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# Leishmaniasis and Malignancy: A Review and Perspective

Mohamed Ahmed Naif Al-Kamel

## Abstract

Leishmaniasis, a widely prevalent disease throughout tropical and subtropical regions of the world, is a chronic protozoan infection of humans and mammals that remains grossly underreported and causes significant global morbidity and mortality. Different species of the intracellular protozoan parasites of the genus *Leishmania* can cause human leishmaniasis, resulting in various visceral, cutaneous, and mucocutaneous manifestations. The risk of leishmaniasis manifesting as a more severe entity is dependent on the infecting parasites' immune evasion potential. Some causal associations between leishmaniasis and malignancy have been evidenced in experimental animals and humans. *Leishmania* spp. infection can play a significant, direct or indirect, role in the pathogenesis and prognosis of some malignant disorders through numerous pathophysiologic cascades. Aging, chronic ultraviolet radiation exposure, and poplar treatment abuse (eg, chameleon saliva, cactus recipes, corrosive chemicals, and topical steroids) have been proposed as the principal triggering factors. Malignancy should be considered in the differential diagnosis of leishmaniasis in endemic regions, such as Yemen. Understanding this relationship could enrich the provision of early diagnosis, proper management, and prompt control of cancer.

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## Introduction

Leishmaniasis, a chronic parasitic infection of humans and mammals, is a neglected disease that is widely prevalent in many tropical and subtropical regions of the world. It remains grossly underreported and predominately affects children and women, with serious clinical consequences. Different species of the intracellular protozoan parasites of the genus *Leishmania* can cause human leishmaniasis, resulting in various visceral, cutaneous, and mucocutaneous manifestations. These parasites are transmitted to a human reservoir or host through bites of a blood-sucking vector, female sandflies. Visceral leishmaniasis (VL), which is lethal if left untreated, and cutaneous leishmaniasis (CL), which can affect the skin and/or mucous membranes with a broad spectrum of clinical manifestations, including dissemination (disseminated CL), are the most common clinical entities.<sup>1-3</sup>

The risk of leishmaniasis manifesting as a more severe entity is dependent on the infecting parasites' immune evasion potential, which is controlled by numerous factors, such as the infecting

*Leishmania* species, genetic constitution (eg, lipophosphoglycan variation, the major abundant surface glycoconjugate, and differences in 63-kDa glycoprotein, the major surface protease, commonly known as gp63), and the general health of the infected individual (eg, poor nutrition, advanced age).<sup>4,5</sup>

*Leishmania* resides as amastigotes and replicate inside the host's phagocytic cells (macrophages, dendritic cells, and neutrophils). To maintain a chronic infectious state within its host, *Leishmania* parasites have developed some successful strategies to prevent activation of effective immune responses and maintain the antimicrobial activities of host cells. These include remodeling the host cells' phagosomal compartments, interfering with the intracellular signaling pathways, alteration of toll-like receptor pathways, modulation of cytokines and chemokines, modification of T-cell responses, evasion of the host's cellular immunity, and generation of nitric oxide and oxygen oxidative radicals.<sup>6,7</sup> In contrast, carcinogenesis can be influenced by several physiologic, exogenous, environmental, genotypic, and phenotypic factors.<sup>8,9</sup>

Leishmaniasis and malignancy are both common health hazards, and some causal associations between these 2 clinical entities have been evidenced in experimental animals and in humans. However, the pathophysiologic implications of *Leishmania* as a carcinogenic mediator has been less well elucidated.<sup>4,8,10</sup>

The present report has reviewed the up-to-date data supporting the theory of the oncogenic potential of *Leishmania* and provided a perspective point from the Regional Leishmaniasis Control Center

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(RLCC) in Yemen, which treats an average of 100 to 150 new patients with leishmaniasis each month.

### Impetus and Method

My clinical encounters at the outpatient clinics of RLCC in Yemen of several presentations of malignancy in patients with a history of leishmaniasis gave me the impetus to seek further data in support of the concept of *Leishmania* as a carcinogen.<sup>11,12</sup> These malignancies included basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and lymphoma (Figures 1-3). These cancers had developed in patients aged 50 to 100 years who had a history of popular treatment abuse and chronic sun exposure. These patients also had CL lesions on their face, providing evidence of *Leishmania* infection.

English-language studies were investigated for reports of the concurrent development of leishmaniasis disease and malignancy. However, the focus was on reported cases of the direct involvement of *Leishmania* spp. in the pathogenesis of malignant lesions.

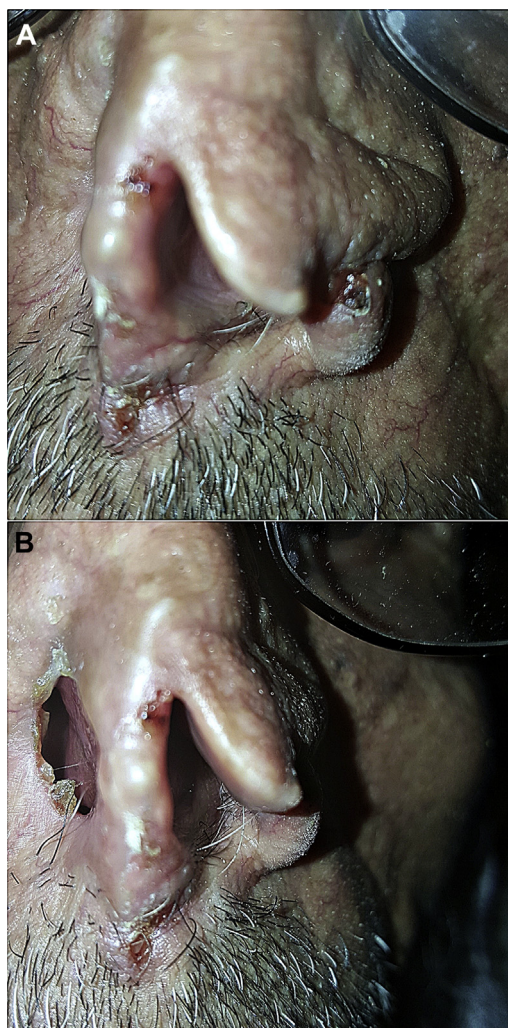
### Associations Between Leishmaniasis and Malignancy

The association between viral, bacteria, and parasitic infections with the development of human malignancy has been recognized for years.<sup>9</sup> Although some parasitic infections have been very strongly associated with specific cancers, the available reported data have potentially linked leishmaniasis infection with the development of malignancy in humans and in animals.<sup>13,14</sup> The potential associations between leishmaniasis and malignancy included the following:

**Figure 1** Large Nodular Ulcerative Basal Cell Carcinoma With Raised Curly Borders and Central Ulceration Superimposed on a Cutaneous Leishmaniasis Nodule and Affected the Right Nostril, Upper Lip, and Right Cheek of an 85-year-Old Patient From Yemen With a History of Chronic Sun Exposure (Regional Leishmaniasis Control Center, 2017)



**Figure 2** (A and B) Recurrent, After Surgical Excision, Basal Cell Carcinoma Ulcers That Had Developed on an Active Mucocutaneous Leishmaniasis Lesion and Destroyed the Nose of a 79-year-Old Man From Yemen (Regional Leishmaniasis Control Center, 2017)



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(1) leishmaniasis mimicking malignancy (Figure 4); (2) leishmaniasis coexisting with malignancy; (3) malignancy developing in patients with leishmaniasis (Figures 1-3); and (4) leishmaniasis developing in patients with malignancy.<sup>13</sup>

Numerous studies have reported a well-established relationship between *Leishmania* spp. and the pathogenesis of malignant lesions, including BCC, SCC, lymphoma, leukemia, and hemangiosarcoma. Amastigotes have been identified in infiltrating macrophages and within the cytoplasm of neoplastic cells from tumors with different histogenesis variants.<sup>15-19</sup>

Other illustrative reports have described the presence of large numbers of atypical mitotic features (marked dysplasia) and diffuse

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**Figure 3** Cutaneous T-Cell Lymphoma Superimposed on Disseminated Cutaneous Leishmaniasis in an Immunocompromised 50-year-Old Female From Yemen (Regional Leishmaniasis Control Center, 2017)



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lymphoid infiltrate of predominantly B-lymphocytes, surrounded by a population of CD3<sup>+</sup> and CD4<sup>+</sup> T-lymphocytes in the excisional biopsies from patients with CL lesions.<sup>13</sup> In addition, prolonged antigenic stimulation and chronic immunosuppression, typical of leishmaniasis, might play a crucial role in the etiopathogenesis of certain cancers, such as T-cell lymphoma.<sup>15,20</sup>

In 2014, a study conducted at the Research Center of the Instituto Nacional de Câncer (Rio de Janeiro, Brazil), concluded that in the differential diagnosis of childhood leukemia, VL should be considered as a potential concurrent disease in regions in which

**Figure 4** Mucocutaneous Leishmaniasis Necrotic Ulcer With a Well-Delineated Elevated Border Mimicking Basal Cell Carcinoma on the Nose of an 81-year-Old Female From Yemen (Regional Leishmaniasis Control Center, 2017)



*Leishmania chagasi* is endemic.<sup>21</sup> In 2013, another study conducted in Egypt confirmed that CL allows for mutation and the development of skin cancer.<sup>22</sup> In 2013, Nwamaka et al<sup>23</sup> recommended that clinicians should not discount the profound immune dysregulation associated with widely disseminated infection, such as VL, and should be vigilant in including lymphoproliferative disorders and lymphomas as complications of *Leishmania* infection. In 2011, Kumar et al<sup>24</sup> highlighted the mutual immunomodulation that resulted in the presentation of leishmaniasis as an opportunistic infection in a patient with Hodgkin lymphoma before chemotherapy. In 2007, Kopterides et al<sup>13</sup> reported that a leishmaniasis-related scar is a recognized factor that predisposes to the development of malignancy. In addition, 88.9% of the studies that speculated on a possible causal association between leishmaniasis infection and the subsequent appearance of skin or mucous membrane malignancy reported that BCC, SCC, or hepatocellular carcinoma had developed at the site of healed leishmanial scars or within a few months after the first symptoms of VL, with 10.1% developing concurrently at the site of infection.<sup>13</sup> Also, in 2005, Mangoud et al<sup>25</sup> found dysplasia in the cells surrounding the leishmanial ulcer and concluded that leishmaniasis disease adversely affects the activation and function of macrophages and dendritic cells, which allows the transformed malignant cells to escape from immune detection and destruction. Finally, in 2005, Ozbilge et al<sup>26</sup> reported that patients with cutaneous leishmaniasis are affected by oxidative stress, which could contribute to the progression of the disease.

Because all the patients who have presented to RLCC in Yemen with malignant disorders in addition to leishmaniasis infection were older individuals with a history of chronic use of unsafe popular treatments and sun exposure, I believe internal factors, such as aging, and external factors, such as ultraviolet radiation and abuse of popular treatments, such as animal (eg, chameleon) saliva, herbal (eg, cactus) recipes, corrosive chemicals, and topical steroids, can play a significant role in triggering a carcinogenic process (Figure 5).

### Pathophysiologic Cascades of Leishmaniasis-induced Malignancy

Although the exact etiology of malignant lesions in organs infected with *Leishmania* parasites is still not well understood and requires further investigation, mutation research has supported the notion that leishmaniasis infection could influence carcinogenesis through numerous pathophysiologic cascades. These include chronic infection, chronic inflammation, metabolic oxidative stress, apoptosis inhibition, inhibition of tumor suppressors, wound healing, genetic transfer, nonspecific tropism, *Leishmania*-driven lymphoproliferation, and leishmaniasis-related scarring.

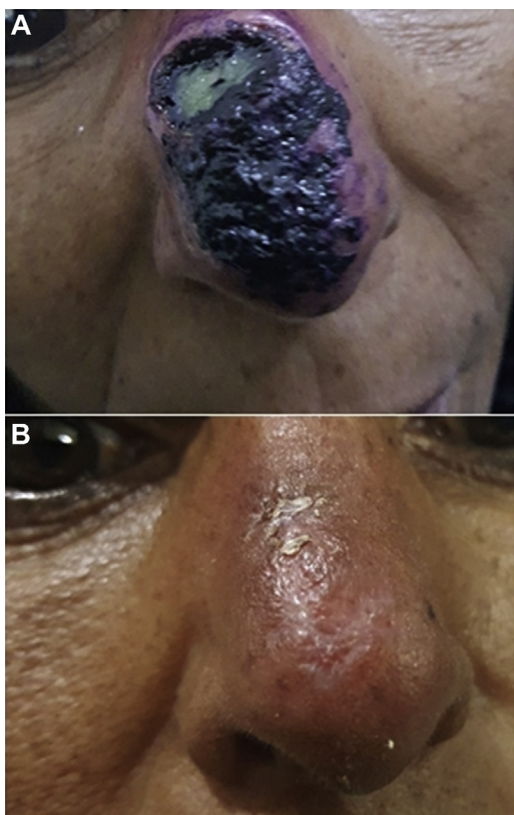
#### Chronic Infection

The chronic irritation hypothesis remains a widely supported mechanism for carcinogenesis by infectious agents. This is because many cancers arise from sites of infection.<sup>8</sup>

#### Chronic Inflammation

Recent data have expanded the concept that chronic inflammation is a critical component of the neoplastic process, fostering

**Figure 5** (A) Mucocutaneous Leishmaniasis Inflammation Complicated by a Necrotic Ulcer and Secondary Bacterial Infection Affecting the Nose of a 65-year-Old Female From Yemen With a History of Corrosive Popular Treatment Abuse and Chronic Sun Exposure (Triggering Factors for Basal Cell Carcinoma). (B) Photograph 1 Month After Medical Treatment With Oral Fluconazole at Regional Leishmaniasis Control Center (Sana'a, Yemen, 2017)



proliferation, survival, and migration of cancer cells. The chronic inflammation process due to prolonged persistence of *Leishmania* spp. in the host leads to repeated cycles of cell damage (caused by the host's immune response to the infection rather than by the infecting organism itself) and compensatory cell proliferation, thus orchestrating a tumor microenvironment.<sup>9</sup>

#### Metabolic Oxidative Stress

The reactive oxygen species and reactive nitrogen species produced by phagocytes during the inflammatory response to *Leishmania* infection, along with reduced total antioxidant capacity, are an important part of the host-defense strategies of organisms to kill the parasite. However, although these reactive oxidant mediators are manufactured for the purpose of killing invading *Leishmania* parasites, they also inflict damage on nearby tissues and induce oxidative DNA damage in noninfected cells. These have been proposed to be of

a pathogenic significance and might contribute to increased mutation rates, genome instability, and cell proliferation.<sup>10,27</sup>

#### Apoptosis Inhibition

Many intracellular protists, such as *Leishmania* spp., are known to induce apoptosis inhibition, an effect that could be a significant step in the progression to malignancy.<sup>28</sup>

#### Inhibition of Tumor Suppressors

*Leishmania* spp. induce modulation of the host immune response, which could lead to inhibition of tumor suppressor surveillance mechanisms.<sup>29</sup>

#### Wound Healing

Host tissue damage during parasite development, along with the active wound healing, has been recognized as a carcinogenic mechanism.<sup>30</sup>

#### Genetic Transfer

The presence of *Leishmania* amastigotes has been documented in the cytoplasm of neoplastic cells from tumors of different histogenesis. The transfer of genetic material from the *Leishmania* parasite to the host can cause DNA damage and directly interfere with cell transformation.<sup>31</sup>

#### Nonspecific Tropism

The reported data have indicated the ability of *Leishmania* spp. to parasitize nonleukocytic neoplastic cells. The presence of *Leishmania* amastigotes within different types of cells indicates a nonspecific tropism for *Leishmania*.<sup>29,32</sup>

#### Leishmania-driven Lymphoproliferation

Prolonged immunosuppression and chronic leishmanial antigenic stimulation have been shown to play a crucial role in the etiopathogenesis of T-cell lymphoma.<sup>33</sup>

#### Leishmaniasis-related Scarring

The development of malignant lesions, in particular, BCC and SCC, at the sites of previous dermal scars is a well-recognized phenomenon. Almost all such cases develop in exposed areas. Thus, it has been hypothesized that the accompanying atrophy and decreased vascularity and adnexal structures in areas of scarring might render the affected tissues more susceptible to the effects of environmental factors, such as ultraviolet radiation.<sup>18,20</sup>

## Conclusion

*Leishmania* spp. infection can play a significant, direct or indirect, role in the pathogenesis and prognosis of some malignant disorders. From my perspective, older age, ultraviolet radiation exposure, and popular treatment abuse, such as animal (eg, chameleon) saliva, herbal (eg, cactus) recipes, corrosive chemicals, and topical steroids, has been supposed as principal triggering factors for the development of cancer at sites of infection with *Leishmania* parasites. Malignancy should be considered in the differential diagnosis of leishmaniasis in endemic regions, such as

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Yemen. Understanding this relationship could enrich the provision for the early diagnosis, proper management, and prompt control of cancer.

## Clinical Practice Points

- The risk of leishmaniasis manifesting as a more severe entity is dependent on the infecting parasites' immune evasion potential.
- The potential associations between leishmaniasis and malignancy include leishmaniasis mimicking malignancy; leishmaniasis coexisting with malignancy; malignancy developing in patients with leishmaniasis; and leishmaniasis developing in patients with malignancy.
- *Leishmania* spp. infection can play a significant, direct or indirect, role in the pathogenesis and prognosis of some malignant disorders.
- Mutation research has supported the notion that leishmaniasis infection could influence carcinogenesis through numerous pathophysiologic cascades, including genetic transfer and nonspecific tropism.
- Older patient age, ultraviolet radiation exposure, and the abuse of popular treatments should be considered as principal triggering factors for the development of cancer at sites of infection with *Leishmania* parasites.

## Disclosure

The author declares that he has no competing interests.

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