Multilocus Parasite Gene Polymorphism and/or Parasite-Selected Mutations in Host Genome May Discriminate Between Relapse and Reinfection in the Failure of Miltefosine Treatment in Visceral Leishmaniasis

TO THE EDITOR—In their comprehensive cohort study, Rijal and colleagues have explored the occurrence of failure in miltefosine treatment in 120 visceral leishmaniasis (VL) patients in Nepal; they observed an initial cure rate of 95.8% with an alarming relapse rate of 10.8% and 20.0% at 6 and 12 months, respectively [1]. Similar studies in India have reported declines in the success rate of miltefosine therapy in VL patients, the initial cure rate of 97.5% sharply fell to a final cure rate of 90.3% after 6 months, lower than Indian phase 3 trials a decade earlier [2]. Interestingly, the study in Nepal reports no difference between mean promastigote miltefosine susceptibility (50% inhibitory concentration) of isolates between cures and relapses [1].

At this juncture of the elimination program, it is quite pertinent to differentiate between relapse and reinfection in the context of drug efficacy and resistance among Leishmania isolates in the Indian subcontinent. Parasite fingerprinting is required at onset of treatment and at relapse; parasite kinetoplast DNA fingerprinting results were used to conclude relapse over reinfection [1]. Interestingly, using microsatellites as discriminatory markers, genetic homogeneity of Leishmania donovani strains in the Indian subcontinent is reported [3]. In contrast, genetic polymorphisms with 2 zymodemes were reported in L. donovani strains in Bihar, India [4]. Therefore, these contradictory results targeting some specific loci will lead to perplexity.

If other diseases are consulted for reference, drug resistance is common in malaria and tuberculosis. Interestingly, Mycobacterium tuberculosis isolates with identical DNA fingerprinting patterns can possess substantial genomic diversity [5]. Because this heterogeneity is not detailed by traditional genotyping, genome sequence–based modeling and experimental evaluation of fluorescent amplified fragment-length polymorphism is a powerful tool for clinical use [6], which might also be helpful to differentiate between disease relapse and exogenous reinfection in VL. Apparently sympatric subpopulations of artemisinin-resistant malarial parasites were reported to contain extremely high levels of genetic differentiation [7]. Therefore, advanced genetic fingerprinting tools are required for Leishmania genotyping, otherwise important information of the disease could be missed or misinterpreted. Recently, whole genome sequencing revealed that miltefosine resistance in Leishmania major mutants can be both genetically and phenotypically highly heterogeneous [8]. Of particular interest, the KALADRUG-R consortium endeavors to develop, authenticate, and propagate new tools for evaluation of drug resistance in Leishmania, one of the focuses being miltefosine resistance (http://www.leishrisk.net/kaladrug).

Conversely, genome-wide association studies of human VL have implicated various host genes and chromosomal loci in disease outcome [9]. Fascinatingly, malaria-selected mutations in human genes promoted parasite survival in endemic
areas, possibly due to its long history of coevolution with humans [10]. Defense against parasitic infections has been ascribed to many polymorphisms that have been maintained over generations in the human genome. In conclusion, queries about the reasons for increasing unresponsiveness to miltefosine treatment in the Indian subcontinent remain unanswered. Either host and/or parasite multilocus gene polymorphisms might be responsible for the phenomena and should be further ascertained. These findings have important implications for clinical trials of new anti-leishmanial drugs.

Note
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