Visceral leishmaniasis in a 10-month-old Austrian girl Epidemiological Aspects and Treatment Strategies with review of the Literature

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Abstract

Background: Visceral leishmaniasis is prevalent in India, western and eastern parts of Africa, Central America and Brasil, but also in the mediterranean area. In the latter region mainly infants and preschool children as well as immunocompromised patients are affected and Leishmania donovani infantum is the etiologic agent. So far there are only rare reports of probably indigenous cases in central Europe.

Case report: A 10-month-old girl from southern Austria was admitted because of protracted fevers, paleness and hepatosplenomegaly after insect stings acquired at home and during vacation at the Italian Riviera. Laboratory evaluation revealed pancytopenia with marked anemia as well as elevated inflammatory parameters, LDH, AST, protein and gammaglobulin. Bone marrow cytology and positive serology confirmed the diagnosis of visceral leishmaniasis.

Treatment with liposomal Amphotericin B (5 mg/kg/day i.v. from day 1 to 5 and on day 10) was well tolerated and resulted in rapid clinical improvement with normalisation of lab values and clearance of the parasites from the bone marrow.

Conclusion: In case of fever, hepatosplenomegaly, pancytopenia and suggestive travel history visceral leishmaniasis should be considered. In this case the possibility of transmission in southern Austria cannot be excluded. Treatment with liposomal Amphotericin B is safe and highly effective.

Keywords: Visceral Leishmaniasis; Epidemiology; Therapeutic options; Liposomal amphotericin B

Introduction

Leishmaniasis is a parasitosis caused by subspecies of trypanosomes of the Leishmania genus. Animals (dogs, rodents) and humans act as hosts; the main carriers are female sandflies of the genus Phlebotomus. The visceral form occurs mainly in India ("Kala-Azar"), parts of West and East Africa, Central America and Brazil. However, visceral leishmaniasis is also observed throughout the Mediterranean region with an incidence of around 1000 cases per year - particularly in infants and small children and increasingly also in immunocompromised patients [1-4]. In Central Europe, leishmaniasis has so far mainly been described as an imported infection. (16:18).

Case Report

The girl from Carinthia in Austria presented at the age of 10 months
because of subfebrile temperatures and pallor that had existed for 10 weeks but general condition was hardly affected. The pediatrician diagnosed mild hepatomegaly and pronounced splenomegaly. The laboratory values collected on admission to the hospital were: leukocytes 6,200/µl with a left shift (5% metamyelocytes, 15% rod nuclei, 15% segmental nuclei, 62% lymphocytes - CD4/CD8 ratio 1.6), hemoglobin 5.8 g/dl (reticulocytes 56%), platelets 77000/µl; CRP 52 mg/l, ESR 140 mm/1h, LDH 694 U/l, AST 38 U/l, CHE 1658 U/l, total protein was increased to 9.1 g/dl due to polycyonal gamma globulin increase of 46.5%. Albumin was slightly decreased. Bilirubin, ALT, gamma-GT, other organ-specific and metabolic laboratory parameters as well as haptoglobin and osmotic erythrocyte resistance were within the normal range. Bone marrow examination revealed hypercellularity with increased erythropoiesis and granulopoiesis and evidence of numerous parasites in reticulum cells characteristic of Leishmania. The diagnosis was serologically confirmed by a titer of 1:256 in the IIIF against Leishmania donovani antigen. Extended anamnesis revealed frequent visits to Hot Springs in Villach (Carinthia, southern part of Austria) from the 4th week of life with numerous insect bites, as well as a stay on the Italian Riviera at the age of 2 months with no proximity to sandy beaches, application of insect repellent and only a few remembered insect bites. Treatment with liposomal amphotericin B (AmBisome®) at a dosage of 3 mg/kg/day on the first two days and 5 mg/kg/day from the 3rd to 5th day of treatment, each as an infusion over 1 hour with a further dose (5 mg/kg) on day 10 was without significant side effects. Apart from a temporary worsening of the anemia up to 4.6 g/dl Hb with need for one red blood cell transfusion and subsequent iron substitution, the therapy led to a rapid improvement in the symptoms. Persistent defervescence was recorded after 2 days, normalization of CRP after 9, AST and LDH after 12 days. No parasites were detectable in the bone marrow smear 2 days after the end of therapy. The leishmania titer decreased parallel to the increased total protein within 3 months to <1:16. Liver and spleen size slowly decreased, reaching normal sonographic values after 4 months. At the same time, the child had also finally recovered from the anemia. 9 months after the start of therapy, the patient had developed according to her age and was also clinically normal during further pediatric check-ups up to the age of 7.

Discussion

About 3 million people worldwide are affected by visceral, cutaneous or mucosal leishmaniasis. Transmission to humans occurs primarily through sand flies of the genus Phlebotomus from dogs or rodents. The pathogens multiply exclusively in mononuclear phagocytes. The visceral form occurs mainly in India (L. donovani donovani), from where the term "Kala-Azar" (black disease) comes; more than half of the global disease burden affects the Indian province of Bihar. The peak of the disease is in school age. Less commonly, visceral leishmaniasis is observed in parts of East Africa, West Africa, Central America, and Brazil. In the entire Mediterranean area (L. donovani infantum), the disease occurs with an incidence of approx. 1000 cases per year, with small children being particularly affected and, in recent years, increasingly people infected with HIV [2-4]. In Central Europe, leishmaniasis has so far mainly been described as an imported infection [5, 6]. Individual reports of presumably autochthonally acquired diseases in humans [7-10] and animals are consistent with isolated occurrences of sandflies north of the Alps, although there are still no reliable findings in Austria. It is most likely introduced by Leishmania-infected dogs – often brought illegally – from the Mediterranean region [1, 11]. There may also be connections with changes in the Central European climate within the framework of the global Warming [12].

Clinical Picture

The disease is often asymptomatic, but manifests itself clinically after an incubation period of 10 days to a year with uncharacteristic general symptoms, long-lasting fever with typical daily double peaks, hepatosplenomegaly with pancytopenia and hypoalbuminemia, and hypergammaglobulinemia. In severe, untreated cases, dysenteric diarrhea, edema, body cavity effusions, hair loss and dry skin with dark pigmentation also occur. In these patients, the disease is usually fatal due to pneumonia, skin and mucous membrane bleeding or exsiccosis. Disease progression appears to be governed by the ratio of Th 1 CD4+ (T helper) cells to CD8+ (T suppressor) cells, with elevated interleukin-10 levels dependent on disease severity [2].

Therapy Options

Treatment of visceral leishmaniasis with amphotericin B deoxycholate is very effective but has significant acute side effects and dose-limiting renal toxicity. So far, the antimony preparations sodium stibogluconate and meglumine antimonate, which have been available since the 1940s and which achieve a treatment success of about 90%, have been considered the substance group of choice despite a long therapy duration of about one month [13]. However, apart from the primary and secondary treatment failures observed in particular in India [14], antimony treatment often leads to side effects, some of which are serious, such as pancreatitis and myelosuppression, as well as dilated cardiomyopathy and cardiac arrhythmias, sometimes with fatal outcomes [14, 15]. Fatal cases of cardiotoxicity have been described, particularly under combination treatment with antimone and amphotericin B. A “wash out” phase of at least 10 days between the two substances is therefore recommended [16]. Although the combination of antimony and allopurinol
has a synergistic effect in vitro, it did not provide any clinical advantage over monotherapy [17]. Combination of antimonene with IFN-γ brought only a modest improvement in the effect [18]. While the administration of granulocyte-macrophage-colony-stimulating factor (GM-CSF) reduced the frequency of secondary infections due to a more rapid increase in leukocytes [19]. Neutralization of IL-10 resulted in significantly accelerated parasitic clearance from the spleen in a recent study [20]. A broad application of these substances in the main endemic areas has not been achieved yet due to their high price. The aminoglycoside paromomycin represents an inexpensive but not yet sufficiently available alternative therapy for endemic areas. Daily IM injections of 11 mg/kg over 21 days showed clinical healing in 99.6% and 94.2% after 1 and 6 months. Although shorter treatment cycles over 14 days are inferior in terms of long-term effectiveness, they are considered a valid basis for combination therapies, also with regard to the possible development of resistance. Mild local and hepatic side effects occurred in up to 5%, nephrotoxicity was not observed [21, 22]. The advantages of therapy with liposomal amphotericin B (AmBisome®) in visceral leishmaniasis are, on the one hand, the significantly superior effectiveness, even in the case of antimony resistance [23] with a significantly shorter duration of therapy compared to amphotericin B deoxycholate and antimonene, but in particular also the significantly reduced toxicity due to accumulation of the substance at the site of action [2, 3, 24-26]. The present data also show a superior efficacy/side effect profile compared to other lipid formulations of Amphotericin B, Amphotericin B Lipid Complex (Abelcet®) and Amphotericin B Colloidal Dispersion (Amphocil®) [2, 27]. Furthermore, the high amphotericin B tissue levels that can be achieved counteract the emergence of resistance, which is rarely observed in clinical isolates but is reproducible in vitro [28]. The significantly higher price of liposomal compared to conventional amphotericin B with, however, only a short duration of therapy and smaller amounts of substance for pediatric patients should be noted. Almost 100% healing success has been achieved with liposomal amphotericin B in visceral leishmaniasis from a cumulative dose of 20 mg/kg in various administration schedules for up to 10 days [24]. In an Indian study, a single infusion of 10 mg/kg liposomal amphotericin B proved to be equally effective and, due to the short inpatient treatment, even cheaper than standard therapy with amphotericin B deoxycholate [29]. A remarkable new development is a highly effective, absorbable oral formulation of amphotericin B with low toxicity in animal experiments [30]. In our patient, treatment with 5 mg/kg/day per infusion from day 1 to 5 and on day 10 had no significant side effects and led to clinical improvement within 2 days with rapid normalization of laboratory values and disappearance of the parasites from the bone marrow within of 12 days. The consistently good general condition and the rapid response to the specific therapy were consistent with the patient's favorable immunological situation, particularly with regard to the lymphocyte subpopulations. Most enterally resorbable substances with activity against Leishmania (allopurinol, metronidazole, ketoconazole, fluconazole, itraconazole and terbinafine) are clearly inferior to the established parenteral preparations in the treatment of visceral leishmaniasis [2, 31].

Increasing antimony resistance in Leishmania, toxicity and complex (inpatient) administration of antimony and amphotericin deoxycholate, as well as the high price of liposomal amphotericin B [32] led to clinical testing of the orally administrable, cell membrane-active, alkylated phospholipid, which was primarily developed in Germany as a cytostatic agent Miltefosine [33]. In Indian follow-up studies, healing rates of 94% (comparable to standard therapy with amphotericin B) were achieved with doses of 100-150 mg daily in adults and 2.5 mg in 2- to 11-year-old children, so that Miltefosine in the years 2004 as the first oral substance for the treatment of visceral leishmaniasis [34]. Gastrointestinal side effects in about 3% of patients and (due to teratogenicity) exclusion of pregnancy before and strict contraception during treatment with miltefosine should be noted [35, 36]. Another indication for miltefosine is maintenance therapy or prevention of recurrence in HIV patients with visceral leishmaniasis [37]. Due to the expected resistance to miltefosine with widespread oral use, combination therapies with liposomal amphotericin B [38] and with paromomycin [39] have already been successfully tested in studies. In general, it should be noted that data on the efficacy of substances effective for leishmania collected in India may be pathogen-related and therefore cannot be transferred with certainty to the Mediterranean region or Europe.

Conclusions

Visceral leishmaniasis is a disease that is rarely observed in Central Europe, although transmission in southern Austria cannot be ruled out in the case described. In the case of fever, hepatosplenomegaly and pancytopenia, especially with a corresponding travel history, leishmaniasis should be included in the differential diagnosis.

Treatment with liposomal amphotericin B is effective and offers clear advantages over treatment with antimony preparations, conventional amphotericin B or paromomycin in terms of duration of treatment, spectrum of side effects and development of resistance. Miltefosine is the first available oral drug with good efficacy and acceptable toxicity for the treatment of visceral leishmaniasis.

References


