Travel Medicine and Infectious Disease (2014) 12, 617–627

Available online at www.sciencedirect.com

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REVIEW

Transfusion transmitted leishmaniasis. What to do with blood donors from endemic areas?

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Received 10 April 2014; received in revised form 11 October 2014; accepted 13 October 2014
Available online 22 October 2014

KEYWORDS
Blood donors;
Leishmania;
Leishmaniasis;
Transfusion

Summary Leishmaniasis clinical spectrum ranges from cryptic infection to fatal visceral leishmaniasis. Cryptic infection can be found in blood donors from areas endemic for leishmaniasis all over the world. Although leishmaniasis is a classic vector-borne disease, cases of transfusion transmitted leishmaniasis have been reported especially in nonendemic areas. Most of these cases regarded infants or children. This paper reviews the literature on this specific feature and the impact of leishmaniasis on transfusion medicine. Relevant literature was found through PubMed. The reference lists of selected articles identified further sources. Conclusions: Blood donations by emigrants or travelers from endemic areas require special attention. Routine diagnostic methods should be implemented in blood banks to exclude donors that are positive for *Leishmania*, and individuals who suffered from visceral leishmaniasis should be prohibited from donating blood. The use of leukodepletion filters at the time of collection should be recommended in at-risk areas especially for high-risk recipients.

1. Introduction

Leishmaniasis is a vector-borne disease caused by *Leishmania* species of protozoan parasites. Among 15 well-recognized *Leishmania* spp. known to infect humans, 13 have a zoonotic nature since canines and rodents are the principal hosts [1]. The clinical spectrum of the disease depends largely on parasite species and host immune response, ranging from asymptomatic infection (80–95% of affected people) to 3 main clinical syndromes (5–20% of current leishmaniasis): visceral leishmaniasis (VL), also known as "*kala-azar*," cutaneous leishmaniasis (CL), and mucosal or mucocutaneous leishmaniasis (ML), also known as "*espundia*" [2,3].

The most severe form is VL which affects about 200,000–400,000 people worldwide, causing approximately

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http://dx.doi.org/10.1016/j.tmaid.2014.10.011
1477-8939/

20,000—30,000 deaths per year. If untreated it has a mortality rate of almost 100%. India, Nepal, Bangladesh, Sudan and Brazil account for 90% of all visceral cases, Brazilian cases represent up to 90% of all cases in the Americas. VL usually presents with fever, splenomegaly, pancytopenia and hypergammaglobulinemia [4].

Leishmania (L.) infantum in the Mediterranean basin, West Africa, and South America (*L. infantum chagasi* (or *L. infantum* MON 1)) is the agent of zoonotic visceral leishmaniasis (ZVL), and dogs are the only confirmed primary reservoir of infection [5]. *L. donovani* causes anthroponotic VL in the Indian subcontinent and eastern Africa.

In the 90s an increase in cases was noticed mainly due to the extension of *Leishmania*-HIV coinfection. It is estimated that in southern Europe between 25% and 70% of adult VL cases are related to HIV infection [6,7]. The increased rate of human VL in HIV-infected patients suggests that most cases could be attributable either to a reactivation of cryptic forms of the disease by HIV immune system suppression or the inability to avoid primary infections [8].

Although VL is the most severe form of the disease, CL is by far the most common, 90% of which occurs in Afghanistan, Iran, Saudi Arabia, Syria, Brazil, and Peru [9]. CL clinical onset is characterized by skin ulcers on the exposed parts of the body, such as the face, arms and legs, their number ranging from 1 to as many as 200, causing serious disability and leaving the patient permanently scarred. Sometimes the cutaneous form may evolve to a disseminated form, known as diffuse cutaneous leishmaniasis (DCL). The main species involved in CL are: *L. tropica*, *L. aethiopica*, *L. major*, and dermotropic zymodemes of *L. infantum* in the "Old World" (i.e. southern Europe, Mediterranean basin, Middle East, Asia, and Africa), and parasites belonging to the *Leishmania Mexicana* (*L. amazonensis*, *L. mexicana*, *L. venezuelensis*) and *Leishmania Viannia* (*L. braziliensis*, *L. guyanensis*, *L. panamensis*, *L. peruviana*) subgenus complexes in the "New World" (Latin America). Most of the Old World species cause benign cutaneous disease, New World species cause a spectrum of disease, ranging from mild cutaneous disease to severe mucosal lesions (i.e. ML) [10].

The third form, ML, can lead to extensive and disfiguring destruction of mucous membranes of the nose, mouth and throat cavities and can even involve the cartilages. Bolivia, Brazil and Peru are the most involved Countries, accounting for about 90% of all cases [11]. As mentioned above just a small number of New World CL evolves into mucosal forms; in these cases its course is chronic and may be life-threatening. Mucocutaneous lesions are quite frequent complications of the *L. Viannia* complex infections (more commonly manifesting in *L. braziliensis* than in *L. guyanensis* or *L. panamensis* infections), whereas they are not typically seen in *L. Mexicana* complex infections, except (rarely) when *L. amazonensis* is involved [12]. All the *Leishmania* spp responsible for CL and ML, apart from *L. tropica* are zoonotic.

Hematophagous female sand flies (order *Diptera*, family *Psychodidae*, subfamily *Phlebotominae*) of the *Phlebotomus* genus in the Old World, and of the *Lutzomyia* genus in the New World, are the vectors of the disease. Nevertheless, fewer than 50 of the approximately 1000 species of sand flies worldwide are counted as vectors. This could be due to both the inability of some sand fly species to support the development of parasite infective stages in their gut, and to the lack of ecological contact with reservoir hosts [13]. Female sand flies acquire the infective form of the parasite (amastigotes) during blood meals, and transmit the evolved, extracellular, stationary phase, metacyclic promastigotes, to new hosts through another meal. Promastigotes are then phagocytosed by macrophages and related cells (monocytes in the blood and in the remainder of the reticuloendothelial system) in the mammalian host, and transformed to amastigotes [14]. Possible transmission routes other than insects have rarely been reported: placenta, semen, injection needles, organ transplantation, blood transfusion and laboratory-acquired infections [15—22].

However, much attention has recently focused on iatrogenic and preventable causes of leishmaniasis that include the transfusion-transmitted route. In infected human hosts, the overwhelming majority of *Leishmania* organisms reside within reticuloendothelial cells and do not circulate freely in the blood. At the time of blood collection, organisms are present inside monocytes of infected donors. Upon storage at 4 °C, the organisms remain within white blood cells (WBCs) for some time, but could eventually emerge as free amastigotes that may transform into promastigotes, able to survive outside the cell in the stored blood [23].

The evidence of human cases of transfusion transmitted leishmaniasis (TTL) is of interest, especially VL, with clinical features and outcomes similar to those of the natural infection, not only in endemic but also in nonendemic areas [24].

In this paper we reviewed the literature on clinical and non-clinical features of TTL and its impact on transfusion medicine. We researched the PubMed database for the period from 1980 through December 31, 2013, using the words "leishmaniasis," "transfusion," and "blood donor." Articles presenting original data on human cases of TTL were included in our review, as were the review articles.

2. Survival of *Leishmania* spp. *in vitro* and in experimental animals in blood and blood products

In vitro studies have clearly shown that, under general blood bank storage conditions, for at least 25 days post-donation, *L. tropica*- or *L. donovani*-contaminated transfusion blood products must be considered at risk. Packed red blood cells, frozen-deglycerolized red blood cells, platelet concentrate, and whole blood have been reported to be involved. In contrast, no reports on fresh frozen plasma have been published, as would be expected. Intracellular parasites survive longer than stationary phase extracellular promastigotes or free amastigotes. The parasites survive for 25 days as intracellular forms in monocytes in the red blood cell fraction kept at 4 °C, for 35 days in the red blood cell fraction frozen with glycerol, for 5 days in the platelet fraction kept at 24 °C, and for 30 days in unprocessed whole blood left at 4 °C. To define the minimum concentration of *L. tropica* needed to