

CASE REPORT

Common symptoms, rare diagnosis – paediatric visceral leishmaniasis in a non-endemic region

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ABSTRACT

We hereby present a case of a 5-year-old Polish girl suffering from visceral leishmaniasis (VL) – a worldwide-spread parasitic disease. Due to persistent fever and hepatosplenomegaly, the patient was initially diagnosed with juvenile rheumatoid arthritis. Ineffective treatment of the disease led to repeated inspection of bone marrow, which was analysed in 3 laboratories in Poland, with only one correctly recognising the parasite infiltration. Detailed history revealed traveling to regions endemic for *Leishmania* spp. in the Mediterranean Sea Region and South America, visited between 3 months – 3.5 years before the onset of the disease. The final diagnosis of the disease was based on bone marrow aspiration and a polymerase chain reaction blood test. Pentavalent antimonial therapy was successfully administered. The case report presents the difficulties in diagnosing VL in a non-endemic country and provides a review of the current literature on the management of VL in children.

KEY WORDS:

paediatrics, visceral leishmaniasis, non-endemic region, pentavalent antimonial.

CASE REPORT

A 5-year-old girl with a history of fever of unknown origin and hepatosplenomegaly was admitted to the Paediatric Rheumatology Unit with suspicion of systemic-onset juvenile rheumatoid arthritis (JRA). The girl was previously hospitalised in the Department of Children Infectious Diseases, where common infections were excluded. To date, there were no chronic diseases in the patient's history. Family history was burdened with rheumatoid arthritis, which the girl's grandmother suffered from.

At admission, a physical examination revealed pallor and local skin redness, palpable cervical lymph nodes, and hepatosplenomegaly.

The laboratory tests showed leukopaenia (WBC 3.32 K/u/l), low CRP and procalcitonin, slightly increased ESR, hypergammaglobulinaemia, elevated liver enzymes (ALT 295 U/l, AST 200.4 U/l, GGTP 39 U/l, LDH

1056,3 U/l), hypertriglyceridaemia (2.29 mmol/l), and high ferritin level (3.4 g/l). The tests did not reveal immunodeficiency nor alterations in the rheumatoid panel test (HLA B27, HLA Cw6, aCCP, RF, ANA, AMA-M2, LC-1, and SLA/LP were negative).

The abdominal ultrasound confirmed hepatosplenomegaly with hypoechogenic homogenous (7–10 mm) focal changes located in the spleen.

The bone marrow aspiration excluded a proliferative process, and there was no suggestion of parasite disease.

Blood and urine cultures were negative. Among viral polymerase chain reaction (PCR) tests only HHV-7 was positive. Moreover, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, cytomegalovirus, *Toxoplasma gondii*, *Bartonella henselae*, *Y. testis*, and *Mycobacterium* spp. infections were excluded. Among serological tests, antibodies to EBNA (Epstein-Barr virus nuclear antigen) were positive.

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The girl was first diagnosed with systemic onset of JRA with lymphoproliferative changes and elements of macrophage activation syndrome (MAS) associated with HHV-7 infection in accordance with the 2016 criteria of MAS/juvenile idiopathic arthritis [1]. After introduction of a remission-induced dose of corticosteroids (2 mg/kg body weight), a temporal improvement with a demission of fever and reduction of hepatosplenomegaly was observed. The inflammatory markers decreased.

A reduction of the steroid dose (to 1.3 mg/kg body weight) resulted in a recurrence of symptoms and progression of hepatosplenomegaly. Moreover, deterioration of liver function was noted (ALT 987 U/l, AST 355 U/l, GGTP 69 U/l, LDH 785.4 U/l). A differential diagnosis excluded metabolic diseases (Gaucher disease, Niemann-Pick disease, Wilson disease). Because the intensive immunosuppressive treatment did not result in clinical and laboratory improvement, a second bone marrow aspiration was carried out. The material was checked in terms of the immunophenotype and possible parasite infiltration because the girl had travelled to the Mediterranean Sea Region and South America before the onset of the disease. The biopsates were sent to 3 different laboratories. The examination did not reveal alteration characteristics for parasite invasion in 2 of the laboratories. The third laboratory at the Department and Clinic of Tropical and Parasitic Diseases in Poznan confirmed the presence of macrophages filled with inclusions typical of *Leishmania* spp. – amastigotes in the bone marrow (Figs. 1, 2). Moreover, *Leishmania* parasites were detected in the blood via real-time PCR.

After consultation with the Voivodeship Tropical and Parasite Diseases Consultant, treatment with 28-day infusions of pentavalent antimonial – meglumine antimoniate, in a dose of 20 mg/kg body weight was administered. During the therapy the girl suffered from tachycardia, which demanded propranolol therapy. At the same time, regression of all clinical and biochemical symptoms of visceral leishmaniasis (VL) was noted. The follow-up showed no complications, and the girl completely recovered.

DISCUSSION

Visceral leishmaniasis, also known as kala-azar, is the most severe form of leishmaniasis – one of the top parasitic diseases around the world with outbreak and mortality potential [2]. *Leishmania* parasites, for which domestic and feral mammals as well as human beings are a reservoir, are spread via bites of infected sandflies (*Phlebotomus* in the Old World and *Lutzomyia* in the New World) [3]. The range of the disease covers the Americas, the Mediterranean Basin, the sub-Saharan Region and East Africa, the Middle East, and Central and Southeast Asia, and concerns mostly neglected and immunocompromised patients [4]. According to the World Health Organisation an estimated 50,000–90,000 new cases of VL occur worldwide annually, with only between 25–45% being reported. A total of 12,739 cases were aggregated in 2020, with 200 in Europe, while there were 6018 in 2021, with 17 in Europe. The reduction in the numbers of reported VL can be attributed to COVID-19 pandemic-related disruptions in surveillance activities. The data that concerns the prevalence of VL in the worldwide paediatric population is scarce and imprecise [5–9].

Having reached the age of 5 years at the end of the treatment, the patient was just above the group of children aged 1–4 years – the most vulnerable in their population [9]. Susceptibility to VL can result from an immature innate immune response, lack of prior exposure, and acquired immunity as well as higher rates of malnutrition among children in comparison to adults [10]. The incubation period of the disease typically ranges 2–6 months; however, it can develop up to several years after the primary parasite invasion [11]. Therefore, in the case of the patient, the infection could have been acquired during a holiday in the Mediterranean Basin (Croatia, Spain, Italy) or South America (Colombia, Brazil) visited between 3 months – 3.5 years before the onset of the disease, where the girl was exposed to sandfly bites. The beginning of VL is usually gradual with pallor, intermittent fever, hepatosplenomegaly, and

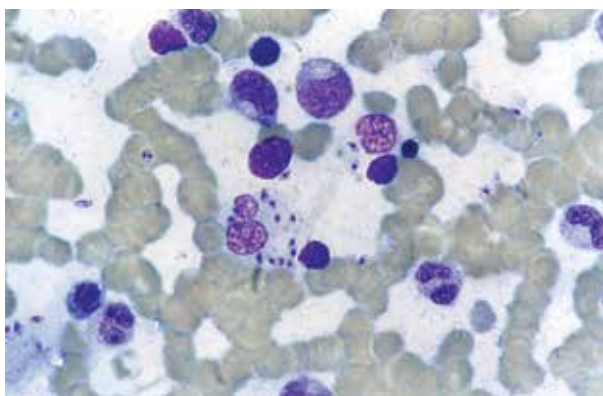


FIG. 1. Macrophages infected with *Leishmania* amastigotes captured in the bone marrow aspirate

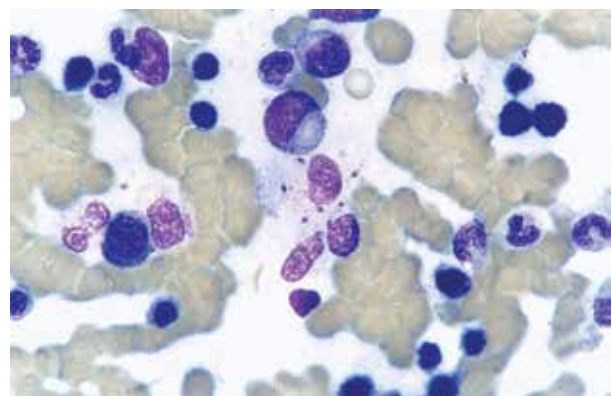


FIG. 2. Macrophages infected with *Leishmania* amastigotes captured in the bone marrow aspirate

appetite loss as the most frequent symptoms [8, 12, 13]. The first 3 of them were observed in the presented patient. The predominant laboratory alterations include anaemia, thrombocytopaenia, elevated inflammatory markers, and hypergammaglobulinaemia [8, 12]. At admission to the hospital, only the last symptom was noted in our patient. Although VL is well known in tropical and subtropical parts of the world, in non-endemic regions it remains a diagnostic challenge for medical staff unfamiliar with tropical diseases. In such countries, including Poland, VL is rarely considered in differential diagnosis of JRA. In the paediatric population symptoms such as recurrent fever, hepatosplenomegaly, and pancytopenia can occur in common infectious diseases as well as oncological, metabolic, and connective tissue diseases.

In the case of the current patient, VL mimicked a connective tissue disease with infiltration of the reticuloendothelial system. The applied JRA corticosteroid therapy induced immunosuppression, which resulted with bone marrow involvement of *Leishmania spp.*, a lack of post corticosteroids leukocytosis, and further hepatotoxicity. This outcome prompted a renewed analysis.

The following methods can lead to the diagnosis of VL: visualisation of the characteristic amastigotes in smears or tissue, parasite culture isolation, molecular detection (PCR), and serologic testing [11, 14]. Out of the definitive ways of diagnosing VL, microscopy of bone marrow aspiration is considered the preferred first source of diagnostic sample [14]. Thus, a second bone marrow sample was collected and sent to 2 additional laboratories, both having more experience with parasitic diseases than the first one. Its examination did not reveal alterations specific to *Leishmania spp.* infiltration in 2 different facilities; simultaneously, such changes were found in the Clinic of Tropical and Parasitic Diseases in Poznań. The disagreement could be attributed to differences in the laboratory equipment and staff familiar with detecting *Leishmania spp.* In non-endemic countries the ability of recognition is often limited by the availability of tests and the experience of medical staff. Therefore, such inter-centre cooperation is essential for the diagnosis of tropical diseases. Moreover, bone marrow aspiration for *Leishmania spp.* detection has specificity and sensitivity that range 52–85%, making false negative results not just likely but probable, which is consistent with the outcomes of the tests performed in this case [11, 14, 15]. Even though PCR is the most sensitive and specific diagnostic approach and reaches 100% in terms of detection of *Leishmania* parasites, it is not recommended for first-line testing for VL. This is because of lack of standardisation of the assay/target and undefined performance characteristics [14, 16].

In immunocompetent patients with VL, liposomal amphotericin B (3 mg/kg/day IV on days 1–5, 14, and 21, total dose, 21 mg/kg, Food and Drug Administration) is

the preferred treatment in Europe, and North and South America. It is a drug with the highest therapeutic efficacy and the most favourable safety profile [17]. According to the Infectious Diseases Society of America and the American Society of Tropical Medicine and Hygiene, in areas where the prevalence of antimony-resistant *Leishmania* species is low (< 10%), pentavalent antimonial (20 mg SbV/kg/day IV for 28 days) can be used as an alternative cure in immunocompetent patients [14]. The Voivodeship Tropical Medicine Consultant, who made the correct diagnosis, recommended the use of antimonial therapy, based on her previous experience. The drug was used accordingly, and the treatment was well tolerated by the girl. Apart from temporal tachycardia, no side effects of the therapy were noted.

To date, apart from 2 published cases, there are no official data about Polish instances of imported VL in children available [18, 19]. In both children the disease was probably acquired during a holiday in the Mediterranean Sea Region (Croatia, Bosnia and Herzegovina, Turkey). Systemic infection, acute leukaemia, and metabolic and connective tissue diseases were initially suspected. Both patients were successfully treated with liposomal amphotericin B.

Interestingly, according to the official data collected by the Main Statistical Department, 6 out of 10 outbound tourist trips of Polish residents for leisure, recreation, or holidays in 2022 were endemic to VL (all of them located in the Mediterranean Region) [20]. Indeed, we identify 26 countries endemic to VL in this region, which together contribute 5–6% cases to the global burden of VL, with an estimated annual incidence of 1200–2000 instances [21]. Between 2003–2008, Morocco, Italy, and Spain reported nearly 50% of cases from the region [4]. As traveling resumes post-pandemic, we foresee a slowly growing number of Polish cases of imported parasite infections, particularly from the region of the Mediterranean Sea Basin. In the absence of effective vaccines or chemoprophylaxis for leishmaniasis prevention, personal protective measures such as insect repellents, adequate clothing, and limiting activity during dawn and twilight should be recommended to reduce exposure to sandfly bites [7, 10].

Finally, as we look further into the future, let us note that VL prevalence is influenced by the geographic dispersion of its vectors – sandflies, which require high temperatures, adequate precipitation, and moisture for their development and survival. Such conditions are mainly found in tropical and subtropical regions [22, 23]. In the Mediterranean Basin, *L. infantum* is the main causative agent, while dogs are the most important reservoir. Prior to 2019, there were no species of *Phlebotomus* reported in Poland [24]. Global warming as well as environmental changes such as deforestation, water distribution modifications (dams, irrigation strategy), urbanisation, and people's migration affect the distribution and spread of VL [2]. According to

ecological niche modelling based on climatic variables, most of the sandfly species reported in the Mediterranean Region are expected to expand their ranges towards the north of Europe, albeit not until the period between 2061–2080 [23]. Thus, the result might be a higher risk of transmission of leishmaniasis, also in Poland, which will require close monitoring in the future.

CONCLUSIONS

In non-endemic regions, including Poland, VL is a life-threatening disease, directly connected with more and more frequent travels to regions indigenous for *Leishmania spp.* In these geographical locations, the disease is often undiagnosed, forgotten, and not included in the differential diagnosis by medical staff not considering a tropical aetiology. Furthermore, due to a potentially very long incubation period and nonspecific symptoms, it is clinically indistinguishable with haematological syndromes. The latter are notably not associated with past travels taken months and years before the onset of the disease. Thus, clinicians should be aware of endemic regions and possible routes of transmission of VL, collecting a wide medical history covering an adequate period. In combination with specific tests, these can be the first steps for recognition of visceral leishmaniasis. If a patient has a history of traveling, a common factor in the era of unrestricted tourism, VL should be considered as one of the top diseases to exclude in terms of recurrent fever in combination with splenomegaly with bone marrow suppression and macrophage activation.

The first line treatment is amphotericin B, although pentavalent antimony can be an alternative drug with high efficacy in non-endemic countries.

DISCLOSURES

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