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CUTANEOUS LEISHMANIASIS PREDISPOSING TO HUMAN SKIN CANCER: FORTY YEARS LOCAL AND REGIONAL STUDIES

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Abstract

Different types of association between leishmaniasis and cancer were established: leishmaniasis mimicking a malignant disorder, such as lymphoma; leishmaniasis arising as a difficult to diagnose and treat infection among patients receiving chemotherapy for various malignant disorders; simultaneous diagnosis of leishmaniasis and a neoplastic disorder in the same tissue samples of immunocompromised patients; and direct involvement of *Leishmania* spp. in pathogenesis/occurrence of malignant lesions, especially of the skin and mucous membranes.

Cutaneous leishmaniasis (CL) is a protozoan skin disease occurring in all the Middle East countries. Only the cutaneous form is a self-curing, which may develop a certain degree of immunity against the parasite, resulting in healing of the lesion(s). However, the parasites probably never disappear completely, since in situations where immune system is compromised, as in AIDS, or suppressed by cancer chemotherapy or in organ transplantation, *Leishmania* spp. may suddenly reappear. The cell-mediated immunity is responsible for skin lesion healing but humeral response plays a protective role against the disease.

Skin biopsies from 65 parasitological proven cutaneous leishmaniasis patients from Egypt, Saudi Arabia, Jordan and Libya were histopathologically studied. The results showed that cutaneous leishmaniasis especially in hot areas pave the way to the mutation and development of skin cancer.

Key words: Leishmaniasis, Skin biopsies, Mutation, Skin cancer.

Introduction

Leishmaniasis is a disease caused by the protozoa, *Leishmania* species, which is transmitted by the bite of a female sand-fly. Leishmaniasis can be classified clinically, as cutaneous, mucocutaneous, and visceral leishmaniasis. Cutaneous leishmaniasis causes skin lesions and easily felt with. In case of mucocutaneous leishmaniasis, mucosal ulcerations usually develop by the metastasis from the disseminated *Leishmania* species rather than by local spread. Secondary infection plays a prominent role in the size and persistence of ulcers. Ulcer progression is slow and steady. Visceral leishmaniasis incubates from weeks to months before being clinically apparent, as subacute, acute, or chronic, and easily manifests in immunocompromised patients. Although the *Leishmania* species differ

clinically and biologically, their characteristics overlap and each clinical syndrome can be produced by multiple species of *Leishmania*.

The typical lesions of the cutaneous leishmaniasis were described as early as 900 BC and have been referred to as "Balkan sore" in the Balkans, "Delhi boil" in India, "Baghdad boil" in Iraq, "Saldana" in Afghanistan, "Alokhet" in Saudi Arabia, "Elnafra" in Yemen, "Hehiya sore" in Egypt, "Om-dobabah" in Sudan and "HabetHalab" in Syria (Morsy, 1983). Visceral leishmaniasis (VL), also known as kala-azar, black fever, and Dumdum fever, is the most severe form of leishmaniasis (Chappuis *et al,* 2007). One of the major threats to control visceral leishmaniasis (VL) is its interaction with HIV infection, as an important opportunistic infection associated with HIV (Alvar *et al*, 2008).

In Egypt, El Khawsky *et al*. (2004) reported that in Alexandria, among 136 incident histologically confirmed (99 basal-cell and 37 squamous-cell) cases of the non-melanomatous skin cancer (NMSC) and 145 controls in hospital for a broad spectrum of the acute non-sun-related dermatological conditions, about 60% of the non-melanomatous skin cancer could be attributed to sun exposure and approximately 40% to skin color. Hussein (2005) stated that the clinicopathologic features of Egyptian skin cancer are still unknown.

The prevalence of cancer on one hand and cutaneous (Kargi *et al*, 2001; Yavuzer *et al*, 2001; Karabekmez *et al*, 2008) or visceral leishmaniasis (Dom-I ngues *et al*, 2005; Daneshbod *et al*, 2010) on the other hand, the co-existence of both may be merely coincidental (Akcali *et al*, 2008). However, a number of epidemiological, experimental (Catone *et al*, 2003; Gurel*et al*, 2005) and laboratory studies proved an association between these two entities in man and reservoir host animals (Quintella *et al*, 2011; Vase *et al*, 2012), particularly in pediatric cancer patients (Bialek, 2005) and in immunodeficiency patients (Biekory *et al*, 2011). Neghina and Neghina (2010) stated that leishmaniasis infection is listed by the WHO among the 6 most important tropical diseases, is endemic in approximately 88 countries worldwide, with a global estimate of 350 million individuals at risk. They added that exported cases are carried by refugees and immigrants from endemic developing countries and that extended military operations are a further source of imported cases. In the new millennium, the import and export of leishmaniasis continue to be of major concern for public health services worldwide as a result of increased mobility.

Perhaps the first case of cutaneous leishmaniasis and skin cancer was reported by Morsy and Sief-El Nasr (1983) in an Egyptian woman returning back from Saudi Arabia. But, the endemic foci of zoonotic cutaneous leishmaniasis (ZCL) (Morsy, 1988a; 1996) and visceral leishmaniasis (VL) (Morsy, 1997) were reported in Egypt, and nowadays anthroponotic cutaneous leishmaniasis (ACL) (Hanafi *et al*, 2013).

In Saudi Arabia numerous authors reported ZCL (Morsy, 1975; 1988b; Morsy and Shoura, 1976), anthroponotic

cutaneous leishmaniasis (ACL) (Morsy *et al*, 2002; El-Beshbishy *et al*, 2012; 2013), IVL (Al-Jurayyan *et al*, 1992; Morsy, 1989), VL (Ibrahim *et al*, 1995), and *Leishmania aethiopica* from rock hyrax, *Procavia capensis* in Najran (Morsy *et al*, 1997).

The study aimed to evaluate the correlation between leishmaniasis mainly cutaneous and cancer and to summarize the occurrence of leishmaniasis as an opportunistic infection associated with malignant disorders and to present the available literature potentially incriminating leishmaniasis with the cancerous lesions development.

Subjects, Materials and Methods

A skin biopsy was taken from each patient with proven ACL or ZCL (Morsy *et al*, 1986) by 5mm punch from the ulcer margin after the consent of the patients. Sometimes light anesthesia injection was given intradermal. The biopsies were fixed in 10% neutral buffered formalin, sections were cut (5μ) and four slides were made from each biopsy (Clyden, 1971) stained with Hematoxylin & Eosin (Kiernan, 2008) for histologic diagnosis and histopathological classification. The interested cases were selected and included.

Results

Only one patient was clinically diagnosed as CL; other diagnoses included: malignant epithelial neoplasms (5), follicular cyst (2), atypical mycobacteriosis (1), sarcoidosis (2) and lymphoma (1). Lesions were single (15) or few (4) nodules predominantly situated on the extremities or face (16). Histopathological findings were diagnosed as CL in only 10 cases. In nine cases *Leishmania* parasite was not identified microscopically; histopathological diagnoses were: granulomatous dermatitis (6), lupoid rosacea (1), and foreign body granuloma (1) and granuloma annulare (1), unaltered epidermis (9), nodular infiltrates (5), numerous multinucleated histiocytes (3), palisaded granulomas with fibroid centers (2), sarcoidal granulomas (4) and elastophagocytosis (1) missed by histopathologic examination. The interesting and specific data are given in figures.

Discussion

In Egypt, the endemic foci of cutaneous leishmaniasis were reported by many authors (Morsy, 1983; Faris *et al*, 1986, 1988; Morsy, 2012; Morsy *et al*, 1987a, b; Morsy *et al*, 1995; Hamadto *et al*, 2007). Regarding sand fly vectors, so many authors dealt with sand-fly, perhaps the first Egyptian was Zein-el-Dine (1972) who gave a preliminary survey on sandflies. El Sawaf *et al*. (1984) proved the vectorial capacity of *P. langeroni* in transmission of IVL. El Sawaf *et al.* (1987) gave a brief report on sandflies in southern Sinai. Morsy *et al*. (1990) gave illustrative diagnostic features of the male and female sand-flies in the Nile Delta. Wahba *et al*. (1990) characterized *L. major* from *P. papatasi* (Scopoli) caught in northern Sinai as the main ZCL vector. Hanafi *et al*. (2001) identified *P. sergenti*, as a new record of the vector of *L. tropica*, in southern Nile valley. El Bahnasawy *et al.* (2013) reported *P. langeroni* in the Egyptian Northern Coastal Zone, but not in Alexandria.

The occurrence of malignant neoplasms in sites of CL lesions is an infrequent but well-known phenomenon. Although the coexistence of cutaneous leishmaniasis and basal cell carcinoma (BCC) may have been coincidental, many authors suggested that an association between these two entities does exist (Morsy*et al*, 1992a, b; Kopterides *et al*, 2007). Leishmaniasis can directly or indirectly alter the diagnosis and course of different malignancies. There are reports of BCC in chronic leg ulcers (Granel *et al*, 2001). Cases of BCC developing in a *Leishmania* scar has also been documented (Aziz Jalali *et al*, 2006). Also, solid organ transplantation and long term immune-suppressive therapy should be considered as risk factors for malignancy, particularly the skin cancers including squamous cell carcinoma, basal BCC and malignant melanoma (Lumbang and Stasko, 2011).

Why malignancies should be considered in differential diagnosis of leishmaniasis lesions difficult to treat? The possible role of cutaneous leishmaniasis, as a predisposing factor for skin cancer, should also be kept in mind. Plechitsova *et al.* (1989) reported a female patient, aged 72, a resident of the endemic area in Uzbekistan, with skin lesions on the face, resembling tuberculous involvement, two years later *Leishmania* was laboratory isolated. Morsy *et al*. (1991) reported two cases of ACL with extreme variation of cutaneous disease encountered in infection with *L. tropica* (Zymodeme LON 72, one isolate and 71 second isolate). Morsy *et al.* (1992b) reported a 13 year old Yemenian boy with cutaneous leishmaniasis. The histopathological picture of the CL lesions showed a marked dysplasia indicating premalignancy which gave a possibility that CL could be considered as one of the predisposing factors for skin malignancy. Morsy *et al.* (1992a) reported the coexistence of cutaneous leishmaniasis and basal cell carcinoma in one patient, in the same site and same lesion and raised the possibility that CL is a predisposing factor for BCC.

Morsy *et al*. (2002) presented a mother and her son with positive leishmaniasis *tropica*. The son had two large ulcerative ACL on his left hand. The mother had a large ulceration and progressive erosion of the soft tissue (the right cheek and right eye) and the cartilage of the nose disfiguring and debilitating her face. The histopathologically, biopsy material obtained from the mother but not the material from her son, showed typical pathological picture of the basal cell carcinoma with progressive changes in the pathogenesis of *L. tropica* to be one of the predisposing factors of the skin cell carcinoma.

Friedman *et al.* (2003) reported an Iranian female with a squamous cell carcinoma (SCC) arose when she was 3 years of age in a scar that was secondary to CL, and stated that SCC should be included as a rare but late sequela of cutaneous leishmaniasis. Mangoud *et al.* (2005) in 35 ZCL patients proven by parasitological, histopathological and immunohistochemical picture, the monoclonal antibodies for T & B lymphocytes, peroxidase anti-peroxidase

for P53 protein, and Feulgen staining for DNA imaging cytometry to DNA contents and S-phase (DNA synthesis of cycling cells were evaluated. They stated that P53 and S-phase fraction and DNA content must be in mind when dealing with a human cutaneous leishmaniasis Casolari *et al*. (2005) reported a case of autochthonous isolated laryngeal leishmaniasis due to *L. infantum* in an Italian immunocompetent host and highlighted the need to consider mucosal leishmaniasis in the differential diagnosis of laryngeal tumors. Böer *et al.* (2006) stated that CL may be misinterpreted as sarcoidosis, foreign body granuloma, lipoid rosacea and granuloma annular, especially when *Leishmania* is not seen microscopically. They suggested that in Northern Europe, PCR for *Leishmania*-specific DNA should be performed routinely in any granulomatous dermatitis presenting as a single or few nodules on the extremities or face, even when a diagnosis of CL was not considered by the referring clinician.

Kopterides *et al.* (2007) stated that leishmaniasis can directly or indirectly affect the presentation, diagnosis and course of various malignant disorders and it should be considered in the differential diagnosis of malignancies in geographic areas where it is endemic and/or in patients with travel history to these areas. Unlü *et al*. (2007) presented a case of basal cell carcinoma arising on a *Leishmania* scar on the nasal dorsum 30 years after the primary lesion.

Wysluch *et al.* (2007) stated that in northern Europe leishmaniosis must be considered as differential diagnosis of malignant tumors of mucous membrane and making a liver transplantation. In the latter aspect, leishmaniosis-infection in a liver transplantation is contraindicated.

Fakhar *et al.* (2008) in Iran reported a case of IVL associated with acute lymphoblastic leukemia (ALL), a 12-year-old girl having bone pain and prolonged fever. A biopsy revealed a hypocellular marrow with huge number of amastigotes. She was treated successfully with two courses of amphotericin B plus IFN-gamma.

Foglia *et al.* (2008) reported an 8-year-old intact male mongrel dog with alopecia and weight loss, pale mucous membranes, enlarged prescapular-lymph nodes, and splenomegaly. The dog showed anemia, thrombocytopenia, and hyper-globulinemia, bone marrow aspirate smears contained numerous *Leishmania* amastigotes and an IFAT was strongly positive for leishmaniasis. Two months after treatment there was leishmaniasis relapse and a firm subcutaneous mass on the medial right thigh. Based on cytologic examination of fine needle aspirates of the mass, a diagnosis of large-cell lymphoma was made. Flow cytometry of tumor cells revealed gammadelta-T-cell lymphoma with CD5+, CD3+, TCR-gammadelta+, CD4-, CD8-, CD 45RA + immunophenotype. They reported that gammadelta-T cells might be involved in host response to leishmaniasis, and prolonged antigenic stimulation and chronic immuno-suppression (typical of leishmaniasis) play a crucial role

in etiopathogenesis of T-cell lymphoma.

Sabri *et al.* (2009) presented a case of an auricular *Leishmania* lesion which was first suspected to be a carcinoma. Khorsandi-Ashtiani*et al*. (2009) presented a 42-year-old man with multiple lesions on his head, neck and hands as a painful, crusted, 8x8 cm plaque with indurated margins on the left parotid region and auricle; a red papule on the right temporal region; an ulcerative lesion on the skin overlying the proximal interphalangeal joint of the fifth finger of the right hand; and a bluish papule on the neck. Histopathological examination was misleading, biopsies showed amastigotes, and therapy resulted in complete recovery.

Llambrich *et al*. (2009) reported that dermoscopy has been proposed as a dia-gnostic tool in the case of skin infections and parasitosis but no specific dermo-scopic criteria have been described for CL. They concluded that characteristic dermoscopic structures were identified in CL, and that important vascular patterns seen in melanocytic and nonmelanocytic tumors are frequently observed in leishmaniasis.

Daneshbod *et al*. (2011) in 11 patients with mucosal leishmaniasis, of which 7 had oral lesions, one known patient with oral leishmaniasis with recurrence of oral lesions; 2 laryngeal lesions; and 3 nasal lesions. One case of laryngeal infection was a recurrence of prior oral lesions. Histologic biopsies for 7 patients showed 2 patients with nasal lesions, exfoliative cytology by washing the nasal cavity. They concluded that clinically or histologically, ML can be mistaken for benign and malignant lesions.

Casabianca *et al.* (2011) described a case of VL characterized by negative serologic testing, a relapsing course, and a fatal outcome 2 years after the patient had been successfully treated for non-Hodgkin's lymphoma with rituximab. They added that VL diagnosis may be delayed or even missed in patients treated with drugs that interfere with specific antibody production unless specific diagnostic methods, such as bone marrow examination and parasite DNA amplification/detection, are routinely employed.

Al-Qahtani *et al*. (2012) reported that leishmaniasis diagnosis may present a serious challenge. It may be difficult to differentiate it from granulomatous conditions like tuberculosis, sarcoidosis, leprosy, fungal infections, Wegener's granuloma, and neoplasms. Here, we present a case of PML in Saudi Arabia Ali *et al.* (2012) stated that differential diagnosis of cutaneous leishmaniasis includes arthropod bites, basal cell carcinoma (BCC) and other malignancies. BCC is the most common form of skin cancer. Martínez-Luis *et al*. (2012) reported the best anti-parasitic and anti-cancer activities as well as isolating the bioactive agents, they isolated pseurotin A (1), 14-norpseurotin A (2), FD-838 (3), and pseurotin D (4), and fumoquinone B (5), which showed good antileishmanial and moderate anticancer activities.

Mannaert *et al*. (2012) stated that Aneuploidy is usually associated with severe abnormalities and decrease of cell fitness, but some organisms appear

to rely on aneuploidy for rapid adaptation to changing environments. Genomes highlight the *Leishmania* importance as a new model for aneuploidy. They added that reports revealed extensive variation in chromosome copy number, proving that aneuploidy is a constitutive feature of *Leishmania* spp. Aneuploidy appears to be beneficial in organisms that are primarily asexual, unicellular, and that undergo sporadic epidemic expansions, including common pathogens as well as cancer.

Singh *et al*. (2012) reported that the leishmaniasis outcome basically relies on skewed balance between Th1/Th2 immune responses. The TLRs play the very important role during inflammatory process of various diseases as the cancer, bacterial and viral infections but TLR signaling is comparatively less explained in leishmanial infection. In the context to Th1/Th2 dichotomy, identification of leishmanial antigens that modulate toll-like receptor signaling would certainly help in the future vaccine development.

Other infectious diseases:

Armengot-Carbó *et al.* (2012) described the case of a 40-year-old man with HIV and severe immunodepression in whom *Leishmania* parasite was detected as an incidental finding on histological study of a perianal SCC. This finding led to the diagnosis and subsequent treatment of previously unsuspected visceral leishmaniasis.

Regarding treatment of both:

Marquis *et al.* (2003) *in-vitro* found that some anti-tumour agent; protoberberine compounds showed pronounced anti-leishmanial activity however, did not affect the macrophage viability and only slightly reduced macrophage nitric oxide generation in response to interferon-gamma significantly reduced parasite loads.

Zubairi *et al*. (2004) found that a chimeric fusion protein (OX40L-Fc) that stimulates T cells through OX40 and a monoclonal antibody that blocks CTLA-4, an inhibitory receptor on T cells, both enhanced granuloma maturation rate, CD4(+) T cell proliferation, and *Leishmania* killing. Costimulation-based therapy induced no adverse fibrotic or necrotic reactions, and had no significant effect on the levels of endogenous anti-inflamma-tory cytokines (IL-10 and TGF-beta). The OX40L-Fc and anti-CTLA4 could be co-administered with conventional anti-leishmanial drugs.

Miguel *et al*. (2007) investigated the activity of tamoxifen, an antioestrogen widely used in treatment of breast cancer, against *Leishmania*, found tamoxifen effectively killed several *Leishmania* species and its activity against the parasite increased by a modulation of the host cell intravacuolar pH induced by the drug.

Tavares *et al.* (2007) tested the widely used drug in cancer chemotherapy; cis-DDP derivatives or cisplatin as anti-*Leishmania* activity; the cytotoxic properties were measured only on promastigotes. The IC50, determined by flow cytometry, after 72 h of drug incubation was four times higher, 7.73+/-1.03 microM in promastigotes compared to axenic amastigotes, 1.88+/-0.10 microM. The cis-DDP response invol-

ved an apoptosis-like death of both the promastigotes and amastigotes. However, DNA fragmentation was only detected in promastigote forms. In contrast mitochondrial transmembrane potential loss was observed for both stages of the parasite. Upon incubation of parasites with the drug an increase on GSH and GSSG levels and reactive oxygen species could be detected in the case of promastigote. A slight increase of GSH level was detected on the amastigote form. They concluded that amastigotes were more sensitive to cis-DDP when compared to promastigotes.

Oliveira *et al*. (2007) studied Bisnaphthalimidopropyl derivatives synthesized in yields ranging from 50% to 70% against colon cancer cells (Caco-2) and *L. infantum*. Cytotoxicity within Caco-2 cells was manifested with IC (50) values between 0.3 and 22 microM. Compounds with the central longer alkyl chains exhibited the highest cytotoxicity. Against *L. infantum*, IC (50) values were encompassed within a narrower concentration range of 0.47-1.54 microM. In the parasites, the presence of nitrogen in the central chain and the length of the central alkyl chains did not especially enhance cytotoxicity. This may be due to the way these compounds are transported in the cells.

Zimmermann *et al*. (2007) reported that prophylactic administration of dendritic cells loaded with a MHC class II-restricted peptide derived from a model tumor Ag [*Leishmania* receptor for the activated C kinase (LACK)] confers protection against LACK-expressing TS/A tumors, whereas therapeutic vaccination fails to cure tumor-bearing mice. Although CD4+T cell-directed dendritic cell vaccination primed effector-like only IL-2(+) in tumor-free mice and not the case in tumor-bearing animals in which both priming and persistence of CD4+T cell memory were suppressed. Suppression was specific for tumor-associated Ag LACK, and not depending on CD25+T cells. They speculated that ability of tumors to limit the vaccine-induced CD4+T cell memory could provide a partial explanation for limited efficacy.

Moein *et al.* (2008) found *Zhumeria majdae* ethanol extract showed potent antileishmanial and antiplasmodial activity in vitro. Bioactivity guided fractionation of the extract led to the isolation of 12,16-dideoxy aegyptinone B. This compound exhibited potent in vitro antileishmanial activity with an IC_{50} of 0.75 microg/ml, and a strong antiplasmodial activity with IC_{50} values of 1.3 and 1.4 microg/ml against chloroquine sensitive and resistant strains, respectively. Also, it showed mild cytotoxicity towards cancer cell lines.

Jiménez-Alonso *et al*. (2008) synthesized a set of bis-pyranobenzoquinones through a direct and highly efficient approach based on a double intramolecular domino Knoevenagel hetero Diels-Alder reaction with similarities to those of some anticancerous and leishmanicidal drugs. Considering that these drugs are substrates for some members of the ATP-binding cassette (ABC) family of proteins that confers a multidrug resistance (MDR) phenotype, they tested some of these compounds as potential MDR modulators

in a *L. tropica* line overexpressing a P-glycoprotein-like transporter. Compounds 9 and 10 are, in that work, the most promising reversal agents of MDR in human cancer cell lines, while compounds 4 and 20 showed potent reversal activity of MDR phenotype in the *Leishmania*.

Cruz *et al.* (2009) assayed leishmanicidal activity drugs formerly developed for other applications, as amphotericin B (antifungal) or miltefosine (antitumor), among others. Kahalalide F, a tumoricidal cyclic depsipeptide currently under phase II clinical trials for several types of cancer and psoriasis proved to have leishmanicidal activity and its synthetic analogues at a micromolar range of concentrations. Its lethality is strongly linked to the alteration of the plasma membrane (PM) of the parasite based on (i) a rapid depolarization of the PM and uptake of the vital dye SYTOX Green upon its addition; (ii) evidence of severe morphological damage to parasite membrane, and (iii) a rapid drop in the intracellular ATP levels, which correlates significantly with leishmanicidal activity for active analogues, some of them with significant improvement of their therapeutic index with respect to the parental molecule. They concluded that this class of lethal mechanism is considerably less prone to the induction of resistance than classical drugs.

Aponte *et al.* (2010) evaluated in vitro the synthesis of 2-(5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidin-4-yl) hydrazone-derivatives (BTPs) against *T. cruzi* trypomastigotes, *Mycobacterium tuberculosis, L. amazonensis* axenic amastigotes, and six human cancer cell lines. BTPs constitute a new family of drug leads with the potential activity against the infectious diseases.

Wanderley and Barcinski (2010) mentioned that different death-styles were described in unicellular organisms, which evolved with phenotypic features similar to apoptotic death of the animal cells, as phosphatidyl serine (PS) exposure, oligonucleosomal DNA fragmentation, and loss of mitochondrial transmembrane potential, hinting that similar mechanisms operate in both situations. They found that entirely different mechanisms of PS exposure co-exist during the life-cycle of *L. amazonensis*: in the case of promastigotes, a sub-population dies by apoptosis; in the case of amastigotes, the entire population exposes PS, not necessarily followed by the apoptotic death.

Buarque *et al*. (2011) found that Pterocarpanquinones (1a-e) and azapterocarpanquinone (2) synthesized through palladium catalyzed oxyarylation and the azaarylation of conjugate olefins showed anti-neoplasic effect on leukemic cell lines (K562 and HL-60) as well as colon cancer (HCT-8), gliobastoma (SF-295) and melanoma (MDA-MB435) cell lines. Also, the pterocarpanquinones 1a and 1c-e, as well as 8 were the most active on amastigotes of *L. amazonensis* in culture.

Abdel-Hady *et al*. (2011) evaluated total phenolic, flavonoids, phenylethanoid glycoside and iridoid content of twenty-three selected Egyptian plants for their anticancer, antioxidant and

antileishmanial effects. These results proved that the most suitable medicinal plant used as anticancer and antioxidant is *Petreavolubilis,* which contain adequate mixture of total phenolic compounds 88.7 mg% and flavonoids 50.80 mg% and that flavonoid compounds are the category of phenolic compounds possess significant antioxidant and anticancer effects while the antileishmnia screening revealed that *Thymus decussatus* extract exhibited the highest effect due to flavonoids and iridoids in adequate combination where iridoid compounds 201 mg% and flavonoid content was 128 mg%.

Salehi *et al*. (2012) developed a novel live vaccine using recombinant *L. tarentolae* expressing E7-green fluorescent protein (GFP) fusion protein for the protection of mice against HPV-associated tumors. The anti-tumor protective effect of *L. tarentolae*-E7-GFP was compared to other vaccination strategies, namely pcDNA-E7 as the DNA vaccine and pcDNA-E7/L. tarentolae-E7-GFP as the prime-boost regimen. They concluded that E7-GFP expressing recombinant *L. tarentolae* induces significant levels of IgG2a and IFN-γ, while there is no significant IL-5 production compared with that of other strategies and control groups before and after challenge with TC-1 tumor cells. They concluded that the E7-GFP recombinant *L. tarentolae* could be a potential live vaccine for induction of immune responses in vivo.

Armengot-Carbó *et al.* (2012) in a 52-year-old woman with a single lesion on her nose, which started as a papule, referred to Sedighe Tahereh Clinic, Isfahan, Iran. The lesion had existed for 14 months and was slowly increased in size, enlarging to a plaque. Diagnosis of leishmaniasis was confirmed with a positive smear about one year before. All five members of her family had a history of proven leishmaniasis. A 3×3 cm indurated ulcer with elevated borders was present on the tip of her nose. Therapeutic plan was glucantime intralesional injection (about 1 ml of 1.5 g vial per week, intralesional injection). After completing a therapeutic course of 20 sessions receiving glucantime intralesionalinjections, she was considered as glucantime therapy resistant. Surgical excision was advised and performed under local anesthesia. The histopathology was that of a BCC, superimposed on a leishmaniasis lesion.

Marhadour *et al.* (2012) found that four derivatives exhibited good activity against promastigote and amastigote of *L. major*, coupled with a low cytotoxicity against the HELA human cell line. The impact of compound lipophilicity on antiparasitic activities was investigated by Log D comparison. Although LmCK1 could be the parasitic target for three compounds (13, 18, 21), the inhibition of another one has the antileishmanial effect of the most promising compounds. Bolhassani and Zahedifard (2012) mentioned that an efficient antigen delivery system is the key issue of developing an effective cancer vaccine. On the other hand, the use of viruses as vaccine vectors such as Vaccinia, Adenovirus, Herpes simplex virus, Paramyxovirus and Retroviruses utilizes mechanisms that evolved in

these microbes for entering cells and capturing the cellular machinery to express viral proteins. Viral/bacterial-vectored vaccines induce systemic T-cell responses including polyfunctional cytokine-secreting CD4+ and CD8+ T-cells. Non-pathogenic parasites as *L. tarentolae*, *T. gondii* and *T. cruzi* have emerged to be a novel candidate for gene delivery and heterologous genes expression.

Leite *et al*. (2012) evaluated a series of novel benzo[4,5]canthin-6-ones, bearing the N'-(substituted benzylidene)-carbohydrazide (11a-e) and N-alkylcarboxamide (13a-g) moieties at position-2 for in vitro antitumor activity, against seven human cancer cell lines, and against *Trypanosoma cruzi* and *L. amazonensis*. The N-methylpiperazyl-6-oxobenzo [4, 5] canthine-2-carboxamide (13f) displayed potent anti-tumor activity with IC (50) values in the range of 1.15-8.46 μM for all cell lines tested. Compounds 13f & 13g bearing an N-methylpiperazyl-carboxamide and N-morpholylcarboxamide at C-2, respectively, showed the potent activities towards both parasites, with IC_{50} in the range of 0.4 to 16.70 μM.

In animals:

Morsy *et al.* (1980) in Jordan identified cats as reservoir host for leishmaniasis. In Egypt, Michael *et al.* (1982) reported anti-leishmanial anti-bodies in stray cats, and Morsy and Abouel-Seoud (1994) reported pet cats as zoonotic reservoir of ZCL. Morsy *et al*. (1999) reported natural *Leishmania* in sand cats captured in Riyadh, Saudi Arabia.

Abanesel *et al.* (2002) on the clinical signs and histopathological features of a primary extra-genital canine transmissible venereal tumour (TVT) three subcutaneous round alopecic nodules were located on the anterior and caudal dorsal region and in the ventral-area of the neck. Diagnosis of TVT was confirmed by histological and ultrastructural investigations. *L. amastigotes* were detected in cytopla- sm of macrophages and neoplastic cells of the tumor mass. The presence of the parasite within neoplastic cells is consistent with a histiocytic origin of TVT.

Grevot *et al.* (2005) described a case of disseminated feline leishmaniosis with cutaneous (ulcerative), visceral (spleen and lymph nodes) and blood involvement in a FIV-FelV positive cat. Diagnosis was achieved microscopy and by several serologic tests and identified as *L. infantum* zymodeme MON-1. They reported that in veterinary practice, feline leishmaniosis must be systematically included in the differential diagnosis when compatible cutaneous lesions were present, mainly in endemic areas of canine leishmaniosis.

Sobrinho *et al.* (2012) stated that cats living in endemic areas of lVL are significantly more likely to be coinfected with feline immunodeficiency virus, which may present confounding clinical signs and therefore cats in such areas should be always carefully screened for the co-infections.

Conclusion

Leishmaniasis is widely present in more than 88 countries worldwide, resulting in up to 80,000 deaths annually.

Leishmaniasis occurs as visceral, cutaneous, or mucocutaneous variants.

Mucosal involvement can occur secondarily to the cutaneous or visceral varieties. However, primary mucosal leishmaniasis (PML) occurs without any present or past cutaneous and/or visceral disease. Leishmaniasis is a protozoan infection whose diagnosis should be confirmed by the presence of the organism in dermal macrophages in skin biopsy, dermal scrapings and fine-needle aspirate (FNA). The differential diagnosis of cutaneous leishmaniasis includes arthropod bites, atypical mycobacteriosis, basal cell carcinoma (BCC) and other malignancies.

Anthroponotic cutaneous leishmaniasis (ACL) is known to cause single, self-healing and uncomplicated lesion mainly on the face. Basal cell carcinoma is a malignant epithelial neoplasm of skin that usually arises in areas of chronic sun exposure. It rarely originates from smallpox vaccination scars, chickenpox scars, previous surgical scars, or burn scars.

Leishmaniosis caused by *L. infantum* is an endemic zoonosis present in the Mediterranean area. Canidae (dog and fox) constitute the main reservoir hosts for the parasite, whilst wild rodents or the cat can be carriers of the protozoan and are considered as secondary potential reservoirs.

Consequently, the early detection of any nuclear mutation and cellular prolife-ration in the skin leishmaniasis lesion(s) must be taken into consideration to avoid the miserable formation of skin cancer. Enhancing granuloma development and effector function, but without inducing the pathology associated with the excess granulomatous inflammation, poses a major challenge for the immunotherapeutic intervention against diseases such as visceral leishmaniasis (VL).

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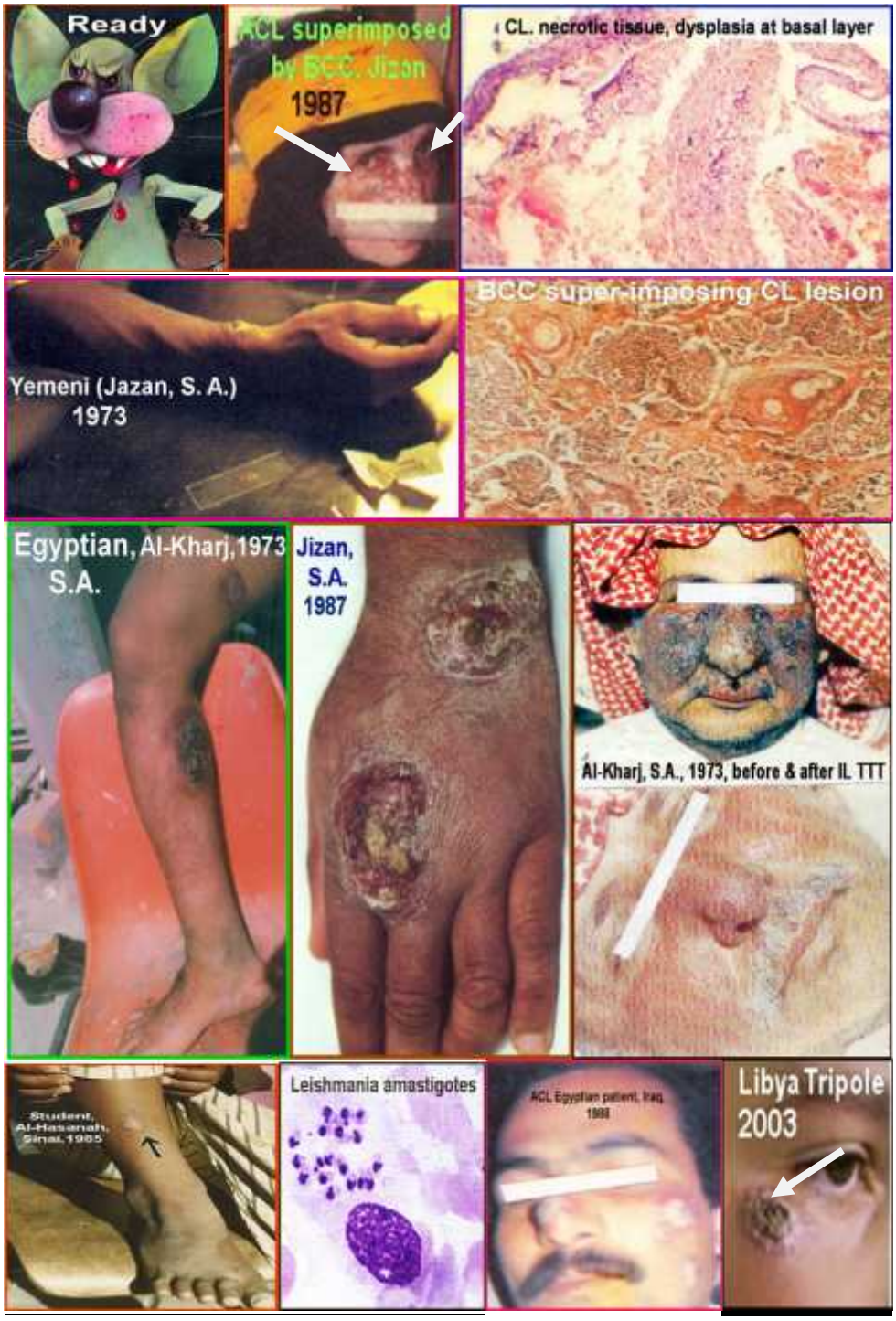
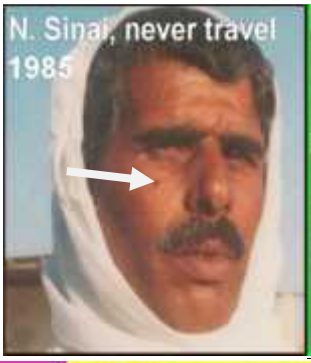

Ready
ACL superimposed by BCC. Jizan 1987
CL. necrotic tissue, dysplasia at basal layer
Yemeni (Jazan, S. A.) 1973
BCC super-imposing CL lesion
Egyptian, Al-Kharj,1973 S.A.
Jizan, S.A. 1987
Al-Kharj, S.A., 1973, before & after IL TTT
Student, Al-Hasenah, Sinai, 1985
Leishmania amastigotes
ACL Egyptian patient, Iraq, 1998
Libya Tripole 2003


Syria, ACL 1987


N. Sinai, never travel
1985


Egyptian, Iraq


refine your research
SCOPUS
This Scopus award is to honour
Tosson Morsy
For his contribution to Medicine
Cairo 25th of March 2008
Charles Pallandt
Director Sales & Marketing Europe


ZCL diagnosed as Pseudolymphoma
curtis of spiegler-Fendit, Egyptian back
from Saudi Arabia 1983

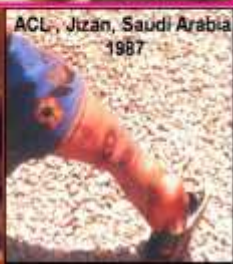

Egyptian manual worker Libyian Egyptian board
ZCL, 2008


ACL Yemeni. Al-Khoba, Jizan


Stray dog, IVL
lesions, Al
Agamy,1984


Egyptian ZCL patient,
Al-Kharj, S.A.1974


Gerbillus
pyramidum, North
Sinai, 1995


ACL, Jizan, Saudi Arabia
1987