

# Post-kala-azar dermal leishmaniasis

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Post-kala-azar dermal leishmaniasis (PKDL) is a complication of visceral leishmaniasis (VL); it is characterised by a macular, maculopapular, and nodular rash in a patient who has recovered from VL and who is otherwise well. The rash usually starts around the mouth from where it spreads to other parts of the body depending on severity. It is mainly seen in Sudan and India where it follows treated VL in 50% and 5–10% of cases, respectively. Thus, it is largely restricted to areas where *Leishmania donovani* is the causative parasite. The interval at which PKDL follows VL is 0–6 months in Sudan and 2–3 years in India. PKDL probably has an important role in interepidemic periods of VL, acting as a reservoir for parasites. There is increasing evidence that the pathogenesis is largely immunologically mediated; high concentrations of interleukin 10 in the peripheral blood of VL patients predict the development of PKDL. During VL, interferon  $\gamma$  is not produced by peripheral blood mononuclear cells (PBMC). After treatment of VL, PBMC start producing interferon  $\gamma$ , which coincides with the appearance of PKDL lesions due to interferon- $\gamma$ -producing cells causing skin inflammation as a reaction to persisting parasites in the skin. Diagnosis is mainly clinical, but parasites can be seen by microscopy in smears with limited sensitivity. PCR and monoclonal antibodies may detect parasites in more than 80% of cases. Serological tests and the leishmanin skin test are of limited value. Treatment is always needed in Indian PKDL; in Sudan most cases will self cure but severe and chronic cases are treated. Sodium stibogluconate is given at 20 mg/kg for 2 months in Sudan and for 4 months in India. Liposomal amphotericin B seems effective; newer compounds such as miltefosine that can be administered orally or topically are of major potential interest. Although research has brought many new insights in pathogenesis and management of PKDL, several issues in particular in relation to control remain unsolved and deserve urgent attention.

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Post-kala-azar dermal leishmaniasis (PKDL) is a complication of visceral leishmaniasis (VL). VL, also known as kala-azar, is caused by species of *Leishmania* that are transmitted by the bite of a female sandfly, and it is estimated that 200 million people are at risk for the yearly 500 000 cases.<sup>1</sup> Most cases occur on the Indian subcontinent (India, Nepal, Bangladesh) and east Africa (Sudan, Ethiopia, Kenya), where *Leishmania donovani* is the causative parasite. Whereas VL is considered to be anthroponotic in India with people as the only known reservoir, in other areas the picture is less clear



Figure 1. PKDL papular lesions.

and transmission may be anthroponotic as well as zoonotic, with rodents and canines as candidate reservoirs. Other VL endemic areas include countries in the Mediterranean basin, where *Leishmania infantum* is the species involved, and the New World, where the identical *Leishmania chagasi* circulates; in both areas canines are the reservoir hosts. Key features in the clinical presentation of VL are prolonged fever, hepatosplenomegaly, and weight loss. Dependent on the geographical region, in *L donovani* endemic areas between 5% and 60% of patients develop a dermatosis called post-kala-azar dermal leishmaniasis (PKDL) during or after treatment. This skin condition has a tendency to become chronic and is characterised by macular, papular, or nodular lesions in which leishmania parasites may be seen. PKDL is therefore considered a reservoir for leishmania parasites, especially during interepidemic periods of VL. Although the condition has been described for about 80 years, only recently has its relevance, in particular in Africa, been fully recognised. Recent studies have provided new insights into the pathogenesis of this condition that has important clinical and epidemiological implications.

## Clinical features

The clinical features have been best described in reports from Sudan and India and are summarised in table 1.

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**Table 1. Comparison of most important features of Sudanese and Indian PKDL**

	Sudan	India
<b>Clinical</b>		
PKDL may occur in absence of previous VL	Yes	Yes
PKDL may occur while still on treatment for VL	Yes	No
PKDL may occur with evidence of visceralized disease (VL)	Yes	Yes
Most commonly described predilection over body	Face>trunk>arms>legs	Face>trunk>arms>legs
Type of rash	PN>MP>microP>M*	Erythema, induration M,P,N
Lymphadenopathy	Frequent	Rare
More severe disease found in	Young children, short interval after VL	Not known
Concomitant other post-kala-azar manifestations	Yes	Yes
<b>Epidemiology</b>		
Frequency of PKDL following VL	50–60%	5–10%
Highest prevalence reported in field study	4.8/100	4.8/1000
Interval between VL and PKDL		
most common	0–6 months	2–3 years
range	0–13 months†	6 months–32 years
Age distribution	Children, mean age 6 years	Young adults
<b>Diagnosis</b>		
Parasites may be demonstrated in smears	20–30%	20–40%
Parasites may be demonstrated by PCR	83%	94%
LST positive	16–65%	0–67%
Most difficult differential diagnosis	Leprosy	Leprosy
<b>Treatment</b>		
Treatment with stibogluconate	2–3 months	4 months
Spontaneous cure	The rule	Not reported, all cases are treated

\*PN=papulo-nodular, MP=maculo-papular, MicroP=micropapular, M=macular, N=nodular. †In neighbouring Kenya, an interval of 30 years has been reported.

### Type of rash

The rash has been best described from Sudan and India. In a recent cross-sectional descriptive study of 105 patients with PKDL in eastern Sudan, a papular or nodular rash was most frequently seen (51%) (figures 1 and 2); other types of rash were maculopapular (23%), micropapular (measles-like) (17%) (figure 3) and macular (9%) (figure 4).<sup>2</sup> In a longitudinal study in the same area in which VL patients were monitored after treatment, the rash was almost always a mixture of a measles-like and maculopapular eruption.<sup>3</sup>

From India, three main presentations have been described, of which one or two may predominate: erythema and induration on the butterfly area of the face that shows photosensitivity; multiple symmetrical hypopigmented macules that may coalesce; and combinations of papules, nodules, and plaques.<sup>4–6</sup> Other unusual manifestations include the annular, warty, papillomatous, fibroid, or xanthomatous types. From China and Nepal the same hypopigmented macular, maculopapular, and nodular types of rash or combinations have been described.<sup>7,8</sup>

Although there are differences in description of clinical findings from Sudan and other areas, in most reports macular (maculo) papular and nodular lesions are described as the hallmarks of PKDL, and are differentiated arbitrarily by size. Nodular lesions probably develop from papules over time, which seems also to be the case in PKDL reported from HIV-endemic areas. The erythema in the butterfly area is probably not appreciated in the darker African skin. Ulceration is not a feature of Indian or Sudanese PKDL.

### Distribution

In Sudanese patients PKDL lesions typically appear around the mouth and spread to other parts of the face (figure 5); subsequent spread to upper arms and chest may follow. This pattern is most consistent in papular and nodular PKDL, but to a lesser extent in macular lesions as they may be more widely spread over the body. After treatment or during spontaneous regression, the lesions around the mouth remain longest and are the first to recur in case of relapse.<sup>9</sup> In most severe cases the whole body may be affected sometimes with mucosal lesions on the lips or palate.<sup>9</sup> Exposure to ultraviolet light may be an important factor in its pathogenesis and initially the distribution of the rash may mirror clothing habits.<sup>3</sup>

In some patients, the PKDL lesions occur preferentially in scars that become more prominent and regress again after treatment of PKDL (Köbner phenomenon).<sup>2</sup> The typical pattern of distribution has resulted in the description of three clinical grades of severity. In grade one a scattered maculopapular or nodular rash occurs mainly in the face with or without some lesions on the upper chest and arms. Grade two is defined as a dense maculopapular or nodular rash covering most of the face and extending to the chest, back, upper arms, and legs, gradually becoming less distally, with only scattered lesions on the forearms and legs. Grade three is defined as a maculopapular or nodular rash covering most parts of the body, including hands and feet. In grade three crusting, ulceration, sloughing, scaling, and spreading to the mucosa of the lip (cheilitis) and the palate may occur (figure 6).<sup>2</sup>



Figure 2. PKDL nodular lesions that are confluent with plaque formation.

The distribution and sequence of spread from the face to other parts of the body has not been described in Indian PKDL in longitudinal studies. However, especially for nodular lesions, similar predilection of the face with less frequent involvement of the arms and trunk further decreasing distally suggests a similar distribution pattern.<sup>5,10</sup>

As in Sudan, macular lesions do not seem to involve the face as frequently and may be more prominent on the trunk and limbs. In some reports it has also been suggested that the macular patches and the erythema precede the appearance of nodules; the influence of ultraviolet light has also been suggested.<sup>4,5,6</sup>



Figure 3. PKDL micropapular lesions (measles-like).



Figure 4. PKDL macular lesions.

#### Other clinical findings

Patients are generally well and do not have fever.<sup>11</sup> In the endemic area in eastern Sudan, where people are very much aware of the disease, which they call “kala-azar”, and where many have lost children because of this disease, the occurrence of a PKDL rash after treatment is regarded as a favourable sign (“the disease has come out”) meaning that the child is going to survive (EE Zijlstra and AM El Hassan, personal observation). In patients who develop PKDL early after VL there is a gradual transition from VL—during which the patient is ill, but without a skin rash, with demonstrable parasites in lymph node, bone marrow, or spleen—to PKDL—where the patient is well, the rash has developed, and parasites are no longer demonstrable except in the skin. Some patients present in the intermediate stage; one study showed that 15% of 416 PKDL patients had evidence of disseminated disease as shown by parasites in lymph node or bone-marrow aspirates. These patients with PKDL and concomitant VL may be more appropriately referred to as para-kala-azar dermal leishmaniasis cases and they take an intermediate position between VL and PKDL; they have larger spleen size (mean 4.1 cm [SD 3.6]) compared with PKDL patients who did not have demonstrable parasites in the bone marrow and lymph nodes (mean 2.8 cm [3.2]) but smaller than VL patients (mean 9.9 cm [5.4]).<sup>2</sup> At least seven patients with similar concomitant VL and PKDL have been reported from India;<sup>12</sup> another five patients with VL and presumably PKDL were seen in Iran,<sup>13</sup> and one patient in France.<sup>14</sup> Figure 7 shows the hypothetical association between the decreasing parasite load, the emerging immunological response, and the ensuing change in clinical syndrome.

Lymphadenopathy may be seen in Sudanese VL and PKDL but it is rare in Indian VL and PKDL.<sup>15</sup>

#### Associated conditions

PKDL may coexist with VL (see above); in Sudan, other post-kala-azar manifestations such as post-kala-azar mucosal leishmaniasis, uveitis, conjunctivitis, and blepharitis may be seen simultaneously in the same patient.<sup>16–18</sup> Other complications after VL include post-kala-azar laryngitis and colitis.<sup>19</sup> Similarly, in studies from India,



Figure 5. PKDL patient with typical perioral lesions.

involvement of the mucosal surfaces, in particular in the mouth and the larynx, as well as eye involvement such as keratitis has also been described.<sup>4,20</sup>

#### Place of PKDL in the spectrum of manifestations of *L. donovani*.

Figure 8 shows the inter-relationship between PKDL and other clinical manifestations of leishmania infection in Sudan. PKDL may occur without a previous history of VL, or may come after or concomitant with a leishmanioma (figure 9). After PKDL subsides, immunity is the rule; in rare instances a patient with PKDL may have a relapse of VL.<sup>21</sup> One study from India estimated this to occur in one of every 700 patients with PKDL. Reinfection, reinvasion from the skin, and renewed multiplication of latent parasites from the viscera have been suggested.<sup>21</sup> A degree of immunosuppression induced by intercurrent diseases such as measles, malaria, and tuberculosis has been suggested by Nandy et al, 1998<sup>22</sup> as an explanation for relapse of VL in PKDL patients.

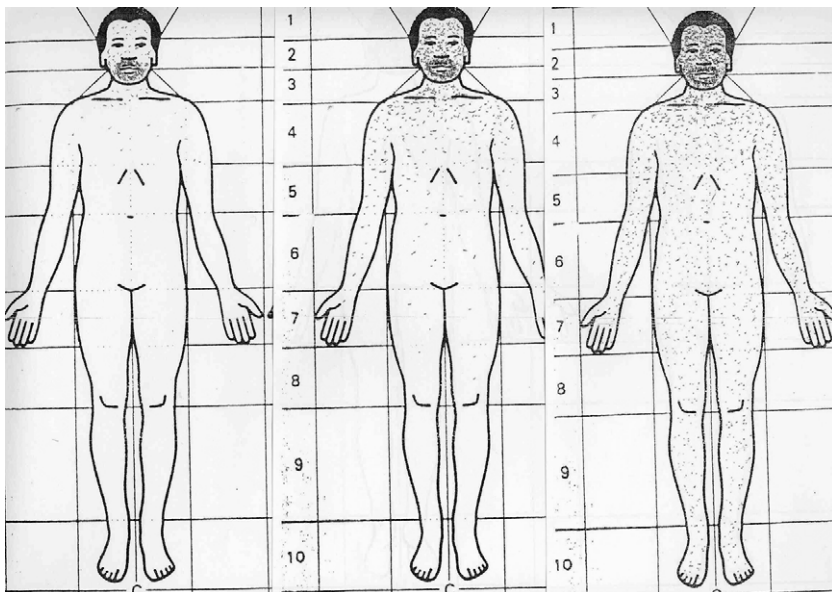


Figure 6. The distribution of PKDL may be described in grades of severity (see text for further explanation).

#### Age and sex distribution

The age distribution of PKDL follows that of VL; in Sudan, the mean age of patients with PKDL and VL was identical (6 years) with equal numbers among boys and girls. Younger children have more severe PKDL,<sup>2,3,11</sup> in India and Nepal, most cases are young adults with male predominance (1.3–3/1).<sup>4,8,23</sup>

There are, however, discrepancies between hospital-based and community-based studies in India suggesting under-reporting of PKDL cases in children (age group 0–9 years) and females.<sup>23</sup>

#### Interval between VL and PKDL

In east Africa (Sudan, Kenya) the interval between VL and PKDL is short; all cases present 0–13 months after treatment of VL with most presenting within the first 6 months.<sup>2,11,24</sup> Longer intervals of 3–30 years have also been reported.<sup>25</sup> 8% of cases have no previous history of VL;<sup>9</sup> others present with concomitant VL and PKDL or may develop PKDL while still on VL treatment (up to 18%).<sup>2</sup>

A different situation exists in Asia (India, Nepal), where PKDL follows VL with an interval of 6 months to 6 years and most patients present after 2–3 years.<sup>4,10</sup> In 15–20% of cases there is no previous history of VL.<sup>4</sup> Longer intervals of up to 32 years have been reported.<sup>26</sup>

#### Epidemiology

PKDL occurs mainly in *L. donovani*-endemic areas and most studies reported are from Asia (mainly India) and east Africa, mainly Kenya and Sudan (table 1).

#### Asia

In India, PKDL follows VL in 5–10% of cases.<sup>4</sup> The first cases of PKDL were reported from India by Brachmachari<sup>27</sup> in 1922, who described the occurrence of eruptions and plaques in the skin containing leishmania parasites in patients previously treated for VL. After decades of intense transmission in India, mainly in Bihar, the incidence of both VL and PKDL declined in the early 1960s, probably the result of residual DDT spraying in the National Malaria Eradication Programme, which affected sandflies as well as malaria mosquitos. After discontinuation of insecticide treatment, a severe epidemic of VL occurred in Bihar and west-Bengal.<sup>28,29</sup> In the interepidemic period, the number of PKDL cases outnumbered the VL cases, suggesting that the PKDL patients may have served as a reservoir.<sup>10,28</sup> Entomological work showed that *Phlebotomus argentipes*, the proposed vectors of VL in India, become infected and develop promastigotes in their midgut when allowed to feed on PKDL patients<sup>29,30</sup> and, therefore, seem capable of

transmitting leishmania. This finding is in agreement with earlier reports that suggest that transmission of VL is anthroponotic in this area and no other vertebrate host than people has been found.<sup>31</sup> The importance of PKDL in the epidemiology of leishmaniasis in India was also shown by Dye and Wolpert,<sup>32</sup> who showed that the presence of as few as 0.5% durably infectious (PKDL) patients during an epidemic may cause VL to become endemic. Although there are few studies on the epidemiology of PKDL in India, one study reported a prevalence rate of 4.8/1000 in two villages in Varanasi district.<sup>33</sup> Other countries in the Indian subcontinent from where PKDL has been reported include Bangladesh and Nepal; both are within the same nosogeographical area of *L. donovani*.<sup>8,34</sup>

In China, VL occurs in the anthroponotic form (probably caused by *L. donovani*) in the eastern plains for which effective control measures have been implemented; after 1960 only sporadic cases of VL and PKDL have been reported from that area.<sup>35-37</sup> There are no reports on PKDL from the zoo-anthroponotic form of VL that occurs in central and north-west China, from where *L. infantum* has been isolated from patients and dogs.<sup>35</sup> From Taiwan both imported cases from mainland China and autochthonous patients have been reported.<sup>38,39</sup>

**East Africa**

In Sudan, reports on PKDL remained scanty after the first report in 1938 by Kirk and Drew.<sup>40</sup> Kirk and Sati<sup>41</sup> described cutaneous infection in 57.5% of VL cases, but no clear distinction was made between PKDL and leishmaniomas. Sporadic cases were reported from two hospital-based studies.<sup>42,43</sup> Similar to what was suggested from India, PKDL cases may have served as a reservoir for parasites at times when numbers of VL cases are low.<sup>44</sup>

In the 1990s a severe VL outbreak occurred in the endemic area in eastern Sudan with incidence rates in one village of 20.4-38.4/1000 person-years.<sup>45</sup> 56% of VL cases developed PKDL with similar age and sex distribution as VL cases.<sup>9,45</sup> Between 1991 and 1996 416 patients with PKDL were seen in a cluster of villages in the same area.<sup>2</sup> As in most patients, the skin lesions will persist for months and in some for years and a considerable number of people in any village can be expected to have PKDL. Indeed, in another study the point prevalence of PKDL in one village in the

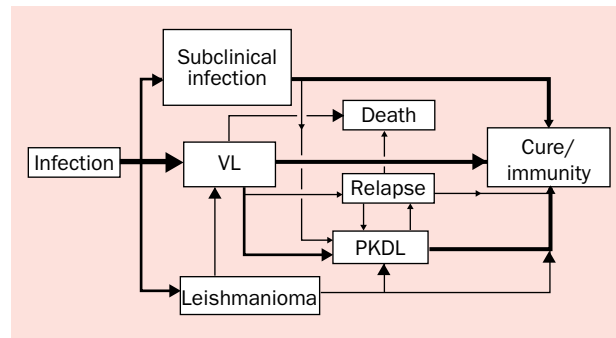


Figure 8. Diagram showing the interrelationship of clinical manifestations that may follow after leishmania infection in Sudan; the thickness of the lines corresponds with the likelihood of the occurrence of the following event. With permission from: Eldryd Parry, Richard Godfrey, Geoffrey Gill, David Mabey, eds. *Principles of Medicine in Africa*. Cambridge: Cambridge University Press; in press.

area was 4.8%.<sup>46</sup> A recent study on the natural history of PKDL in the same endemic area showed that the mean duration of PKDL was 9.7 months (range 2-28 months) before clearing.<sup>3</sup> It seems likely that PKDL could have a role in transmission in Sudan, but so far this has not been proved; it is not clear whether transmission of VL in Sudan is anthroponotic or zoonotic, or both. *L. donovani* has been shown by culture and PCR in materials from patients with VL, PKDL, and from rats and dogs; cultures that were further analysed by enzyme electrophoresis showed that all zymodemes of *L. donovani* found in PKDL patients have also been seen in patients with VL and in dogs.<sup>47,48</sup>

In Ethiopia, where the endemic area of eastern Sudan extends into the Metema-Humera focus, a recent study showed a PKDL rate of 14% in patients who were seen only once at 6 months after treatment. By contrast with the Sudanese focus HIV infection is spreading in this area. PKDL was more common in HIV-positive patients (27.3% and 13.3% in HIV-positive and HIV-negative patients, respectively).<sup>49</sup>

In Kenya, PKDL was first described by Manson-Bahr<sup>50</sup> in 1959. Reported PKDL rates after VL show considerable variability in four studies of 0.05%,<sup>51</sup> 1%<sup>50</sup>, 6%,<sup>24</sup> and 30%.<sup>52</sup>

From *L. infantum*-endemic areas reports on PKDL are scarce. Along the Mediterranean basin, sporadic cases occurred in Spain, Italy, France, and Israel; cases have also been reported from Iran.<sup>53-65</sup> In one study in Spain up to 15% of patients developed cutaneous lesions after VL, which could be referred to as PKDL.<sup>54</sup> In another report a patient had a PKDL rash for 15 years caused by a not previously described zymodeme of *L. infantum* (MON-253) without obvious immunosuppression or HIV infection.<sup>61</sup> More recent reports are from HIV-VL coinfecting patients, in whom the clinical presentation of VL can be unusual and cutaneous lesions have been described to precede, accompany, and follow VL after treatment. A case of a dermatofibroma parasitised by leishmania parasites has been described; another patient developed Kaposi's sarcoma-like lesions in the course of treatment of a third relapse of VL. It is unclear whether these are non-typical forms of PKDL or parasitised skin lesions in the course of VL.<sup>62,64</sup>

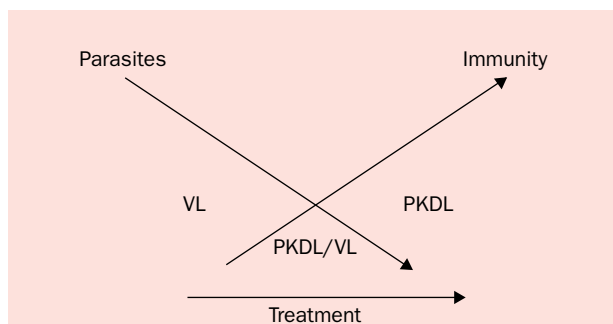


Figure 7. The hypothetical relationship between decreasing parasite load, increasing immunity, and ensuing clinical presentation during treatment of visceral leishmaniasis.



Figure 9. PKDL in combination with leishmanioma. The girl did not have a history of VL.

One HIV-infected patient from Italy developed PKDL after successful treatment of VL followed by highly active antiretroviral therapy (HAART); *L infantum* was identified in the skin by PCR.<sup>58</sup> A similar patient was described from Israel.<sup>59</sup> PKDL has also been reported in patients with other forms of immunosuppression—eg, kidney transplant recipients or patients with Hodgkin's lymphoma.<sup>14,57,65</sup> In South America, where VL is mainly caused by *L chagasi*, PKDL seems uncommon; in one HIV-infected patient with VL caused by disseminated *Leishmania braziliensis* (a parasite that normally is restricted to the skin or mucous membranes) cutaneous lesions developed while relapsing from a previous episode of VL.<sup>66</sup> In another case PKDL developed after VL caused by *Leishmania amazonensis*.<sup>67</sup>

### Parasites

Several studies from Sudan showed that in cultures from bone marrow or lymph node aspirates from patients with VL analysed by isoenzyme electrophoresis, *L donovani*, *L infantum*, and *Leishmania archibaldi*, which takes an intermediate position in the cladogram, are seen.<sup>68–70</sup> However, the three species were all seen to be *L donovani sensulato* by Southern blotting and fingerprinting and were clearly different from a *L infantum* reference strain,<sup>69</sup> which supports association between VL and PKDL in this area with *L donovani* rather than with *L infantum*.

Of the three species, seven zymodemes have been seen to be circulating in the VL endemic area in eastern Sudan. Four zymodemes have now been isolated from PKDL patients: (MON-18 *L donovani*; MON-30 and MON-267 *L infantum*; and MON-82 *L archibaldi*),<sup>71</sup> which does not suggest an association between a particular parasite subspecies and risk of developing PKDL. Similarly, although polymorphism was shown among *L donovani* strains using PCR single-strand conformation polymorphism, no correlation was found with the clinical manifestations of VL and PKDL.<sup>72</sup>

In India, Bangladesh, and Nepal strains that were isolated from VL and PKDL patients were all typed by electrophoresis as zymodeme LON-41 or MON-2,<sup>73–76</sup> earlier typing found serologic similarity between strains,<sup>77</sup> and the strains isolated from PKDL could cause VL in animal

experiments.<sup>22</sup> Other studies suggest that different strains are involved in VL and PKDL; differences in antibody responses with variable patterns of reactivity by VL and PKDL serum samples have been shown.<sup>78</sup> One study showed the cloning of a kinetoplast DNA mini-fragment from leishmania strains that was specific for strains from PKDL patients but not for strains from VL.<sup>79</sup> Bozza et al<sup>80</sup> provided support for this and showed that a strain from a PKDL patient had close relationship with *L tropica* and not with *L donovani* or *L infantum*.

### Pathogenesis and immunology

The exact mechanisms underlying the development of PKDL still remain to be elucidated. There is accumulating evidence, however, that (developing) immune responses have a major role.

In VL a specific cell-mediated immune (CMI) response to the leishmania parasite is absent, and only develops after treatment. This can be measured in vitro in experiments in which peripheral blood mononuclear cells (PBMC) are stimulated or in vivo by the leishmanin skin test.

Early studies from India showed CMI responses during VL while two-thirds of patients with PKDL had a positive response after stimulation of PBMC, with a more marked CMI response in newly acquired PKDL (duration a few months to 1 year) compared with chronic PKDL (duration 8–30 years).<sup>81</sup> In another study, all ten PKDL patients showed absent specific CMI response before treatment with intact response to (phytohaemagglutinin) mitogen, whereas in VL patients CMI responses both specific and generalised were absent. After treatment with antimony, specific CMI responses were restored in both VL and PKDL patients but this response was slower and took a larger amount of drugs in PKDL.<sup>82</sup>

More recent studies showed that during VL the immune response of PBMC to leishmania antigens is absent or skewed towards a Th2-type of response.<sup>83</sup> After treatment the response changes from a Th2 to Th1 or a mixed Th1/Th2 type.<sup>83</sup> The PBMCs of all Sudanese PKDL patients proliferate in response to leishmania antigen and produce interferon  $\gamma$ ; in about 20% of patients the cells also produced interleukin 10.<sup>84</sup>

In a further longitudinal study in Sudan, Gasim et al<sup>85</sup> monitored 29 VL patients for 6–24 months from the time of diagnosis to the time of cure or development of PKDL. In both groups parasites were detected in the skin during VL, PBMC did not show proliferation to leishmania antigen, and interferon- $\gamma$  production was absent. Patients with VL who went on to develop PKDL had higher interleukin 10 concentrations in the skin and peripheral blood than those who did not develop PKDL. At follow-up, both groups did not differ in the acquisition of a degree of immunity as evidenced by proliferation of PBMC to leishmanial antigen as well as production of interferon  $\gamma$  and interleukin 10. However, it was noted that at day 30 after VL treatment, those who developed PKDL had higher PBMC immunological responses compared with those who developed PKDL later, suggesting that there is an association between the occurrence of the PKDL rash and the

appearance of leishmania-specific lymphocyte reactivity. The development of PKDL apparently depends on capacity to mount an immune response since in patients co-infected with HIV and VL, PKDL may develop after the start of HAART suggesting that PKDL develops in the context of immune reconstitution. This finding was also supported by an increased CD4 count, restored interferon- $\gamma$  production, and decreased interleukin-10 concentrations during PKDL compared with measurements during the VL episode.<sup>58,59</sup>

There seem to be discrepancies in the immunohistopathological findings in PKDL lesions from Indian and Sudanese patients. In the early stages of Indian PKDL limited numbers of CD4+ and CD8+ lymphocytes were seen in hypopigmented lesions; as the disease progresses to the nodular type, in dermal lesions as well as in lymph nodes a preponderance of CD8+ cells was found.<sup>86</sup> By contrast in all lesions of Sudanese patients with PKDL most cells were CD3+ T cells with preponderance of CD4+ over CD8+ cells.<sup>84</sup> Macrophages were seen in variable numbers. Natural killer cells were scarce. Interleukin 10 was the most prominent cytokine in the lesions. However, interferon  $\gamma$  was seen in all and interleukin 4 in most lesions. It was suggested that balance of the cytokines in the lesions may determine the outcome of the disease.

The leishmanin skin test (LST) measures delayed type hypersensitivity in the skin by injection of killed leishmania amastigotes intradermally into the forearm. After 48–72 h the induration is measured in mm; a reaction 5 mm or more is usually considered positive. The LST is typically negative in VL and positive in 80% of successfully treated patients after 6 months.<sup>87</sup> PKDL patients take an intermediate position: those with PKDL and concomitant VL are LST positive in 11% and those without concomitant VL in 37%.<sup>2</sup>

### Pathology

Irrespective of the clinical forms the epidermis shows several changes in different combinations. These include hyperkeratosis, parakeratosis, focal acanthosis, or atrophy of the rete pegs, and liquifaction degeneration of the basal cells.<sup>88</sup> The last is associated with focal infiltration of the basal layer by lymphocytes. Under electron microscopy the lymphocytes are in intimate contact with melanocytes and basal keratinocytes. The latter cells seem to be damaged by the infiltrating lymphocytes, which is the major cause for the depigmentation seen clinically. The dermis is infiltrated by a mixture of lymphocytes and macrophages. By contrast with lesions of cutaneous leishmaniasis caused by *Leishmania major* (oriental sore) plasma cells are virtually absent in PKDL lesions. Lymphocytes are the dominant cells in most biopsies. In about half the cases epithelioid cells, scattered individually or forming compact granulomas, are seen. Compact granulomas are seen more frequently in nodular than macular and papular lesions.<sup>88</sup> A neuritis involving small cutaneous nerves in PKDL lesions has been shown that may cause confusion in the differentiation from leprosy.<sup>89</sup>

The reported presence of parasites in biopsies varies, probably because of differences in type of rash and duration of lesions. In one Sudanese study all 15 biopsies showed parasites.<sup>11</sup> In another comparative study, parasites could be

seen in only 17% of haematoxylin and eosin-stained sections; using a monoclonal antibody specific for *L. donovani* leishmania parasites improved sensitivity to 88% of the biopsies.<sup>90</sup> In India parasites are reported to be seen in about 90% of biopsies.<sup>91,92</sup> Parasites are more easily shown in nodules than in papules and macular lesions.

### Predictors of PKDL

No convincing clinical predictors have been identified that are helpful to predict who will develop PKDL and who will not. One Sudanese study showed spleen size at time of VL to be correlated with development of PKDL,<sup>85</sup> but another study did not confirm this.<sup>2</sup> In a further study from Sudan it was suggested that inadequate treatment regimens may be important.<sup>2</sup> This possibility was also suggested from India where all patients presenting with PKDL had short duration of treatment for VL.<sup>3</sup> It is unclear whether more effective treatment of VL—eg, with liposomal amphotericin would prevent PKDL; one limited comparative study in Sudan between stibogluconate and liposomal amphotericin B (AmBisome) in the treatment of VL, showed less PKDL in the amphotericin B group than the stibogluconate group.<sup>93</sup>

Several studies on Sudanese patients examined factors relating to the parasite and various immune responses.<sup>2,3,85,94,95</sup> Persistence of parasites after successful treatment of VL may play a part. Osman et al<sup>94</sup> showed that leishmanial parasite DNA was present by PCR in microscopically negative inguinal lymph nodes taken after treatment of VL in 82% of cases. Interestingly, 36% of these developed PKDL and 23% developed relapse of VL, whereas none of the 18% who were PCR negative developed these complications. Gasim et al<sup>95</sup> showed that patients who had high C-reactive protein levels (>40  $\mu\text{g}/\text{mL}$ ) at the time of VL had higher risk of developing PKDL compared with those with C-reactive protein below 30  $\mu\text{g}/\text{mL}$ . In another study high concentrations of interleukin 10 in the blood, and the presence of this cytokine in normal-looking skin during VL, predicted the subsequent development of PKDL.<sup>85</sup>

PKDL is more severe at a younger age and the conversion rates in the LST are lower in more severe PKDL. This may be the result of generalised ultraviolet light exposure since very young children often walk about undressed; it may also indicate the immaturity of the immune system in the very young.<sup>2,3</sup>

Another factor associated with the severity of PKDL is the interval between end of VL treatment and occurrence of PKDL; significantly more severe PKDL occurs after a shorter interval, suggesting a continuing Th2 response.<sup>3</sup>

### Diagnosis

In most endemic areas diagnosis will be made clinically by a history of previous VL, the temporal association with VL, the distribution and appearance of the lesions, by ruling out other disorders, and by the response to treatment. Parasitological confirmation may be sought if in doubt. Studies from India showed that smears are more likely to show amastigotes if taken from a larger lesion or from nodular (67–100%) lesions compared with papular

**Table 2. Overview of studies on treatment of PKDL; only studies with more than one patient are included unless no other data on a particular drug are available.**

Reference	Year	Country	Type of study	Drug	Daily dose	Duration	Number studied	Outcome
Yesudian <sup>113</sup>	1974	India	Case series	Amphotericin B	Max 25 mg alternate days	Variable	2	1 cured after 717.5 mg in 3 months; 1 cured after 375 mg in 6 weeks
Thakur <sup>28</sup>	1984	India	Case series	SSG or SAG	10 mg/kg adult 20 mg/kg child	20 days 20 days	20	7 (36%) cured; 13 (64%) relapsed
Saha <sup>114</sup>	1985	India	Case study	Rifampin	600 mg bd	2 courses of 15 days	1	1 cured
Thakur <sup>115</sup>	1987	India	Randomised study	SSG	10 mg/kg 15 mg/kg 20 mg/kg	120 days 120 days 120 days	36 36 36	18 cured 24 cured 33 cured
Rai <sup>23</sup>	1989	India	Case series	SAG	10 mg/kg	40 days	13	13 cured
Thakur <sup>10</sup>	1990	India	Case series	SSG	20 mg/kg*	120 days	53	47 (88%) cured after 120 days 2 cured after 180 days 2 cured after 200 days†
Muigai <sup>24</sup>	1991	Kenya	Case series	SSG Nil	20 mg/kg	30 days	7 5	6 cured, 1 relapsed, cured after SSG+allopurinol 5 self cured
Ramesh <sup>116</sup>	1992	India	Case series	Ketoconazole	800 mg	Variable	4	1 cured after treatment for 9 months; 2 stopped because of side-effects; 1 defaulted
El-Hassan <sup>11</sup>	1992	Sudan	Case series	SSG	20 mg/kg 10 mg/kg	30 days 15 days	8 7	4 cured, 4 relapsed 2 cured, 5 improved with residual lesions
				Ketoconazole	10 mg/kg	30 days	2	2 not improved
Ramesh <sup>91</sup>	1993	India	Case series	SAG	20 mg/kg‡	105-150 days	14	9 cured after 120-130 days 3 cured after 105 days 2 cured after 150 days
Khalil <sup>117</sup>	1996	Sudan	Case series	Terbinafine + itraconazole	250 mg 200 mg	4 weeks 4 weeks	9	1 cured after 2 weeks extension 8 initially improved but relapsed later
Ramesh <sup>118</sup>	1996	India	Case series	Allopurinol	20 mg/kg	variable	3	2 cured after 20 and 24 months; 1 improved but stopped after 6 months (side-effects)
Hashim <sup>119</sup>	1995	Sudan	Case series	Liposomal amphotericin B			2	2 cured
Thakur <sup>120</sup>	1997	India	Comparative study	Amphotericin B	1 mg/kg	3x20 days§	11	11 cured
				SAG	20 mg/kg*	6-10 x 20 days§	11	7 cured
Garg <sup>8</sup>	2001	Nepal	Case series	SAG	20 mg/kg	30-72 days	21	21 cured

\*Maximum daily dose 850 mg. †Not mentioned for two patients. ‡Maximum daily dose 1g. §Courses of 20 days with 20 days drug free interval. SSG=sodium stibogluconate. SAG=sodium antimony gluconate.

(36–69%) and macular lesions (7–33%).<sup>4,96</sup> Cultures may give higher yield than smears but are likely to be contaminated. Monoclonal antibodies and PCR increase the diagnostic yield considerably to 88% and 83–94%, respectively, but these techniques are restricted to well equipped laboratories.<sup>90,97–99</sup>

Serological tests such as the direct agglutination test (DAT) and ELISA are of limited value in endemic areas and so far no specific and practical serological test exists for PKDL since after VL leishmanial antibodies may persist for years and a positive antibody test in a patient with suspected PKDL may be the result of previous VL. Similar titres in the DAT and rK39 IgG ELISA are reported in Indian and Bangladesh PKDL compared with VL.<sup>100,101</sup> In Sudan the positivity rate in the rK39 strip test was equal among patients cured of VL without PKDL and patients with PKDL.<sup>102</sup>

Adaptations of the antigen used may be helpful. One study showed antibody profiles to differ in VL and PKDL since only 10% of PKDL patients showed an antibody response to a 200 kDa axenic amastigote antigen compared with 97% of patients with VL; in both conditions antibodies to leishmania amastigote soluble antigen could be shown.<sup>103</sup> In another study from India, western blot analysis also showed different humoral responses in serum samples of PKDL patients compared with VL patients; two antigens (110 and 65 kDa) elicited an antibody response in 97–100% of PKDL patients, compared with 51–71% of VL patients and none of the control patients including patients with leprosy.<sup>104</sup> Given the often long interval between VL and PKDL in India, it was argued that this immune response was likely to be the result of the occurrence of PKDL rather than persistence of antibody of VL. A competitive ELISA using *L. donovani*-specific monoclonal



antibody was positive in all seven Indian PKDL patients tested and may prove useful to monitor the success of treatment.<sup>105</sup> Serological tests such as DAT and rK39 strip test may help exclude other conditions, in particular leprosy;<sup>101,104</sup> a rK39 strip test detected 91% of PKDL cases with 100% specificity in India.<sup>106</sup>

After VL, 80% of patients are expected to develop a positive LST after 6 months. For PKDL patients in Sudan, varying LST positivity rates of 16%, 32%, and 65% have been reported which is probably a function of time after VL, severity of PKDL, and antigen used.<sup>2,3,9</sup> There is no difference in conversion rates between those who develop PKDL and those who do not.<sup>2</sup> In India conversion rates vary between 0% and 67%.<sup>81,82,107</sup>

Both in Indian and Sudanese PKDL the differential diagnosis includes a large number of other skin conditions of which leprosy is not uncommonly mistaken for PKDL; distinguishing between these two conditions may be difficult.<sup>108–112</sup> An overview of differential diagnoses has been published.<sup>2</sup>

### Treatment

There are few controlled studies on the management of PKDL and most data come from small case series. In addition, there are differences in approach according to geographical area. An overview of studies available is given in table 2.

#### Spontaneous healing

In Sudan, spontaneous healing frequently occurs; in one study in non-severe PKDL this was found in all 134 patients, of whom 84% healed within 1 year.<sup>3</sup> Patients with grade-one and mild grade-two PKDL may therefore be left untreated under careful follow-up. Those who will develop persistent lesions may be identified by significantly higher titres in the DAT and a more often negative LST.<sup>3</sup>

#### Treatment with pentavalent antimony

In Sudan, patients with severe PKDL, those with lesions that have persisted for more than 12 months, and those with concomitant anterior uveitis or mucosal lesions are best treated from the start; treatment is with sodium stibogluconate.<sup>3</sup> No firm data are available on the optimal treatment regimen; clinical experience has shown that since 20 mg/kg per day for 30 days was not satisfactory, treatment may need to be prolonged to 2–3 months or alternative treatment may be necessary.<sup>2,11</sup>

In India treatment is the rule and cure rates are 64–92% with sodium antimony gluconate (SAG) 20 mg/kg per day for 120 days.<sup>4,111,115</sup>

#### Other treatment

Especially in India, where resistance to SAG is a serious problem, alternative treatment options have been explored. There is one case of successful surgical removal of a localised lesion by shave excision.<sup>121</sup> Pentamidine has been shown to be effective (cure rate 93%) but with serious toxicity.<sup>28</sup> Ketoconazole in high dose (800 mg/day) has to be given for up to 9 months to achieve cure;

therefore it is probably better used in lower dose as a second drug in combination with SAG.<sup>116</sup> In Sudan, a combination of terbinafine and itraconazole was not effective.<sup>117</sup> In India, rifampicin was shown to be effective in one case report; in another case series allopurinol cured two patients after 20–24 months, while a third patient improved but developed side-effects after 6 months.<sup>114,118</sup>

Amphotericin B was shown to be effective with low toxicity in antimony-unresponsive Indian VL patients and seen to be superior to pentamidine.<sup>122</sup> Experience with amphotericin B in PKDL is limited,<sup>113,120</sup> in one study in India, amphotericin B appeared more effective (all 11 patients cured after 120 days) compared with SAG (seven of 11 cured after up to 400 days of up to ten courses of treatment), although the result was not significant. Amphotericin B is, however, more expensive and showed some nephrotoxicity.<sup>113</sup> Similarly, liposomal amphotericin B, which is probably the most effective drug for VL, could be of potential benefit in PKDL; however, so far this has been reported effective in three case reports only.<sup>56,119</sup> The new oral compound miltefosine that has been shown effective in the treatment of Indian VL is of considerable potential interest for treatment of PKDL since patients who are otherwise not ill may resent a repeated and lengthy course of daily treatment with intramuscular or intravenous stibogluconate.<sup>123</sup> Topical application may be an alternative because miltefosine has good skin penetration and is used as topical treatment for skin metastasis of breast cancer; it has been shown to be effective in experimental cutaneous leishmaniasis.<sup>124,125</sup>

### Unresolved issues and areas for research in PKDL

#### Pathogenesis and epidemiology

- Conclusive identification of risk factors for PKDL
- Differences between *Leishmaniasis donovani* and *Leishmaniasis infantum* with regard to development of PKDL: involvement of certain subspecies, immune responses after infection, parasite load, response to treatment, genetic factors
- Explanation of differences in interval between VL and PKDL between African and Asian PKDL; need for longitudinal studies
- Confirmation of PKDL as a reservoir in transmission of VL
- Identification of treatment regimens and drugs (or combinations of drugs) for VL to prevent development of PKDL

#### Management

- Firm clinical and/or laboratory markers of PKDL that predict rapid self-cure or need for treatment
- Identification of effective and non-toxic treatment regimens for PKDL
- Evaluation of miltefosine as a potential candidate for treatment (oral or topical administration)
- Clinical and/or laboratory markers that predict parasitological cure after treatment

#### Control

- Use of bednets as a tool to prevent sandflies from feeding on PKDL patients
- Education and training of health workers to diagnose and manage patients with PKDL in areas of high incidence
- Integration of diagnosis and management of PKDL in control strategies in VL endemic areas



Figure 10. This girl had PKDL for 3 years. After the first course of sodium stibogluconate (top) some lesions are healing but with scar formation. Multiple depressed scars after a second course of treatment (bottom).

Treatment studies in PKDL are hampered by the absence of a clear and early marker of cure. Since parasites may be scarce or absent in smears taken at diagnosis, parasitological cure is difficult to assess in repeated skin smears. Taking repeated biopsies is unattractive and impractical. Similarly, molecular techniques are not helpful

### Search strategy and selection criteria

The data in this review were from papers identified from PubMed searches using the terms, “post-kala-azar dermal leishmaniasis”, “post-kala-azar”, “dermal leishmaniasis”, “PKDL”, and “PKADL”. Additional data originated from papers in reference lists of reviewed articles and from the authors’ personal archives. Reference were selected for their scientific contribution to various aspects of PKDL. Case reports were used for areas in which not other studies were available. English and French papers were reviewed.

and repeated demonstration of leishmanial DNA may not reflect the presence of live parasites. Parasitological cure may well precede clinical cure leading to unnecessary long treatment regimens with considerable toxicity. In addition, clinical response may differ according to PKDL type; nodules and papules disappear in 120 days, macules in 200 days.<sup>10</sup> PKDL usually heals completely, but in longstanding cases scarring may occur (figure 10).

### Conclusion

PKDL is now recognised as a frequent complication of VL in most endemic areas with important clinical and epidemiological implications. Although in the past decade studies have considerably increased our understanding of PKDL, many issues remain unresolved and should be the subject of further research (panel). These might include studies that increase our basic understanding in pathogenesis and management, but should also be focused on the public-health aspects of PKDL, especially in relation to developing control strategies in VL endemic areas.

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### Conflict of interest

None declared.

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