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Visceral leishmaniasis: an update of laboratory diagnosis

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ABSTRACT

Visceral leishmaniasis, is an infection due to obligate intracellular protozoa of the genus *Leishmania*. There exist two varieties of visceral leishmaniasis, that vary in their transmission aspects: zoonotic visceral leishmaniasis and anthroponotic visceral leishmaniasis. Their clinical features are comparable with several differences. Laboratory diagnosis of visceral leishmaniasis consists of microscopic observation of parasite, culture from appropriate samples, detection of antigen, serological tests, and identification of parasite DNA. In this review, we will discuss the different techniques of diagnosis and the interest of the recent methods such as rapid diagnostic test and direct agglutination test.

1. Introduction

Visceral leishmaniasis (VL), is an infection due to obligate intracellular protozoa of the genus *Leishmania*[1]. Natural transmission of the parasite happens primarily by way of the bite of contaminated female of phlebotome. In the Old World it is represented by the genus *Phlebotomus* but in the New World it is called *Lutzomyia*. Another way of transmission may occur among the intravenous drug abusers by sharing syringes[2]. That parasitic disease is caused by infection by *Leishmania donovani* (*L. donovani*) in the Indian subcontinent as well as Eastern Africa but in the Mediterranean basin, Central Asia and South America it is caused by *Leishmania infantum*[3].

2. Epidemiology and clinical features

It is a health problem of poor and neglected populations. It is

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affecting 79 countries worldwide and accounts 58 000 new cases every year[4]. There exist two varieties of VL, that vary in their transmission aspects: zoonotic VL is transferred from animal to vector to human while anthroponotic VL is transferred from human to vector to human. In the past, humans are occasional hosts and animals, basically dogs, remain the reservoir of the parasite. Zoonotic VL is located in areas of *Leishmania infantum* transmission as opposed to anthroponotic VL which is located in areas of *L. donovani* transmission[5].

After an incubation interval that usually takes between 2 and 6 months, VL subjects present signs and symptoms of persistent systemic infection such as fever, fatigue, weakness, lack of appetite and losing weight as well as parasitic invasion of the blood and reticulo-endothelial system including enlarged lymph nodes, spleen and liver. Generally fever is coupled with rigor and chills and could be intermittent. Fatigue and weakness are compounded by anaemia, which is a result of the persistent inflammatory state, hypersplenism and occasionally by bleeding. The clinical expression of VL is comparable in various endemic areas but there exist some differences. For instance, enlarged lymph nodes are not often found in Indian VL patients while are frequent in Sudanese

VL patients[6,7]. Hyperpigmentation, that probably brought the name kala-azar (black fever in Hindi), only has been mentioned in VL patients from the Indian subcontinent, nowadays this sign is rare and was probably an element of extended infections in the time while efficient treatment was inaccessible. Since the disease developments, splenomegaly could augment, producing abdominal distension and also pain, which can be amplified by a concomitant hepatomegaly. Signs and symptoms of bacterial co-infections that include pneumonia, diarrhea or tuberculosis may confound the clinical representation while initial diagnosis. VL signs generally remain for a few weeks to months before patients find treatment or die of bacterial co-infections, major bleeding or intense anaemia[8].

3. Laboratory diagnosis

Diagnosis of VL in laboratory consists of microscopic direct observation of the parasite, culture from appropriate samples, detection of antigen, different serological tests, and identification of parasite DNA. Until day parasitological method stays the gold standard for the diagnosis VL. Microscopic demonstration of amastigotes in splenic aspirates, buffy coat and also peripheral blood mononuclear cells have been proven to have elevated sensitivities and ideal specificity[9].

3.1. Demonstration and isolation of parasite

The frequently used technique for diagnosing VL was the demonstration of parasites in splenic or bone marrow aspirate. The existence of the parasite in liver biopsy, lymph nodes, or aspirate specimens or the buffy coat of peripheral blood may also be revealed. Amastigotes look like round or oval bodies measuring 2 to 3 μ m in length and are identified intracellularly in monocytes and macrophages. In preparations colored with Giemsa or Leishman stain, the cytoplasm looks pale blue, with a quite large nucleus that stains red. At the same plane as the nucleus, but at a right position, it is a deep red or violet rod-like body known as a kinetoplast[9]. To improve the sensitivity of parasitological diagnosis, antibodies conjugated with fluorescent against surface antigens of the parasite were performed in endemic settings in Spain, Brazil, Italy, Tunisia, and Iran[10].

Culture of the parasite may increase diagnostic sensitivity, however it is laborious, prolonged, and expensive, therefore infrequently employed for clinical diagnosis. Nowadays there exist new techniques of culture increasing sensitivity, like the microculture method. Current improvements concerning this procedure require employing the buffy coat and peripheral blood mononuclear cells[11,12].

3.2. Immunological diagnosis

3.2.1. Non-invasive and rapid methods

Immunological diagnoses are founded on the finding of both leishmania antigens and antileishmanial antibodies in the blood samples. Various serological tests are already produced for VL to substitute parasitological techniques that have been checked out in several endemic regions[13]. Recent serological tests are dependent on four kinds of techniques: ELISA, indirect fluorescent antibody, direct agglutination test and western blot. The sensitivity relies on the assay and its techniques, however the specificity will depend on the antigen instead of the serological test applied[14].

3.2.2. Fluorescent antibody test

The indirect fluorescent antibody test is among the frequently used tests for anti-leishmanial antibody detection employing fixed promastigotes. The test is founded on detecting antibodies, that can be proven in the very initial phases of infection as they are undetectable six to nine months following cure. Titres over 1:20 are significant and higher than 1:128 are diagnostic. In spite of this, there exist a possibility of a cross reaction with trypanosomal sera[15,16]. The indirect fluorescent antibody test demonstrates accepted sensitivity (87% to 100%) and also specificity (77% to 100%)[17,18].

3.2.3. ELISA

Detection of antileishmanial antibodies by means of ELISA is highly frequent, and its sensitivity/specificity largely relies on the antigen employed. Before, ELISA with crude or soluble antigens of promastigotes or amastigotes was applied, however cross reactivity was prevalent resulting in providing it the lowest consideration in diagnosis. With the advancement in technology, numerous recombinant antigens are integrated VL diagnosis with rK39 located on the top of every recombinant antigens (sensitivity: 67%–100%; specificity: 93%–100%)[19].

3.2.4. Direct agglutination test

The direct agglutination test is a semi-quantitative test that employs microtitre plates wherein increasing dilutions of patients serum or blood are combined with stained killed *L. donovani* promastigotes[20,21]. Once specific antibodies are existing, agglutination will be visible over 18 h with the naked eye. This method was already extensively validated in many endemic areas that gave sensitivity and specificity rates of 94.8% and 97.1%[22], respectively.

3.2.5. Rapid diagnostic test

The recombinant K39 protein antigen used in the rapid diagnostic test is accessible, reproducible and low-priced, which is not difficult

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