna Lisa Ridolfo: Data curation, Formal analysis, Writing – review & editing. Spinello Antinori: Conceptualization, Project administration, Supervision, Writing – review & editing.

Data availability statement

Data will provide by the corresponding author upon reasonable request.

Declaration of competing interest

None to declare.

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