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CASE REPORT

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Nasal mucocutaneous leishmaniasis (MCL) with necrotizing granulomatous inflammation inducing cytotoxic T-cell lymphoma in a male Yemeni patient

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Abstract

Leishmaniasis is a protozoal infection transmitted by sandfly vector; there are three main types of leishmaniasis: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL). Herein, we present a case of endonasal mucocutaneous leishmaniasis in a 34-year-old Yemeni patient who presented with disfiguring nasal swelling associated with fever, a swab from the lesion and direct microscopic examination proved to have mucocutaneous leishmaniasis; he was successfully treated with intravenous antimonial stibogluconate, 1 month after treatment biopsy from the lesion revealed cytotoxic T-cell lymphoma, the purpose is to alert the physicians and otolaryngologists to consider leishmaniasis in the differential diagnosis of nasal granulomas and also to highlight the importance of early diagnosis of cancer in survivors of cutaneous leishmaniasis, especially in areas where cutaneous leishmaniasis is still highly prevalent, as the chronic local inflammation may disfigure the face if not recognized early and adequately treated; also, early cancer diagnosis can prevent mortality

Keywords Necrotizing granuloma, Mucocutaneous leishmaniasis, Nasal granuloma, Cytotoxic T-cell lymphoma

Background

Cutaneous leishmaniasis is widespread in Yemen, and its incidence is not well reflected; a few published documents are available [1], the cutaneous form is caused by leishmania tropica and leishmania major, and further visceral leishmaniasis (kala-azar) is endemic in Yemen [2]. We describe a case of a male patient 34 years old from Yemen living in a mountainous area who presented to our fever hospital with prolonged fever and nasal disfiguring swelling; he had no known medical history, and the biopsy revealed chronic granulomatous inflammation with no evidence of malignancy at that time. Tuberculosis was looked for, but the routine investigations were all negative; also, tissue culture for TB came negative after 4 weeks of incubation, because of the uncommon nature of the lesion; a mucosal biopsy was taken and led to chronic granulomatous inflammation and excluded malignancy and fungal infections. The diagnosis of leishmaniasis was confirmed by the demonstration of leishmania amastigotes in the mucosal lesions; he was successfully treated with 4 weeks of intravenous sodium stibogluconate. One month after treatment, another biopsy from the lesion was taken before surgical reconstruction that revealed evidence of cytotoxic T-cell lymphoma.

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Case presentation

Thirty-four-year-old male patient from Yemen presented to Embaba Fever Hospital (Giza, Egypt) with deformed nasal swelling (Fig. 1) and prolonged fever. The patient was born and lived in Yemen and had never traveled out of his country; he is working in a juice shop and has no special habits of medical importance; he is living in a mountainous area in a village related to the Ibb Governorate in North Yemen; his history dated back to 6 months before admission when he started to suffer from nasal obstruction especially at night with gradual onset and slowly progressive course, the otolaryngologist diagnosed the case as enlarged adenoid, and it was removed surgically, after which the obstruction was relieved.

One month later, he suffered nasal and eyelid swellings, as well as pain and mouth bleeding during swallowing; there were obvious weight loss, anorexia, and persistent fever; he had no known medical history, and the family history was not contributory. He received several antibiotics (clindamycin and ceftriaxone) as well as analgesics and antihistamines with no satisfactory improvement; he presented to our hospital after progressive deterioration to bloody rhinorrhea, discharge of blood clots, nasal obstruction, and deformity as well as prolonged unexplained fever.

During hospital admission, the nasal lesions evolved into a perforation and necrosis of the nose cartilage with the total destruction of the nasal architecture (Figs. 2 and 3).

On examination

The patient was febrile: temperature, 38 °C; pulse, 88/m; BP, 110/70 mmHg; respiratory rate, 20/m; to be oxygen saturation: 96% on room air; there was a massive hyperkeratotic and crusting lesion exuding pus over the ala of the nose extending to the nasal mucosa and upper lip; the patient was slightly pale with no jaundice, lymphadenopathy, or lower limb edema, and visible edema was noticed over both eyelids.

Systemic examination: chest, heart, abdomen, and neurological examination were all normal.

Investigation

Incisional biopsy from the nasal lesion shows chronic granulomatous inflammation, no evidence of caseation necrosis, no evidence of fungal infection, and no evidence of malignancy in the examined biopsy, but fungal culture shows few *Candida* species (*Candida krusei*). Complete blood count, biochemical metabolic and serological investigation are shown in Tables 1 and 2.

Table 1 Complete blood count

Test	Result	Unit	Reference range
Complete blood count			
WBC	4.4×10^3	U/L	4–11
Hemoglobin	8.8	g/dL	11–16
Hematocrit	31.2	%	33–44
Red cell count	3.260.000	UL	$3.8–5.4 \times 10^6$
MCV	78	FL	78–96
MCH	27	Pg	26–32
MCHC	33.7	g/dL	31–36
RDW	13.4	%	11.5–14.5
Platelets	291×10^3	µ/L	$150–450 \times 10^3$
Differential count			
Basophils	1	%	0–1
Eosinophils	0	%	0–3
Stab	0	%	0–7
Segmented	66	%	40–75
Lymphocytes	29	%	20–40
Monocytes	4	%	1–10

Table 2 Biochemical, metabolic and serological investigation

C-reactive protein	13.5 mg/L	No. 0–5
ESR	1st hour 60 mm/h. 2nd hour 80 mm/h	No. 0–20
ALT	38 µ/L	No. 24–63
AST	36 µ/L	No. 15–37
ALP	244 IU/L	No. 44–147
Coagulation profile		
Prothrombin time	12 s	No. 11–13.5 s
Control time	12 s.	
Concentration	100%	
INR	1	No. 1–1.3
APTT	26 s.	No. 20–40
BUN	7 mg/dL	No. 6–24
Creatinine	0.69 mg/dL	No. 0.7–1.3
HCV ab	Negative	Negative
HBSAg	Negative	Negative
Total bilirubin	0.571 mg/dL	No. 0.2–1
Serum amylase	223, 175 µ/L	No. up to 88
Serum lipase	304, 230 µ/L	No. 10–60

Tissue culture for bacteria grows *Klebsiella pneumonia* carbapenem-resistant Enterobacteriaceae and *Escherichia coli*.

Gene X-Pert test for TB from the nasal discharge is negative.

TB culture (tissue culture) shows no growth after 6 weeks of incubation.

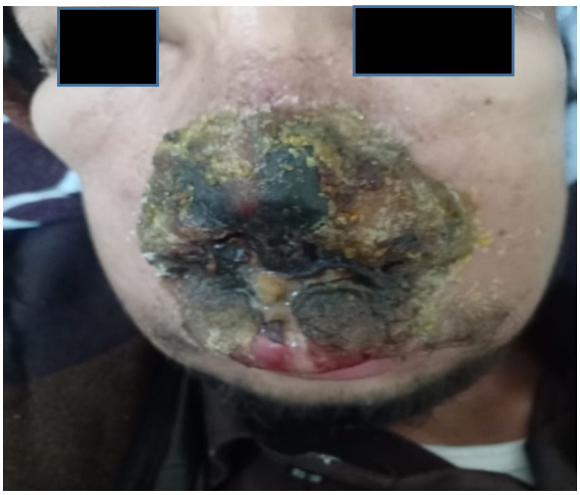

Fig. 1 Massive hyperkeratotic and crusting lesion exuding pus over the ala of the nose extending to the nasal mucosa and upper lip

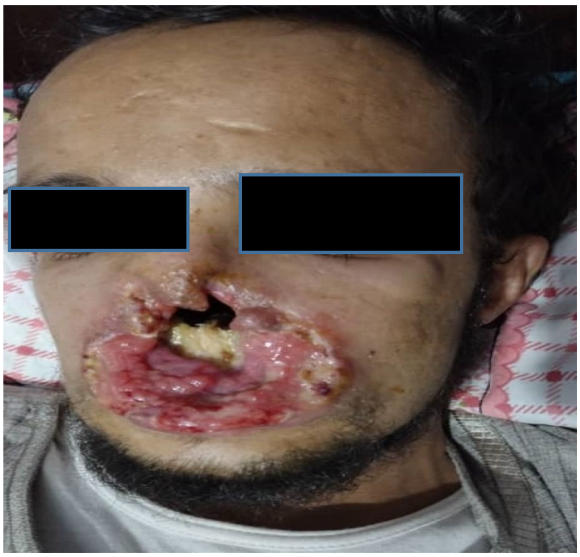

Fig. 2 Necrosis of the nose cartilage with the total destruction of the nasal architecture

Multi-slice CT scan of the paranasal sinuses shows evidence of bilateral nasal turbinectimies, non-visualized bony and cartilaginous nasal septum with large hard palate bony defect and bone rarefaction and erosions of the left medial maxillary wall as well as the anterior maxillary alveolar process opposite the central incisors and canine roots, deficient skin, and subcutaneous nasolabial region with a deficient nasal pyramid, obliterated left nasolacrimal duct, near total opacification of the left maxillary sinus, and mild mucosal thickening of the right sphenoid sinus with frothy secretion within, denoting acute infection, mild mucosal thickening of the right maxillary, and left frontal sinuses as well as right ethmoidal air cells, mild mucosal thickening of lateral walls and floor of the nasal cavity with frothy secretions, bilateral anterior maxillary region subcutaneous soft tissue thickening, and no sizable nasopharyngeal masses (Figs. 4 and 5).

Leishmania amastigotes were detected on tissue smear for microscopic examination (Figs. 6 and 7).

The patient received sodium stibogluconate IV injections in a dose of 20 mg/kg/day for 28 days with excellent response and clearance of amastigotes from the lesion; ceftazedime 1 g/8 h, intravenous (iv) fluids infusion, Diflucan 200 mg/day IV, amino acids IV infusions, and repeated tissue smear for microscopic examination of leishmania after treatment were negative for amastigotes; the fever subsided and his general condition somewhat improved, and he was discharged for plastic reconstructive surgery.

After 4 weeks of treatment with sodium stibogluconate, examination of leishmania amastigotes in blood and tissue smear was negative (Fig. 8).

Before preparing for the reconstructive surgery, a histopathological examination of a punch skin biopsy was requested, it revealed orthokeratosis with focal parakeratosis, hyperplastic epidermis with spongiosis, exocytosis, foci of interface dermatitis, and scattered necrotic keratinocytes.

Dense superficial and deep perivascular and periadnexal infiltrate composed predominantly of large atypical lymphoid cells with pleomorphic vesicular nuclei and prominent nucleoli and ample cytoplasm; some cells have hyperchromatic nuclei, and focal epidermotropism is seen. The atypical cells infiltrate the follicular structures and show angiocentrecity with infiltration of the vessel walls by atypical cells and focal vessel wall destruction. Many atypical mitoses are seen. Extravasated erythrocytes are seen, and the infiltrate extends into the subcutaneous tissue. Immunohistochemistry

Fig. 3 The fallen necrotic tip of the nose

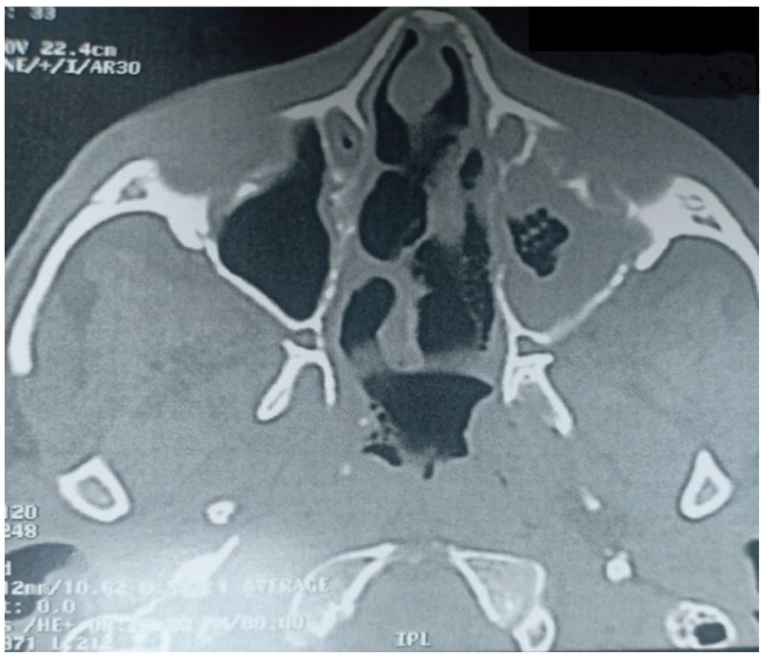

Fig. 4 Erosions of the left medial maxillary wall, near total opacification of the left maxillary sinus

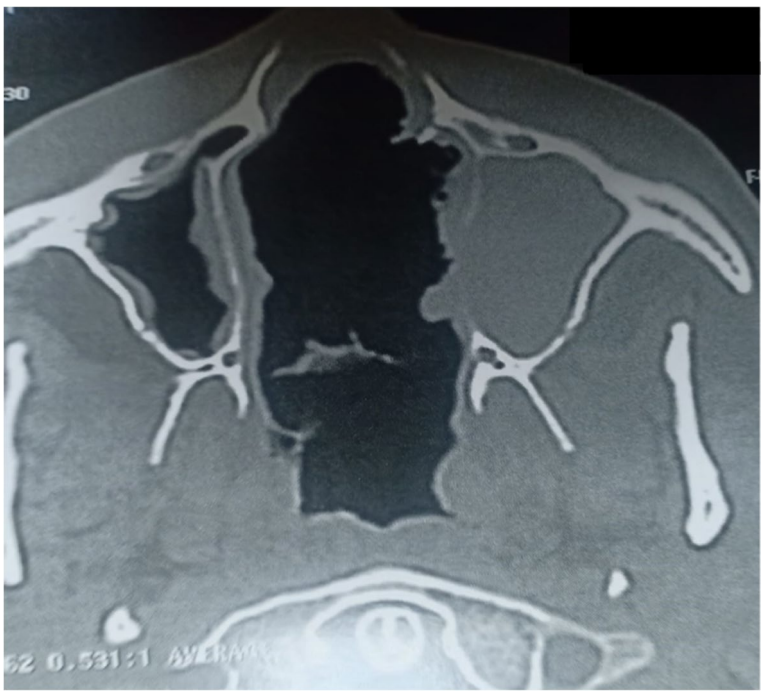

Fig. 5 Mild mucosal thickening of the right maxillary and left frontal sinuses as well as the right ethmoidal air cell

(IHC) revealed that the atypical cells are CD3-positive T-cells, CD20 stained very sparse reactive cells, CD30 shows weak focal positivity, and CD56 only stained sparse cells; the constellation of clinical, histopathological, and immunohistochemical features is consistent with cytotoxic T-cell lymphoma.

PET-CT scan revealed pathologically proven T-cell lymphoma at initial staging showing metabolically

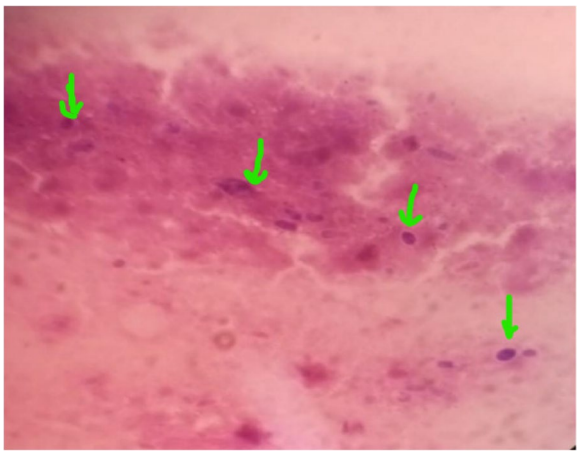

Fig. 6 Leishmania bodies. Amastigotes in the skin and subcutaneous tissues smear (Giemsa's stain, oil immersion). Many of the amastigotes (often referred to as Leishmania bodies) in this infected macrophage clearly show the spherical nucleus and bar-shaped kinetoplast. These amastigote features distinguish these organisms from other protozoan or fungal parasites

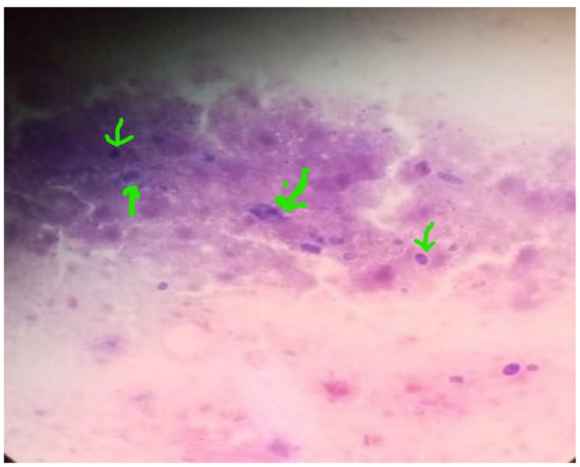

Fig. 7 Leishmania bodies. Amastigotes in the skin and subcutaneous tissues smear (Giemsa's stain, oil immersion). Many of the amastigotes (often referred to as Leishmania bodies) in this infected macrophage clearly show the spherical nucleus and bar-shaped kinetoplast. These amastigote features distinguish these organisms from other protozoan or fungal parasites

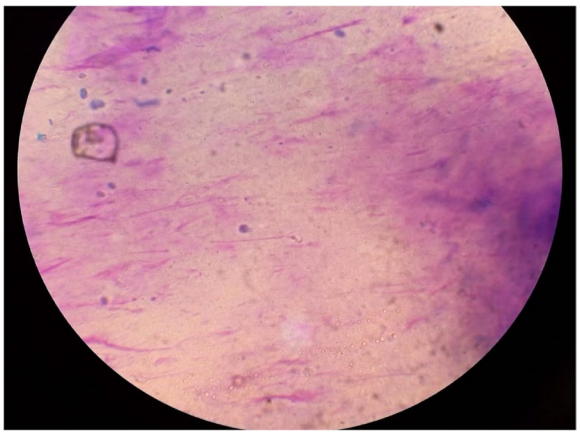

Fig. 8 Clear film after treatment with sodium stibogluconate, no leishmania bodies in the skin, and subcutaneous tissue smears

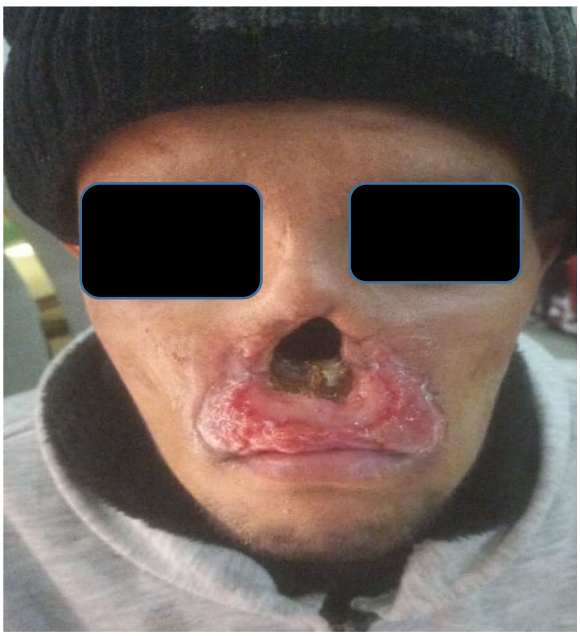

Fig. 9 The patient after treatment with chemotherapy and surgical cleaning of the wound

active (FDG avid) ill-defined cutaneous and subcutaneous soft tissue sheets at the tip of the nose, nasolabial fold, and the upper lip; no other metabolically active (FDG avid) lymphomatous nodal infiltration all over the whole body; and mild hepatosplenomegaly with no metabolically active focal lesions.

After 5 sessions of chemotherapy, together with meticulous care of the wound, he was marvelously improved and became readily prepared for reconstructive surgery.

Repeated nasal skin punch biopsy for immune-histopathology after chemotherapy shows a few cells positive for CD4 and some cells positive for CD8.

The last PET/CT conclusion revealed a significant regressive course since the last study; the rest of the surveyed body is free from any other FDG hyper-metabolic neoplastic lesions.

There were no newly developed active neoplastic lesions (Fig. 9).

Discussion

Mucosal leishmaniasis is a worldwide disease, and the majority of cases occur in Latin America [1]; mucocutaneous leishmaniasis is the result of parasite dissemination from the skin to the naso-oropharyngeal mucosa of certain species of leishmania subgenus [3]; this dessimination occurs through the blood or lymphatic vessels from CL papule to the nasal mucosa [4].

There are no solid data on the incidence of leishmania infections in Yemen, but the disease is certainly underreported [5].

Reports from Yemen have described the occurrence of CL in Hajjah, Amran, Sadah, Sanaa, Al-Hudeidah, and Taiz. Ibb, Mahweer, Raimah, and Al-jouf governorates in northern, western, and southern Yemen of both zoonotic and anthroponotic types and caused mainly by leishmania tropica and leishmania major [5-9].

The lesions start in the nasal mucosa and spread to the oral and pharynx mucosa, the larynx, and the skin of the nose and lips [10] which are associated with difficulties in respiration and eating with considerable risks of mortalities [1].

Severe cases can involve mid-facial ulcerative destructive lesions on the nose, upper lip, and palatal midline with the total destruction of the nasal architecture with distinctive esthetic deformities [1].

The preferential site of this disease is the cartilaginous nasal septum, but the lesions can also involve the upper airway and digestive tract; nasal septal lesions may evolve into a perforation and necrosis of the nose cartilage.

Mucosal leishmaniasis never heals spontaneously, and the lesions are prone to secondary bacterial infections [1].

The diagnosis of ML is based on the demonstration of leishmania amastigotes in the mucosal lesion samples stained with hematoxylin-eosin [11]; the protozoan is found in the scraping of cutaneous or mucosal ulcerations (especially scraping the borders). A biopsy is another diagnostic tool; it should be obtained from the active border of the lesion. A smear may reveal the parasites in free form or inside macrophages or less frequently in polymorphonuclear leukocytes ranging in number from 2 to 20 in a single cell [3]. The main factors responsible for difficulties or delay in diagnosis from various studies were usually as a result of the presentations mimicking other diseases known for such presentations and also the fact that the amastigotes were difficult to detect in several cases on microscopy [12].

Many drugs are used in the treatment, but the only effective treatment is achieved with current pentavalent antimonials [1].

Infectious agents are thought to cause pathological alterations including DNA mutations, cell cycle modulation, dysregulation of DNA repair mechanisms, chronic inflammation, and immune system impairment, favoring tumorigenesis [13].

Leishmaniasis affects the activation and function of macrophages and dendritic cells and is responsible for chronic inflammation. Chronic inflammation promotes cancer through multiple mechanisms like genomic instability and DNA damage which may cause genetic and epigenetic mutations initiating cancer [10].

Leishmania species infection can play a significant, direct, or indirect role in the pathogenesis and prognosis of some malignant disorders [1]: 65 skin biopsies from parasitologically evident cutaneous leishmaniasis from Egypt, Libya, Saudi Arabia, and Jordan; the results showed that cutaneous leishmaniasis, especially in hot areas, pave the way to the mutation and development of skin cancer.

Mangoud et al. reported that dysplasia was detected surrounding the leishmanial ulcer in 5–35 CL cases [14]. Environment generated following leishmania infection can promote cancer progression and vice versa [15].

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 [16].

Conclusion

Mucocutaneous leishmaniasis should be included in the differential diagnosis of nasal granulomas specifically in patients living in or who have traveled to endemic areas for leishmaniasis as early diagnosis, and treatment can prevent serious sequela and complications; in such patients, ML should be first investigated before empiric immunosuppressive therapy is begun.

In patients presenting with pyrexia of unknown origin where amastigotes prove difficult to detect with all available laboratory facilities, a therapeutic trial should be considered a treatment option, and physicians should always be aware of this fact [17].

Further studies are necessary to precise the impact of leishmania infection on cancer development in leishmaniasis-endemic areas based on repeatedly clinical observation; this evidence could inform and guide early diagnosis or prevention of skin cancer in survivors of cutaneous leishmaniasis or where cutaneous leishmaniasis is still highly prevalent.

The repeated clinical observation that cutaneous leishmaniasis may be a risk factor for skin cancer necessitates further research studies; this evidence guides the prevention or early diagnosis of skin cancer in survivors of cutaneous leishmaniasis.

Leishmania infection should be considered in the differential diagnosis of lymphoma progression in patients living in or migrating from endemic countries, presenting with fever of unknown origin, and a blood leishmania PCR systemically performed in suspicious cases [17].

Abbreviations

CL	Cutaneous leishmaniasis
MCL	Mucocutaneous leishmaniasis
VL	Visceral leishmaniasis

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Authors' contributions
As collected the patient data and wrote the manuscript. H. Ibrahim was the major contributor in writing the manuscript. All authors took part in the realization and implantation of this work. The authors read and approved the final manuscript.

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