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Review

Leishmaniasis and autoimmune diseases in pediatric age

M. Nozzi *, M. Del Torto, F. Chiarelli, L. Breda

Paediatric Rheumatology Unit, Department of Paediatrics, "G. d'Annunzio" University, Chieti, Italy

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ABSTRACT

Leishmaniasis is a group of diseases caused by the protozoa Leishmania, endemic in the Mediterranean countries.

Clinical manifestations can be divided into three different forms: cutaneous leishmaniasis, mucosal leishmaniasis and the visceral leishmaniasis, the most severe form which is potentially lethal if untreated.

Immunology and pathogenesis are complex: many different aspects of immune response, resistance and susceptibility to Leishmania have been studied but many others remain to be clarified.

The gold standard in diagnosis of visceral Leishmaniasis is the presence of amastigotes in bone marrow or tissue sections.

Patients can be initially misdiagnosed as having an autoimmune disease because it may mimic diseases like systemic lupus erythematosus, autoimmune hepatitis, dermatomyositis or others disorders.

As in pediatric age the risk of life-threatening complications is very high, leishmaniasis, must be kept in mind to the clinician, in order to avoid wrong diagnosis and an inappropriate immunosuppressive therapy.

1. Introduction

Leishmaniasis is a group of diseases, caused by a protozoan parasite.

Manifestations of this disorder can be divided into three different forms: cutaneous leishmaniasis (CL), characterized by self-resolving local cutaneous lesions, mucosal leishmaniasis (ML) of the oral and upper airways mucosa and the visceral leishmaniasis (VL), very severe form, which is potentially fatal if untreated.

VL may present with both clinical and laboratory autoimmune manifestations and infected patients may be initially misdiagnosed as having an autoimmune disease [1].

Such patients may therefore be treated with immunosuppressive drugs, with the consequences related to their improper use.

Therefore, especially in endemic areas, VL must be excluded before starting immunosuppressive drugs in patients with autoimmune laboratory manifestations. In addition, VL can simulate an acute exacerbation of pre-existing autoimmune disease, therefore VL should be considered in patients with autoimmune disorders who do not respond to immunosuppressive treatment [1].

2. Visceral leishmaniasis: epidemiology, clinical and laboratory features, diagnosis and treatment

VL, also known as kala-azar, is a disseminated infection caused principally by *Leishmania donovani* and *Leishmania infantum* (synonym *Leishmania chagasi* in South America).

Occasionally, *Leishmania tropica* in the Middle East and *Leishmania amazonensis* in South America can produce VL [2].

The zoonotic form is transmitted by the sand fly (Phlebotomus in the Old World and Lutzomyia in the New World), with dogs as the main reservoirs.

Occasional nonvector transmission has also been reported through with human-to-human transmission without an animal reservoir (blood transfusion, sexual intercourse, organ transplants) [3,4].

Abbreviations: CL, cutaneous leishmaniasis; ML, mucosal leishmaniasis; VL, visceral leishmaniasis; PCR, polymerase chain reaction; IFNγ, interferon gamma; IL, inteleukin; TNFα, tumor necrosis factor alpha; RF, rheumatoid factor; ANAs, antinuclear antibodies; AIH, autoimmune hepatitis; RBC, red blood cells; anti-DNAdS, Anti-double-stranded-DNA; anti-Sm, anti-Smith; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome.

* Corresponding author. Address: Department of Paediatrics, University of Chieti, Via dei Vestini 5, 66100 Chieti, Italy. Fax: +39 0871 574831.

E-mail address: manuela.nozzi@gmail.com (M. Nozzi).

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VL has a high mortality and morbidity, especially in tropical countries where this disease is very prevalent because it is a poverty-related disease.

The worldwide prevalence is estimated about 12 million cases with an incidence varying between 0.2 and 0.4 million new cases a year [5].

Classical clinical features of VL include high fever, anorexia, weight loss, hepatomegaly, splenomegaly, pallor, cough and gastrointestinal symptoms [6].

Splenomegaly may be absent in immunocompromised patients or in the early stages of the disease [7].

Because of a severe involvement of reticuloendothelial system, laboratory findings include pancytopenia, ipoalbuminemia and hypergammaglobulinemia with occasionally evidence of liver damage and a significant increase of liver enzymes [8,9].

Diagnosis is based on demographic, clinical and laboratory findings.

The presence of amastigotes (leishman bodies) in bone marrow or tissue sections as splenic smears of lymph node samples is the gold standard in diagnosis of VL.

Other diagnostic procedures include serologic assay, cultivation of the organism and polymerase chain reaction (PCR) assay [10].

The therapeutic options for VL depend on different factors, such as the geographical area of the infection, development of resistance to habitual treatments, malnourishment and concomitant infections [4].

The traditional treatment for VL, introduced in the late 1940s, has been the use of pentavalent antimonials. However, the development of resistance in particular areas of the world, with failure rates of up to 60%, and the potential toxicity of the drug, made it necessary to seek new treatment options.

Thus, since the 1980s, amphotericin B deoxycholate was introduced becoming the first choice treatment.

Oral miltefosine and safe AmBisome along with better use of amphotericin B have been rapidly implemented in the last decade. A combination therapy will substantially reduce the required dose, the duration of drug administration and the occurence of drug resistance [4,11].

3. Pathogenesis: from skin to viscera

Leishmania protozoa lacerates blood vessels during feeding, and parasites are introduced intradermally. So, free amastigotes, detected in the bloodstream, can be directly delivered to visceral organs by blood-filtering organs or infected cells.

Neutrophils are the first cells recruited to the site of the sand fly bite. Infected neutrophils or free parasites are then taken up by dendritic cells and macrophages, which migrate away from the site of the bite.

Actually, the route used by infected cells to reach the visceral organs remains poorly understood [12].

The host macrophage population targeted by Leishmania also differs between cutaneous and visceral species: cutaneous species infect inflammatory monocyte-derived macrophages and dendritic cells, while visceral species infect Kupffer cells, spleen macrophages, and bone marrow macrophages [13,14].

These different macrophage populations express different levels of cell surface molecules, differ in their response to interferon gamma (IFNγ) stimulation, and in their capacity to produce cytokines, activate T lymphocytes, and kill pathogens.

Therefore, cutaneous and visceral species have adapted to replicate in distinct host macrophage environments.

Anyway, no direct comparison of the susceptibility and killing potential of these different macrophage populations during Leishmania infection, has been found [12].

The outcomes of infection are caused by the host immune and nutrition status, the parasite involved and co-infections.

4. Cytokines and leishmaniasis

Immunology and pathogenesis of Leishmaniasis are complex and a large number of genetic and cellular factors have been implicated in mediating resistance and susceptibility.

VL is often associated with altered chemokine expression profiles because Leishmania parasites are able to modify it in host [15].

Findings in the field of immunology of human VL suggest important roles of different cytokines. It is known that infection control requires Th1-differentiation cytokines as interleukin (IL)-12, IL-18, and IL-27, and Th1 cells and macrophage activation.

After infection, rapid hepatic accumulation of chemokines produces a Th-1 response through IFNγ and facilitates parasite clearance by macrophages.

Like IFNγ, IL-12 is also responsible for a protective response, increasing its production.

On the other hand, in the spleen, a dominance of Th2 cytokines sustains parasite persistence. Another important role is played by tumor necrosis factor alpha (TNFα): it has exerting cytotoxic effects on invading pathogens and its receptor TNFR is associated with VL pathogenesis [16].

Nowadays, there is no generalized consensus for the mechanisms of host susceptibility.

Immune response in human CL and VL were associated with an interaction of T helper 1 (Th1)/Th2 cytokines. The major players of this response were IFNγ and IL-4 in case of both VL and CL, while IL-10 emerged as the most potent factor for VL pathogenesis [16].

5. Host status and leishmaniasis

The host genetic background influences the development of disease with impaired immune responses against the parasite [16].

HIV infection is more strongly associated with VL, particularly with signs and atypical clinical presentations, both in cutaneous and visceral infections [17].

HIV increases the risk of VL development in *L. donovani*-exposed populations by several hundredfold, through either decreased resistance to a new primary infection or reactivation of a previous subclinical infection [18,19].

Congenital visceral leishmaniasis was described first in 1926 by Low and Cooke [20]. The course of the disease seems to be identical in congenital transmitted and otherwise acquired kala azar. Most of children develop the disease in the first year of life with fever, pancytopenia, and splenomegaly [21].

However, in congenital cases the route of transmission remains unclear. Most likely the infection occurs during labor via blood exchange from the mother to the child. Transplacental transmission during pregnancy before birth is improbable, because no parasites were found in the organs of an aborted fetus from infected mothers [22].

Malnutrition was identified as a risk factor for severe VL and death, in both children and adults [23].

6. Leishmaniasis and autoimmunity

VL may present with both clinical and laboratory autoimmune manifestations including arthralgia, cutaneous vasculitis, increased titers of rheumatoid factor (RF), antinuclear antibodies (ANAs), presence of cryoglobulins and low serum complement levels [24–26]. Some of VL manifestations are associated with immune responses of the host to Leishmania that mimic autoimmune dis-