



Editorial

Is the Clinical Diagnosis of Cutaneous Leishmaniasis Justified in Endemic Regions?

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Leishmaniasis is a transmissible infection brought about by an obligatory intracellular protozoan from the genus *Leishmania*. It occurs worldwide in tropical and subtropical regions and can be burdensome in resource-constrained countries. The infection ranges in severity from mild cutaneous lesions to more severe and sometimes life-threatening visceral and distorting mucocutaneous sicknesses. Importantly, cutaneous leishmaniasis (CL) is prevalent in the Middle East with a pooled prevalence of 12%. It imposes a significant health and socioeconomic burden (1).

Iraq is located within the topographical belt of CL. The available data revealed that CL infects 2.9-10.5 per 100,000 individuals (2). Active nationwide surveillance and control measures depend upon the accurate detection of cases. Diagnostic challenges are triggered when the lesions erupt in a non-endemic region, when the clinical appearance is ambiguous, or an atypical variety is detected even in an endemic area.

A large debate exists on the efficacy of clinical examination in diagnosing CL in endemic regions or when the facilities for parasite detection are either inaccessible or negative. Anecdotal studies in endemic regions such as Saudi Arabia (3), Pakistan (4), and Sri Lanka (5) showed that the diagnosis of CL is largely dependent upon the clinical picture. In Iraq, the disrupted healthcare infrastructure and defective programs for controlling and treating zoonotic infections as a result of decades of conflicts have driven dermatologists to evaluate various aspects of CL in the light of the clinical picture (6). We believe that the drawbacks of the referring to the clinical examination to diagnose CL are multifaceted.

First, it is noteworthy that in addition to the clinical diagnosis, particularly in regions where the disease is endemic, there are different techniques to detect CL which vary in sensitivity. As Iraq is

one of the countries importantly affected by CL, the issue of firming the diagnosis of infection has become a matter of concern for many years. Al-Hucheimi et al (7) found that slit-skin smear test was positive in 66.7% of cases, and 84.2% of specimens were positive by the slide-touch skin biopsy. However, histopathological examination revealed findings predictive of CL in 59.6% of cases. Interestingly, the polymerase chain reaction (PCR) test was greatly specific (100%) and sensitive (92.5%) for CL diagnosis. Tawfeeq and Ali (8) reported that microscopy, conventional PCR, and nested PCR had a sensitivity of 80.7%, 86.6%, and 100%, respectively, and all three tools had 100% specificity. We believe that in addition to confirming CL diagnosis,

PCR is useful in defining the correlation between the clinical pictures of the disease and the type of *Leishmania* species.

During the preceding few years, dermoscopy has proven to be an effective instrument to assist the noninvasive diagnosis of different dermatological disorders (9). Its application has revealed characteristic patterns and correlations with the site and type of CL lesions in certain endemic regions (10-11). In Iraq, the main dermoscopic features of CL were found to be generalized erythema (100), hyperkeratosis with central ulceration, white scar-like patch, yellow tears, white starburst sign, and milia-like cyst in 100%, 53.8%, 41.8%, 35.2%, 34.1%, and 2.2% of cases, respectively. Considering the site, hyperkeratosis with ulceration/erosion were most commonly detected on the lower limbs while linear irregular vessels were the commonest findings on the upper limbs and face (12). Awareness of dermatologists in Iraq on dermoscopic CL patterns is crucial to help diagnose and avoid misdiagnosis if the clinical examination is solely employed to diagnose CL.

Second, CL importantly infects the people of the subtropical and tropical regions. Clinical presentations and infective species of the parasite are important factors driving the diagnosis. The increase in the prevalence of atypical presentations of CL is worrisome and presents a challenge in patient management (13). Interestingly, CL could mimic almost all forms of dermatoses and it is called "the great imitator." The similarity could at times lead to misdiagnosis, improper therapy, and significant morbidities. Atypical varieties could develop because of the interplay between the host's immune reaction and parasitic factors. Improper treatment of CL or superadded secondary infection could also change the natural course of the disease, resulting in bizarre, misdiagnosed cases (14). Atypical cases ought to be taken into consideration in longstanding and painless lesions which might resemble dermatitis, erysipelas, verruca, paronychia, sporotrichosis, and herpes zoster. Less commonly, deep-seated mycosis, sarcoidosis, cutaneous lymphoma, squamous and basal cell carcinoma, or pseudolymphoma like lesions might require to be put in the differential diagnosis (14). Knowledge of the atypical and rare presentations could help have a wider perspective for considering various aspects of CL during clinical examination and ultimately avoiding misdiagnosis. Therefore, a great index of suspicion is needed to diagnose CL, particularly in non-endemic or newly documented endemic regions. Relying upon clinical diagnosis could lead to missing a significant number of CL cases. Hence, smear, histopathological examination, culture, and PCR represent important elements to sharply distinguish CL from its clinical and histological look-alikes (13-14).

Third, a new pandemic disease, called COVID-19, was broadcasted in March 2020. It is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is RNA virus which belongs to the Coronaviridae family, Orthocoronavirinae subfamily, and Nidovirales order. The pandemic triggered a global public health concern (15). The COVID-19 infection is a multi-systemic disease with the capability to infect different body organs. The skin is the beholder of the cytokines storm with the thrombophilic multi-organ injuries, and it is directly influenced by the epithelial tropism of the COVID-19 virus documented by the demonstration of the virus in the epithelial cells of the epidermis and eccrine glands (16). The ACE2 receptor is suggested to be a target of the virus though other receptor molecules might possibly be involved, such as TMPRSS2 (17).

Though patients infected with COVID-19 commonly present with respiratory manifestations, a clinical spectrum of various cutaneous features is further described. The skin patterns most commonly correlated with COVID-19 infection were found to be maculopapular exanthematous/morbilloform lesions, vesicular lesions, chilblain-like lesions, urticarial lesions, and livedoid lesions. Other cutaneous patterns due to COVID-19 infection were erythema multiforme-like lesions and dermal features correlated with multi-system inflammatory syndrome (18-19). Many of the above-mentioned skin lesions might in some way resemble CL. The COVID-19 pandemic has greatly impacted dermatology practice in Iraq and dermatologists faced enormous challenges in managing various skin disorders (20). A study on COVID-19-infected patients in Iraq has revealed a diversity of dermatological manifestations, including hair loss (30%), acneiform rash (20%), diffuse urticaria (14%), diffuse petechiae (12%), mucocutaneous rash (6%), chilblain-like lesions (6%), purpura (6%), vesicular rash (4%), and acrocyanosis (2%) (21). Though COVID-19 pandemic has noticeably vanished in many countries around the world, involving Iraq, the emergence of resistant, new strains is continually worrisome. Since the reported skin patterns of COVID-19 are different, dispersed, and sometimes confusing with CL manifestations, it is expected that merely relying upon clinical examination could misdiagnose a significant number of CL in COVID-19-positive patients.

Fourth, due to immunocompromised status, human immunodeficiency virus (HIV)-positive individuals have an accentuated risk to acquire various infections, including leishmaniasis and CL could be the initial presentation of HIV infection (22). There is a bidirectional relationship between HIV and leishmaniasis. Both HIV and leishmania could infect macrophages and dendritic cells and ameliorate the activity of other cells without co-infecting, like B and T lymphocytes. The HIV/leishmania co-infection is viewed as a determinant hindering the adjustments of molecule expression on cell surface, generation of soluble items, and intracellular death sequences, resulting in the enhancement of infectivity, replication, and both pathogens spread (23). Hence, the clinical pictures of CL-HIV co-infection are determined by the interplay between the parasite species and host cell-mediated immune reaction giving the opportunity to ameliorate the clinical picture or trigger atypical presentation of CL and occurrence of reactivated CL lesions (24). Therefore, the clinical variants of CL in these patients are protean such as diffuse cutaneous, sporotrichoid, contact dermatitis-like, psoriasiform, erysipeloid, warty, impetigo-like, zosteriform, acneiform, and eczematoid variant (24-27). Officially, contaminated blood brought the AIDS/HIV disease to Iraq in 1986, primarily affecting hemophilic patients. Cultural norms and severe economic hardships brought on by sanctions and antecedent wars have slowed educational and treatment efforts over decades (28). Though Iraq is characterized as a low HIV/AIDS prevalence country (0.1%) (29), HIV risk factors have steadily increased since 2003 due to low literacy, gender-related discrimination, poverty, and constrained knowledge of HIV transmission routes. The state of limited governmental financial resources, crisis of people internal displacement, socio-cultural barriers, and inadequate nationwide preventive measures are expected to potentiate HIV/AIDS spread in

Iraq. As a result, the trend of the cumulative yearly number of new HIV cases is continually increasing with time and this might end in an epidemic/endemic. The available data showed an increment in the trend of the yearly number of new HIV cases (alive and total) from 2010 to 2019. The number of HIV cases was 10 (1.8%) in 2010, and 29 (5.4%) in 2015, increasing to 157 cases (29.1%) in 2019, with a yearly infection increment rate of 14.7%. Importantly, the variation in the yearly distribution of the number of new HIV cases was significant statistically ($P < 0.0001$) (30). As a result, we believe that referral to clinical examination would not guarantee the firm diagnosis of CL in HIV-infected patients in regions where HIV and CL are notable communicable diseases.

Fifth, tuberculosis (TB) represents a critical public health concern, particularly in developing countries. Cutaneous TB (CTB) constitutes 1-1.5% of extrapulmonary TB, which is caused by *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and the attenuated variety of the *Bacillus Calmette-Guérin* (BCG) vaccine. It could be brought on by hematogenous spread, contiguity, and autoinoculation as well as by the BCG vaccine (31). It usually manifests as *Lupus vulgaris*, TB verrucosa cutis, scrofuloderma, and tubercular abscess. The hypersensitivity response to the TB bacilli could lead to papulonecrotic tuberculids and *Lichen scrofulosorum* (32). It can have a myriad of clinical manifestations, many of which are atypical such as TB presenting as progressive diffuse facial granulomas, sporotrichoid TB, TB simulating squamous cell carcinoma, scrofuloderma as tubercular ulcer, *Lupus vulgaris* resembling furuncle, psoriasis, dermatitis, CL, and leprosy (32). For practicing dermatologists, particularly in developing countries, diagnosis of CTB represents an elusive and difficult challenge due to the need to consider a wide differential diagnosis and the presence of hard challenges in making a diagnostic confirmation (33). In Iraq, TB continues to impose a public health concern. According to the latest yearly statistical report launched by the Ministry of Health and Environment in 2022, TB incidence in Iraq is reported to be 16 per 100,000 population (34). Interestingly, *Lupus vulgaris* as the major presentation of the old CTB no longer exists at the present time in Iraq but substituted by various and wide cutaneous clinical presentations which could resemble other skin diseases. Cold abscesses/discharging sinuses were the commonest detected clinical variant in 52.77% of patients, followed by tuberculous chancre in 23.61%, tuberculosis verrucosa cutis in 15.27%, and orificial TB in 8.23% of patients (35). Due to overlapping clinical manifestations between CL and CTB, reliance on clinical examination is expected to misdiagnose a good number of CL.

Sixth, with the continuing advancement in technology, the incorporation of artificial intelligence (AI) in the evaluation of medical images has paced the path to precise assessment being done automatically, which has decreased physicians' workload, lessen mistakes and time in making the diagnosis, and enhanced accomplishment to predict and detect different diseases (36). Interestingly, an AI-based algorithm for automatic diagnosis of CL has been evaluated and proven to be precise, fast, easy-to-apply, and cost-effective. It is expected that AI will become an alternative to the present methods of CL diagnosis (37,38).

In conclusion, clinical diagnosis of CL is not a substitute for laboratory diagnosis even in endemic regions, and confirmation of the diagnosis by suitable laboratory tests is demanded to guide therapy, predict prognosis, and subsequently contribute to breaking the transmission cycle of the parasite and reducing the prevalence.

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