

Atypical Manifestations of Visceral Leishmaniasis in Children

Estibaliz Valdeolmillos¹, Belén Borrell¹, Francisco J. Merino², Begoña Corral³, Cristina Calvo^{1,*}

¹Department of Pediatrics, Severo Ochoa Hospital, Leganés, Madrid, Spain

²Department of Microbiology, Severo Ochoa Hospital, Leganés, Madrid, Spain

³Department of Radiology, Severo Ochoa Hospital, Leganés, Madrid, Spain

*Corresponding author: ccalvorey@ono.com

Received August 17, 2015; Revised September 17, 2015; Accepted October 08, 2015

Abstract Visceral leishmaniasis (VL) or kala-azar is an endemic parasitic disease caused predominantly, in its Mediterranean type, by *Leishmania infantum*. Fever and splenomegaly are the most common clinical manifestations, detected in more than 80% of patients. We present two cases with atypical manifestations, without fever and with spleen nodules in the context of an outbreak of VL in Spain.

Keywords: visceral leishmaniasis, infants, splenomegaly, spleen nodule

Cite This Article: Estibaliz Valdeolmillos, Belén Borrell, Francisco J. Merino, Begoña Corral, and Cristina Calvo, "Atypical Manifestations of Visceral Leishmaniasis in Children." *American Journal of Medical Case Reports*, vol. 3, no. 11 (2015): 359-261. doi: 10.12691/ajmcr-3-11-3.

1. Introduction

Visceral leishmaniasis (VL) is a severe systemic disease caused by *Leishmania donovani*, complex pathogenic protozoa. It has a global annual incidence between 0.2 and 0.4 million cases. It characteristically affects immunocompetent hosts from endemic areas, but occasionally can affect immunocompromised patients [1]. The Mediterranean type of VL is mainly caused by *Leishmania infantum* that frequently infects infants and young children. Dogs are the main reservoir of leishmaniasis in *L. infantum* transmission areas [2].

VL in children characteristically presents with high fever, pancytopenia and progressive splenomegaly, although it may appear more insidiously with intermittent fever, pallor, weight loss and development of splenomegaly which is evident only around a month after the onset of symptoms [3]. Its course is usually fatal without treatment. However, VL not always presents with these typical symptoms, making diagnosis difficult unless a high index of suspicion is taken.

During the last years, there has been an outbreak of cutaneous and visceral leishmaniasis in the south-west area of Madrid (Spain). Its origin appears to be associated with an increased population of wild hare (*Lepus granatensis*) in nearby parks. These hare are infected with *L. infantum*, and act as a reservoir. From July 2009 to December 2012, 542 cases of leishmaniasis were reported in Madrid, being 30% of VL. 12% of the VL cases had atypical presentations, mainly in adults [4]. Out of the total, 15 cases were infants under 1 year of age (11 with visceral leishmaniasis and 4 with cutaneous leishmaniasis)

and 8 cases were aged between 12 and 23 months (7 with visceral leishmaniasis and 1 with cutaneous leishmaniasis).

In this context, we report two cases of atypical LV in infants.

2. Case 1: Afebrile VL in a 14 Month-old Infant

A 14 month-old female, previously healthy, was referred to our Hospital following pallor and splenomegaly for 20 days. She had no history of fever, bleeding tendency, and gastrointestinal or respiratory symptoms. She was native to Southern area of Madrid (Leganés). Parents were from Morocco. She had never traveled outside Spain. She had no domestic animals and no bites were observed. On physical examination her vital signs were within normal range. She had splenomegaly without hepatomegaly.

Her primary laboratory data revealed microcytic anemia, mild leukopenia and transaminases mildly increased. Immunoglobulins and coagulation parameters were within normal limits. Serology was negative for Mononucleosis-like syndromes. Abdominal ultrasonography revealed a markedly splenomegaly of 115 mm without hepatomegaly or any other lesions.

Specific anti-leishmanial antibodies, detected by indirect fluorescent antibody test (IFAT), were at titers of 1:320. Detection of leishmania antigen in urine was positive. A specific polymerase chain reaction (PCR) for *Leishmania* spp. was then performed on blood (Laboratory of Leishmaniasis, National Center of Microbiology, Instituto de Salud Carlos III. Madrid) by technique previously validated and published [5],[6], and

showed the presence of protozoan DNA, confirming the diagnosis of VL.

The patient started treatment with liposomal amphotericin B (4 mg/kg in 6 doses). Gradually, anemia, hypertransaminasemia and splenomegaly were resolved. Notably, the patient remained afebrile throughout the whole process. Six months after the treatment the patient remains without fever or splenomegaly and blood test also are normal. Clinical and analytical data before and after treatment are shown in Table 1.

3. Case 2: Multiples Splenic Nodules in Afebrile VL

An 8-month-old male, previously healthy, admitted with pallor and hepatosplenomegaly for 1 month. He had no history of fever or others symptoms.

Laboratory test showed increased transaminases and microcytic anemia. Serological studies for Mononucleosis-like syndromes yielded negative results.

Abdominal ultrasonography revealed a marked splenomegaly with diffuse multifocal hypoechoic nodules, of a maximum diameter of 9 mm (Figure 1).

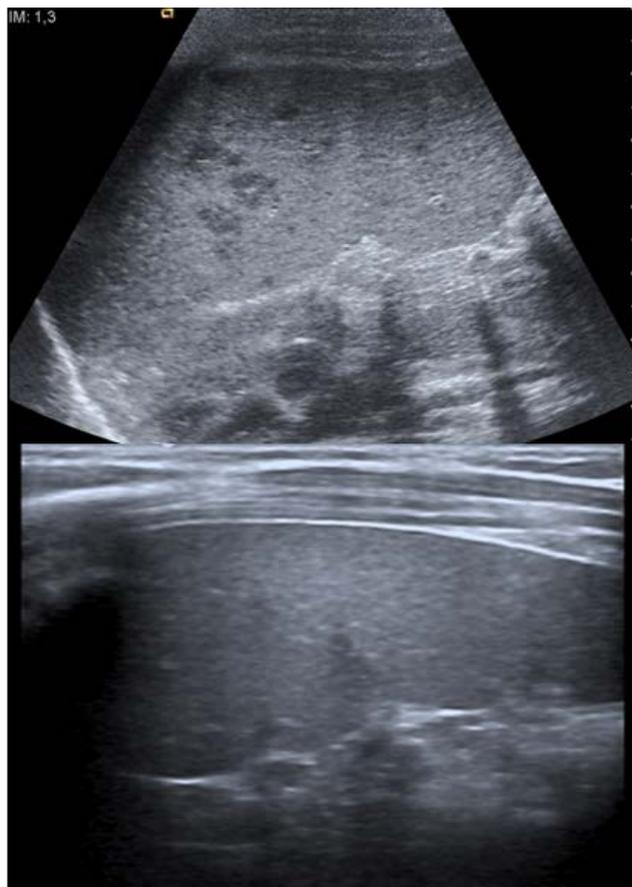


Figure 1. A 8-month-old male with visceral leishmaniasis. Upper: transverse sonogram of the spleen shows multiple hypoechoic nodular lesions; the largest one measuring 9 mm. Down: sonogram of the same patient one year later shows a normal spleen

Serological assays were performed and detected anti-leishmanial antibodies by IFAT with titers of 1:320. Detection of leishmania antigen in urine was negative. A PCR for *Leishmania* spp. was performed (National Center of Microbiology) on bone marrow aspirate and was

positive for the presence of protozoan DNA, confirming the diagnosis of VL. Treatment with liposomal amphotericin B (4 mg/kg in 6 doses) was also started.

Hepatosplenomegaly was resolved in the following weeks and hepatic markers as well decreased gradually. Finally, spleen nodules completely resolved after 5 months. The patient remains asymptomatic one year after the resolution. Clinical data before and after treatment are also shown in Table 1.

Table 1. Clinical data of the patients before and after treatment

	Caso 1		Case 2	
	Before	After	Before	After
Hemoglobin g/dL	8.3	12.9	8.7	11.4
Leukocytes/mm ³	9620	10980	5830	8460
AST U/L	78	37	72	35
ALT U/L	110	15	85	16
ERD mm/h	65	5	38	5
Serology	1/320	-	1/320	1/80
PCR	+	-	+	
Splenomegaly	++		++	

AST: aspartate aminotransferase, ALT: aspartate aminotransferase, ERD: erythrocyte sedimentation rate, PCR: polymerase chain reaction.

4. Discussion

Delays in the diagnosis of VL are frequent due to the absence of specific symptoms, the variability of incubation time and, most likely due the low level of awareness of the disease among pediatricians. The difficulty of microscopic identification in bone marrow smears, and negative results on serological tests in the early stage of the disease may further hinder early diagnosis [7]. Fortunately, the introduction of PCR techniques in both blood and bone marrow aspirate, have greatly facilitated the diagnosis of infection in developed countries. In fact, PCR positivity in blood allows diagnosis without performing a bone marrow aspirate, which otherwise would be essential for confirmation of the infection.

An epidemic outbreak of leishmaniasis, causing an increase in incidence from 1.5 / 100,000 to 22.2 / 100,000 took place in the southern part of Madrid during the period 2009-2013. This outbreak has been linked to the presence of wild hares in the area which have been described as the parasite's reservoir [8]. The risk of VL transmission in our child population highlights the importance of an increased awareness about the potential presentation of cases with atypical manifestations. This awareness is very relevant both during epidemic situations and in areas where the disease is endemic.

The most common clinical findings are fever, splenomegaly, and anemia. Although fever is the most common symptom may be absent in immunocompromised patients, and subclinical forms, especially in endemic areas, as we have noticed. A case of an immunocompetent 11-month Iranian infant affected of VL without fever has recently been described, with similar characteristics to our patients [9]. Infants are especially likely to have atypical forms, without fever as in our two patients. Pediatricians should always rule out VL in patients with splenomegaly

and cytopenia of any cell line, among other diagnoses such as malignant leukemia or lymphomas, benign tumors or more frequently infectious mononucleosis.

We must be also aware of the possible presence of splenic nodules in patients with VL, because it requires differential diagnosis with other pathologies as type I Gaucher disease, granulomatous disease, bacterial abscess, fungal infection, *Mycobacterium tuberculosis* infection, or lymphoproliferative disorders. Nevertheless, this peculiar finding may not be extraordinary in patients with VL. Case reports of spleen nodules in VL patients have been recently previously described in adults [10,11], but rarely documented in infants [12]. Melchionda [13] in Italy has described 4 children affected with VL, with spleen nodules, although all had persistent fever. They were under 2-years-old and the nodules disappeared after treatment, as it was the case in our patient. In our second case, the presence of spleen nodules in the absence of fever, made the diagnosis of VL especially difficult.

The evolution of patients with treatment was favorable. Although there are other treatment options as conventional amphotericin B, liposomal amphotericin short course has been described effective, safe and with fewer side effects [14]. Treatment with antimonials still having their usefulness in developing countries, but it is very long and has a high cardiac toxicity, which has been clearly shifted.

In conclusion, we must be aware of atypical situations, especially in endemic areas and during epidemic situations. VL should be considered as a potential diagnosis when splenomegaly and spleen nodules are detected, even in the absence of fever. This increased awareness has the potential of detecting underdiagnosed cases of VL, allowing for earlier treatment and better outcome.

Competing Interest

The authors declare no conflict of interest.

References

- [1] Ready PD. "Leishmaniasis emergence in Europe". *Euro Surveill.* 10; 15(10):pii=1950. Available:

- <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19505> PMID:20403308.
- [2] Marty P, Pomares C, Michel G, Delaunay P, Ferrua B, Rosenthal E. "Mediterranean visceral leishmaniasis". *Bull Acad Natl Med.* 195 (1):181-8. Jan.2011.
- [3] Mueller YK, Kolaczinski JH, Koech T, Lokwang P, Riongoita M, Velilla E, et al. "Clinical epidemiology, diagnosis and treatment of visceral leishmaniasis in the Pokot endemic area of Uganda and Kenya". *Am J Trop Med Hyg.* 90 (1):33-9. Jan.2014
- [4] Arce A, Estirado A, Ordobas M, Sevilla S, García N, Moratilla L, et al. "Reemergence of leishmaniasis in Spain: community outbreak in Madrid, Spain, 2009 to 2012". *Euro Surveill.* 18 (30):20546. Jul.2013.
- [5] Cruz I, Cañavate C, Rubio JM, Morales MA, Chicharro C, Laguna F, et al. A nested polymerase chain reaction (Ln-PCR) for diagnosing and monitoring *Leishmania infantum* infection in patients co-infected with human immunodeficiency virus. *Trans. R. Soc. Trop. Med. Hyg.* 96(Suppl. 1):S185-S189. 2002.
- [6] Cruz I, Cañavate C, Rubio JM, Morales MA, Chicharro C, Laguna F, et al. Comparison of new diagnostic tools for management of pediatric mediterranean visceral leishmaniasis. *J Clin Microbiol.* 44(7): 2343-2347. Jul 2006.
- [7] Elmahallawy EK, Sampedro Martinez A, Rodriguez-Granger J, Hoyos-Mallecot Y, Agil A, Navarro Mari JM, et al. "Diagnosis of leishmaniasis". *J Infect Dev Ctries.* 8 (8):961-72. Aug.2014.
- [8] Molina R, Jiménez MI, Cruz I, Iriaso A, Martín-Martín I, Sevillano O, et al. "The hare (*Lepus granatensis*) as potential sylvatic reservoir of *Leishmania infantum* in Spain". *Vet Parasitol.* 190 (1-2):268-71. Nov. 2012.
- [9] Sayyahfar S, Ansari S, Mohebbi M, Behnam B. "Visceral Leishmaniasis without Fever in an 11-Month-Old Infant: a Rare Clinical. Feature of Kala-azar". *Korean J Parasitol.* 52 (2): 181-91. Apr. 2014.
- [10] Mao G1, Yang G, Cheng Y, Zee CS, Huang W, Ni W, et al. "Multiple nodular lesions in spleen associated with visceral leishmaniasis: a case report of MRI-findings". *Medicine (Baltimore).* 93(29):e272. Dec. 2014.
- [11] Bükte Y, Nazaroğlu H, Mete A, Yılmaz F. "Visceral leishmaniasis with multiple nodular lesions of the liver and spleen: CT and sonographic findings". *Abdom Imaging.* 29 (1):82-4. JanFeb. 2004.
- [12] Raeymaeckers S, Docx M, Demeyere N. "MRI-findings of nodular lesions in an enlarged spleen, associated with visceral Leishmaniasis". *Eur J Radiol.* 81(10):2550-3. Oct. 2012.
- [13] Melchionda F, Varan S, Carfagnini F, Belotti T, Di Muccio T, Tigani R, et al. Spleen nodules: a potential hallmark of Visceral Leishmaniasis in young children. Melchionda et al. *BMC Infectious Disease.* 14:620. 2014.
- [14] Figueras Nadal MC, García de Miguel MJ, Asensi Botet F, Velasco Bernardo R, Canals Baeza A, Ausín Aoi I. Short course treatment for visceral leishmaniasis with liposomal amphotericin B in immunocompetent patients. *An Pediatr (Barc)* 59(6): 535-540. Dec 2003.