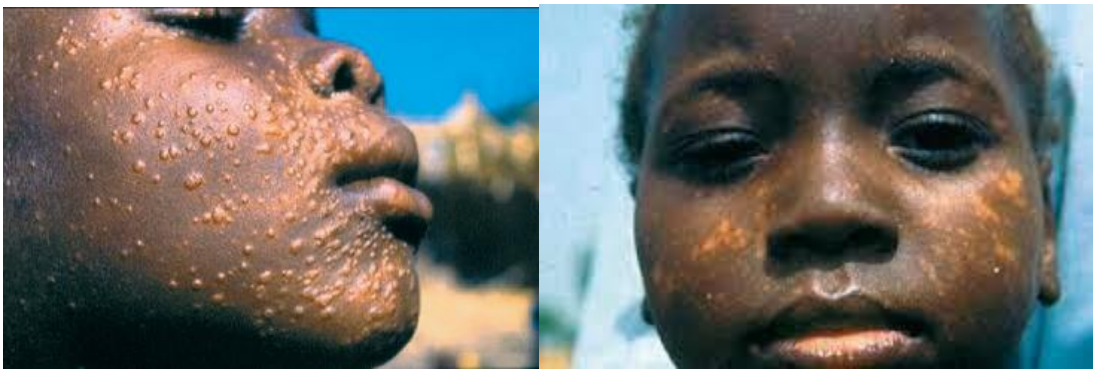
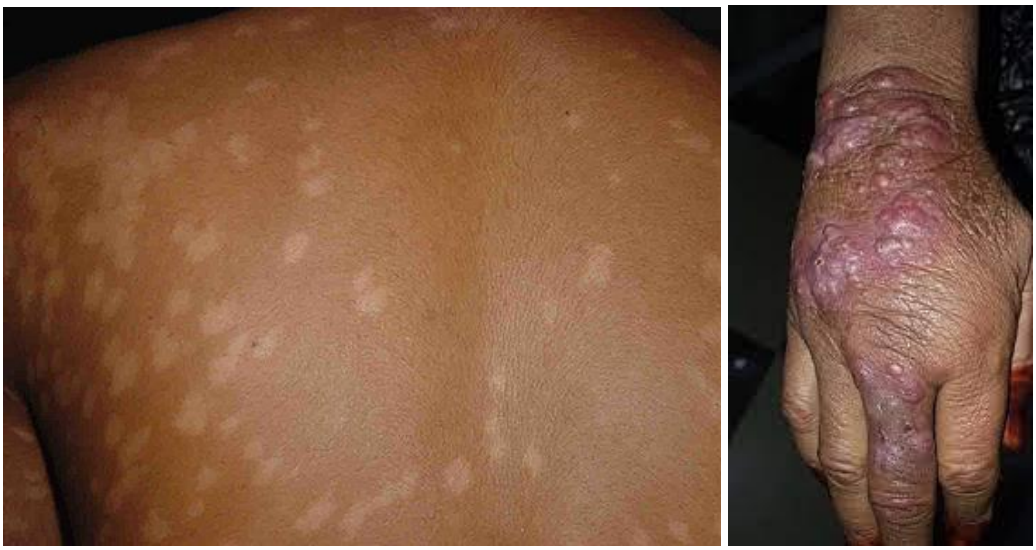
**POST (KALA-AZAR) DERMAL LEISHMANIASIS (PKDL**

Post-kala-azar dermal leishmaniasis (PKDL) follows visceral leishmaniasis (VL, kala-azar) in 10–60% of cases. It is characterized by an asymptomatic skin rash, usually starting in the face and consisting of macules, papules, or nodules. While the principal localization of the rash is often in the face, starting around the mouth, the rash may spread to the upper chest and arms, often corresponding with areas of the body that are not covered by clothing. Over time, or in severe cases, all parts of the body may be covered by the rash. Diagnosis is often made clinically. The differential diagnosis is extensive, and parasitological confirmation is preferred prior to therapy. The response to treatment is difficult to assess since lesions take a long time to heal, thus possibly exposing patients unnecessarily to prolonged drug treatment. Confirmation of the diagnosis is needed; these may be parasitological (from microscopy, PCR), serological (from blood, or from the lesion), immunological (from blood, tissue), pathological (from cytology in a smear, histology in a biopsy), repeated clinical assessment (grading, photography), or a combination of the above.

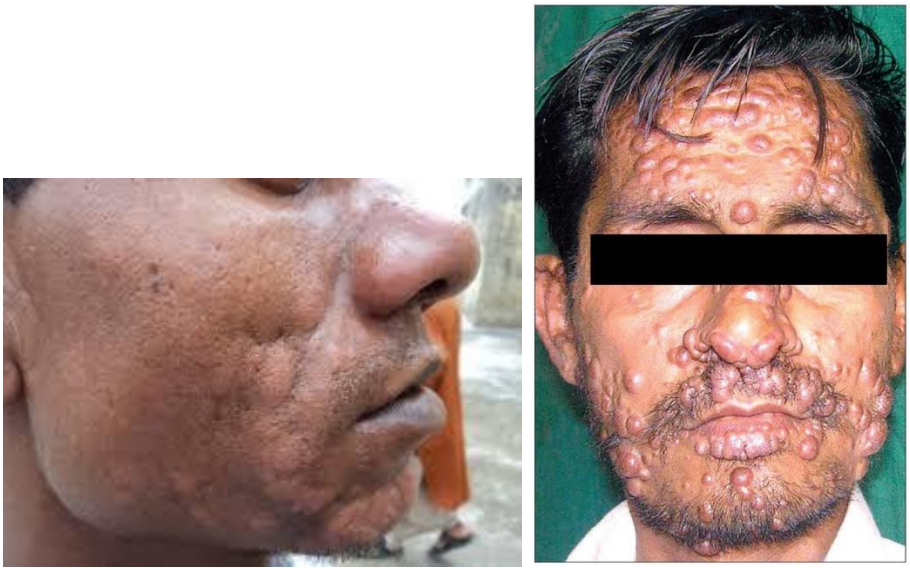
Visceral leishmaniasis (VL, kala-azar) is most common in Asia (India, Bangladesh, Nepal), East Africa (Sudan, South Sudan, Ethiopia, Kenya, Uganda), where it is caused by *Leishmania donovani*, and South America (Brazil), where *Leishmania infantum* is involved. VL cases caused primarily by *L. donovani* may be followed by post-kala-azar dermal leishmaniasis (PKDL). In Africa (Sudan), PKDL is much more common (up to 50–60% of VL cases) with mainly papulonodular lesions, compared with Asia (5–20%) where most cases show macular lesions. In addition, the interval between VL and PKDL is short in Africa (< 12 months), whereas in Asia, it is often 3–5 years or more. The underlying mechanism that determines development of PKDL is not completely defined but may be associated with factors that influence the evolving immune response to the parasites that can be found in the skin lesions. The immune response varies according to clinical type and is stronger in macular PKDL than in papulonodular PKDL



Papular rash in Sudan



Bangladesh, macular rash



Bangladesh Coinfection with HIV

**Post-Kala Azar Dermal Leishmaniasis.** Post-kala azar dermal leishmaniasis (PKDL) was first detected in patients with VL in India, occurs in up to 20% of these patients, has been called dermal leishmanoid, and is associated with *L. donovani* only. PKDL has also been seen in >50% of Sudanese VL patients treated in the current epidemic. In India, skin lesions may appear 2 to 10 years after successful therapy for VL; in East Africa, lesions appear within a few months; and in the Sudan, onset also occurs in about 2 months. Macules and papules usually appear first around the mouth and spread to the face and then to the extensor surfaces of the arms, the trunk, and sometimes the legs. In the beginning they look like small hypopigmented patches; these then enlarge and may progress to nodules that often resemble leprosy. The lesions are somewhat delicate but do not tend to ulcerate unless traumatized. In some cases, PKDL is seen in patients with no history of visceral disease. Some patients with past or concomitant PKDL also have ocular lesions including conjunctivitis,

blepharitis, and anterior uveitis; these conditions all respond to antimonial therapy, including steroid and atropine eyedrops.

**Coinfection with HIV**

A wide variety of descriptions of dermal leishmaniasis in HIV co-infection has been reported. Lesions are commonly described as florid, symmetrical, non-ulcerating, nodular lesions with atypical distribution and numerous parasites. Pre-existing, unrelated dermal lesions may become parasitized. Parasites lose their tropism and no longer exclusively cause VL or CL. PKDL in HIV co-infected patients is more common and more severe and is not restricted to *Leishmania donovani*. In VL, dermal lesions occur in up to 18% of patients and may present as (severe) localized cutaneous leishmaniasis, disseminated cutaneous leishmaniasis (DL) or diffuse cutaneous leishmaniasis (DCL); there may be an overlap with para-kala-azar dermal leishmaniasis. In CL, dissemination in the skin may occur resembling DL or DCL; subsequent spread to the viscera may follow. Mucosal lesions are commonly found in VL or CL and HIV co-infection. Classical mucocutaneous leishmaniasis is more severe. Immune reconstitution disease (IRD) is uncommon in HIV co-infected patients with leishmaniasis on antiretroviral treatment (ART).

**Disease Assessment**

Clinical assessment of PKDL at first presentation includes recording and description of individual lesions or groups of lesions, as well as the presence or absence of systemic symptoms and signs. In 10% of patients, PKDL occurs concomitantly with VL, often including fever, splenomegaly, hepatomegaly or lymphadenopathy, and poor nutritional status. In Asia, all patients with PKDL without systemic VL are treated, while in Africa (Sudan), only those with severe PKDL are treated as the majority of cases will self-heal. The differential diagnosis may be different in Asia and Africa but usually includes leprosy, vitiligo, and miliaria rubra (prickly heat rash). Misdiagnosis is common and reported in up to 26% of cases in India. Biopsy histology will also be helpful to distinguish between differential diagnoses.

In any PKDL patient, typically the lesions are described as macules, papules, nodules, plaques, or a mixed form. In Africa (mainly Sudan), a maculopapular rash (90% of cases) is most common, and in advanced cases, the papules will increase to form nodules or plaques; a pure macular rash is uncommon. In Asia, a macular rash is more common (90% of cases in Bangladesh); in hospital settings, the most common presentation may be mixed/polymorphic (53%), followed by macular lesions (23%) and papulonodular lesions (21%); unusual forms include the erythrodermic, and fibroid type, or presentations with plaques or ulcerations In contrast with Africa, advanced cases with massive lesions have been described in India.

**Diagnosis**

A confirmed diagnosis of PKDL is preferred and is mandatory in research studies. This may be done by demonstration of leishmanial parasites by microscopy in a slit skin smear, micro-biopsy, fine needle aspirate (FNA), or conventional biopsy, with limited sensitivity of 32–50%. Parasites can more easily be found in up to 95% of mixed papulonodular lesions and in only up to 40% in macular lesions; biopsies from the buccal mucosa or the tongue have higher.

While the examination of biopsy material can be helpful, PCR has higher sensitivity than microscopy. PCR has been first explored in the diagnosis of PKDL in Sudan, and extensive further studies were done in Asia. Later developments included RFLP analysis and nested PCR

that increased sensitivity from 69 to 93%. More recent studies show that parasite DNA is detected by PCR in a slit skin smear or biopsy in 96–100% of cases. PCR proved more sensitive than immunohistochemistry in biopsies from PKDL patients. qPCR or real-time PCR allows detection and quantification of a number of parasites.
Serological tests such as DAT, rK39 ELISA or rK39 RDT lack specificity as antibodies persist from previous VL. RDT rK39 direct on skin lesions has not been evaluated during or after treatment. Assessment of the developing immune response would be most useful as this may predict the risk of cure or relapse. *In vitro* measurement of the cytokines, chemokines, or lymphocyte subsets should be explored, and a CPI or ratio may be examined further to identify the most accurate immunological profile associated with cure. *In vivo* application of the leishmanin skin test (LST) deserves further study; the leishmanin needs to be well standardized and validated and requires production under good manufacturing practice.

**Treatment**

Treatment of PKDL with antimonials usually brings improvement; however, the skin changes persist indefinitely. The course of therapy is generally longer than that required for VL and may require 120 days. In Africa, patients with PKDL may self-cure. It is important to remember that these patients may serve as reservoirs of infection during interendemic cycles, since some patients with PKDL tend to have large numbers of parasites in the skin. Persistent lesions currently require daily injections of sodium stibogluconate for 2 to 4 months, and even then, the treatment may not be successful. Treatment with liposomal amphotericin B (AmBisome) has been found effective and is considered less nephrotoxic than nonliposomal amphotericin B because it specifically targets the macrophages in which the *Leishmania* parasites develop. Apparently, there are also intrinsic differences in the antibodies generated in the sera from patients with PKDL and VL. Diagnostic methods would be identical to those used for the isolation and identification of amastigotes found in CL.