Leishmaniasis and autoimmune diseases in pediatric age

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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].
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 [4,14].

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 has been 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 occurrence 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 is 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 TH 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-
eases; besides, autoimmune phenomena, common in Leishmaniasis, might be due to a release of self antigens, caused by protozoa tissue destruction. So, it probably stimulates the autoreactivity and consequently, autoantibody production.

According to other etio-pathogenic hypotheses, these manifestations can be related to polyclonal B-cell activation and altered-regulated and suppressor T cell functions [27,28] or molecular mimicry between Leishmania antigens and host antigens causing cross-reactivity [28,29].

So it is possible that patients with VL can be initially misdiagnosed as having an autoimmune disease (systemic lupus erythematosus, autoimmune hepatitis [AIH] or others) and they could be treated with immunosuppressive drugs, with fatal consequences [30]. Indeed, several reports have been described misdiagnosed as autoimmune diseases and receiving immunosuppressive therapy, particularly anti-tumor necrosis factor agents [31]. Therefore, physicians should keep in mind that VL has to be ruled before starting immunosuppressive treatment, in patients with autoimmune clinical features and laboratory findings.

We performed a literature review to identify all cases of leishmaniasis in children associated with autoimmune diseases.

We identified both pathologies of autoimmune nature associated with leishmaniasis, such as autoimmune hemolytic anemia and cases of infection by Leishmania misdiagnosed as autoimmune diseases, as in the case of AIH or dermatomyositis.

Finally, we analyzed the cases of leishmaniasis associated with rheumatologic pathologies, particularly in juvenile idiopathic arthritis, where this protozoan infection may be a secondary complication usually in patients treated with biologics.

Different cases of children with VL and immune anemia have been reported [32–36]. Since 1930s, it was described leishmaniasis associated to hemolytic anemia [37].

Several studies have demonstrated that erythrocyte life span is shorter during the active phase of the disease [34]. Coombs test positivity is frequent in patients with kala-azar and it suggests a trigger autoimmune mechanism in a multifactorial frame [32].

Various factors are implicated in the pathogenesis of anemia: dyserythropoiesis, sequestration of red blood cells (RBC) in the enlarged spleen, pro-inflammatory cytokines inhibiting erythropoietin synthesis, iron deficiency, immune mechanism and alteration in RBC membrane permeability [38].

Pontes De Carvalho et al., showed in a population study of the endemic area of Rio de Janeiro and the north-east of Brazil, no association between the degree of anemia and erythrocyte-bound IgG and or spleen dimension [39].

On the other hand, a negative direct Coombs reaction does not exclude VL [40].

Alioglu et al. in 2007, described a case of a three year old child who presented with symptoms suggestive of had a Evans syndrome, or the combination of autoimmune hemolytic anemia, autoimmune thrombocytopenia during infection with kala-azar, initially treated with cyclosporine A and oral prednisolone [32].

Due to the partial response to immunosuppressive treatment, a diagnosis of VL was suspected and a second bone marrow aspiration showed Leishmania amastigotes in the histocytes. The patient was diagnosed as having VL and received liposomal amphotericin B with complete recovery after 5 months.

The authors concluded that Pediatricians should consider the probability of VL in children of all ages who present with Evans syndrome especially in geographic areas in which the parasitic infection is endemic [32].

Autoimmune phenomena, especially AIH, are common in VL. Many autoantibodies are formed in kala-azar, even diseases specific one, including ANA, anti double-stranded-DNA (anti-DNAdS), Anti-Smith (anti-Sm), anti-SSA/Ro, anti-SSB/La and many others [28].

Positivity of one or more of these tests with aspecific features, may be misinterpreted as autoimmune disorders, such as in AIH.

In literature several children with VL misdiagnosed as hepatitis have been described [41–48]. Liver involvement, during VL, consisted in pericellular and portal cell infiltration and fibrosis, necrosis, hypertrophy and hyperplasia of Kupffer cells and thrombosis. The pathogenesis of damage is unclear, but it has probably an immunological basis; it can be reversible after treatment [43]. Common laboratory findings in these patients are: pancytopenia, hypergammaglobulinemia, and raised liver enzymes.

Severe presentations, with fibrosis and portal hypertension, are associated with a poor diagnosis, throughout the world, not only in endemic areas [43].

As in other autoimmune diseases, Leishmaniasis should be excluded in order to avoid fatal consequence, once introduced an immunosuppressive therapy.

Sciveres et al. in 2009, described a 5-year old boy, treated with high-dose methylprednisolone and cyclosporine, after an AIH diagnosis. The patient, suddenly developed a fungal interstitial pneumonia. So, cyclosporine was stopped and fluconazole started.

After a bone marrow smear showed amastigotes. Finally the patient was treated with pentava- lent antimony derivative [49].

Authors emphasized that this is the first case of dermatomyositis due to Leishmania.

Later, other authors suggested that Leishmaniasis may present with atypical or unusual feature that mimics rheumatic diseases [50].

As discussed in other diseases, even in juvenile idiopathic arthritis (JIA), cases of misdiagnosis have been described, and proved over time Leishmaniasis, especially for the systemic onset JIA. Galanakis et al. and Löhrl et al., described two different cases of children with a diagnosis of JIA unresponsive to treatment [51,52].

In both cases, the suspicion of Leishmaniasis was confirmed by a positive bone marrow aspiration. VL, in systemic JIA children may perfectly mimics and causes a very serious complication, known as Macrophage Activation Syndrome (MAS) [53,54].

Infections are the most frequently complications in patients receiving anti-cytokine-therapy with increased risk of tuberculosis and fungal infection.

Many cases of Leishmaniasis have also been reported in children treated with biologics such as anakinra, an IL-1RA agonist [53,55] or anti TNF-alpha treatment, Infliximab [56,57]. These patients were subsequently successfully treated with anti-Leishmania drugs.

7. Conclusion

Leishmaniasis is one of the most lethal tropical disease; its pathogenesis is complex and still not well known. Many different aspects of immune response to Leishmania have been studied and many others remain to be clarified.
Therapeutic and prophylactic strategies targeted at chemokines and their receptors will provide an area for research. Leishmaniasis and particularly VL may present with clinical and laboratory manifestations suggestive of autoimmune disease and causing misdiagnosis. Experts suggest to consider always VL in the differential diagnosis of autoimmune diseases and in particular, to screen VL in patients before starting therapy. This is particularly true in children, where the effects of an inappropriate therapy could even prove fatal.

References
