

## Commentary

### PKDL - a drug related phenomenon?

Post-kala-azar dermal leishmaniasis (PKDL) is a cutaneous manifestation of visceral leishmaniasis (VL), characterized by skin lesions, nodules or papules, frequently on the face. It often appears 2-7 years after the apparently successful treatment of VL by antimonial drugs. It has long been considered a curious phenomenon, difficult to treat and difficult to explain. Recent studies have sought to determine parasite, host and treatment factors that might explain the cause(s) of PKDL.

First, is there anything special about the parasite? PKDL is caused by *Leishmania donovani* in India and Sudan, with a few cases reported to be caused by *L. infantum* / *chagasi* and historically by either species in China. Recent molecular studies in India and Sudan on PKDL and VL clinical isolates have not identified or defined any strains characteristically associated with the problem<sup>1-3</sup>. It seems unlikely to be a parasite determined manifestation of leishmaniasis. Second, is there anything different about PKDL patients, their immunological status, susceptibility or other factors? Clinical reports have not identified sex, age or racial origin as defining factors<sup>4</sup>. A possibility that genetic disposition might be involved was indicated in Sudan where genotypic studies identified linkage of the interferon- $\gamma$  (IFN- $\gamma$ ) receptor to PKDL and not to VL. But further studies are required to clearly define susceptibility factors. The immunological status of PKDL patients continues to be characterized but the picture is complex with mixed T cell responses and elevated levels of interleukin-10 (IL-10) and tumour necrosis factor alpha (TNF- $\alpha$ )<sup>6-9</sup>.

The last factor in the puzzle to be considered is drug treatment. Although there have been reports of PKDL in untreated patients, the generally accepted view is that this cutaneous manifestation of VL appears only after treatment. In their excellent review Zijstra and El-

Hassan<sup>4</sup> (2001) refer to the earliest cases of PKDL reported in Sudan by Christopherson in 1921 and in India by Brahmachari in 1922, a time when trivalent antimonial drugs (for example, antimony tartrate) were the norm for treatment. The sporadic reports on PKDL in India and Sudan that were published in the following decades referred to disease following treatment with pentavalent antimonials, a form of drug seen now as a pro-drug for trivalent antimonials<sup>10</sup>. Is PKDL only associated with antimonial treatment? In Bihar, India, amphotericin B has been introduced as a front line drug following the development of resistance to pentavalent antimonial treatment. There are now also alternative treatments for VL in India following the registration of miltefosine in 2002<sup>11</sup> and paromomycin in 2006<sup>12</sup>. It is now possible to test whether PKDL is a specific result of antimonial treatment. Thakur *et al* in this issue<sup>10</sup> present a retrospective analysis of data on the incidence of PKDL following the wider use of amphotericin B and discuss the hypothesis that antimonial treatment and PKDL are inextricably linked. We know from recent clinical and experimental studies that sodium stibogluconate has specific and profound influence on the immune response through effects on cell signalling, cytokines and on immune complex induced granulocyte macrophage colony stimulating factor (GM-CSF) levels<sup>14,15</sup>. More importantly, and directly related to Thakur's analysis, Saha *et al*<sup>16</sup> have recently reported a comparative study showing that sodium stibogluconate and amphotericin B had contrasting effects on IL-10 and transforming growth factor (TGF)- $\beta$  levels in PKDL and VL patients, factors already implicated in the development of this intractable disease.

Further studies are needed to get to the bottom of the PKDL phenomenon. Prospective clinical trials with a 2-3 year follow-up are required to really test the hypothesis that PKDL is a specific sequela of antimonial

treatment. However, the low incidence of PKDL reported by Thakur *et al*<sup>13</sup> would challenge any trial design in India. The significantly higher incidence of PKDL in Sudan makes this the obvious endemic region to determine the impact of alternative treatments on the incidence of PKDL. Unfortunately we will have to wait until miltefosine, paromomycin or AmBisome are shown to be effective against VL in Sudan before their impact on PKDL can be investigated. In the meantime, the elimination of VL is a priority for India, Nepal and Bangladesh and the accompanying reduction in the incidence of PKDL will assist this effort by removing a potential human reservoir.

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