World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Visceral Leishmaniasis co-existing with Multisystem Inflammatory Syndrome in a child

Elda Skenderi [1,*], Gjeorgjina Kuli-Lito [2], Alberta Shkembi [3], Florinda Malaj [1], Anxhela Ruci [1], Besmira Bogdani [1] and Irisa Duka [1]

[1] *Pediatrician, General Pediatric Ward, University Hospital Center "Mother Tereza", Tirana, Albania.*
[2] *Professor, Chef of Pediatric Infectious Disease Ward, University Hospital Center "Mother Tereza", Tirana, Albania.*
[3] *Psychologist, University Hospital Center "Mother Tereza", Tirana, Albania.*

World Journal of Advanced Research and Reviews, 2023, 20(03), 1818–1823

Publication history: Received on 21 November 2023; revised on 28 December 2023; accepted on 31 December 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.20.3.2702

Abstract

Leishmaniasis is a zoonotic disease caused by an intracellular protozoan parasite. The clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to Visceral leishmaniasis which is a serious, progressive, and potentially lethal systemic disease. "Multisystem Inflammatory Syndrome in Children" (MIS-C), which develops after the infection rather than during the acute stage of COVID-19 is a novel systemic syndrome that includes fever, elevated inflammatory parameters and organ dysfunction not attributed to other infectious causes. Here is presented a case the case of a 3-years old girl presented with persistent fever, and elevated inflammatory markers which was found to suffer simultaneously two severe conditions; Visceralis leishmaniasis and MIS-C. As these diseases have some similar clinical and laboratory features a high index of suspicion should be kept for both of them while valuating an ill child with fever and increased inflammatory markers.

Keywords: Visceralis leishmaniasis; MIS-C; Inflammation; Child; Diagnosis

1. Introduction

Leishmaniasis is a zoonotic disease caused by an intracellular protozoan parasite. It is transmitted to humans through the bite of a small female sandfly of the genus *Phlebotomus* in the Old World (Eastern Hemisphere) and *Lutzomyia* in the New World (Western Hemisphere). The burden of parasites in the sandfly is enormous so the bite of one infected insect is enough to cause the disease, a single sandfly can egest more than 1000 parasites per bite [1, 2]. Leishmaniasis infections are considered zoonotic diseases, as an animal reservoir is required to contain a persistent endemic condition. Humans are considered incidental hosts. Infections in wild animals are usually not pathogenic, with the exception of dogs, which may affect severe disease. Common Old World hosts are domestic and feral dogs, rodents, foxes, jackals, wolves, raccoon-dogs. Less common modes of transmission include congenital transmission, contaminated needle sticks, blood transfusion, sexual intercourse, and, rarely, inoculation of cultures [3, 4].

The parasites exist in the flagellated promastigote stage in sandflies and in artificial culture and then transform into the nonflagellated amastigote form in animal and human hosts. After the bite, some of the flagellates that enter in the human's circulation are destroyed, whereas others enter the intracellular lysosomal organelles of macrophages of the reticuloendothelial system, where they lose their flagella and change into the amastigote form. The amastigote forms also multiply by binary fission, until the host cell ruptures, liberating the amastigotes into the circulation. The free amastigotes then invade fresh cells, infecting the entire reticuloendothelial system. Some of the free amastigotes are drawn by the sandfly during its blood meal, completing the cycle [5].

* Corresponding author: Elda Skenderi

Depending on the species of parasite and the host's immune status, the parasites may incubate for weeks to months before presenting as skin lesions or as a disseminated systemic infection involving the liver, spleen, and bone marrow. The clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to a mutilating mucocutaneous disease and even to a lethal systemic illness.

Visceral disease, the most devastating and fatal form of leishmaniasis, is classically known as kala-azar or the Indian name for "black fever/disease," which is a reference to the characteristic darkening of the skin that is seen in patients with this condition. Visceral leishmaniasis is a serious, progressive, and potentially lethal systemic disease. It tends to affect individuals in poor states of health, with poor nutritional status, and with even the most minor decreased immune status much more severely than individuals with good health, good nutritional status, and intact immune systems. It is characterized by the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia, and hyper-gammaglobulinemia. The fever is continuous or remittent and becomes intermittent at a later stage. It is also characteristically described as a double rise in 24 hours, in which waves of pyrexia may be followed by a period without fever. Patients may also report night sweats, weakness, diarrhea, malaise, and anorexia. Melanocyte stimulation and xerosis can occur, causing characteristic skin hyperpigmentation [6, 7].

Diagnosis of Leishmaniasis is performed through isolation, visualization, and culturing of the parasite from infected tissue or serologic detection of antibodies. Liposomal amphotericin is the treatment of choice in Visceral Leishmaniasis [8].

The aim of this case report is to highlight the possibility of co-existence of two serious conditions in children, Visceralis leishmaniasis and post COVID-19 Multisystem inflammatory syndrome in children (MIS-C).

2. Case report

A three-years old female was admitted at the University Hospital Center "Mother Teresa" in Tirana, with a history of 10 days persistent high fever. Previously she was treated in a local hospital for 5-days with broad spectrum antibiotics but fever persisted and the general conditions deteriorate.

All the family members were healthy and she had been healthy too till then. Vaccination was performed according to the age of the child. The family did not keep domestic animals at home and consumed safe food.

On physical examination the child appeared ill, with high fever 39.5℃. Although he was irritated, no stiff neck nor other neurological anomalies were observed. Sclera were slightly injected, and a slight pharyngeal injection too. No cervical lymphadenopathy, edema or rash on the skin were observe. There were observed tachypnea with elevated respiratory rate of 35-40 breaths/min and fine rales on both fields in respiration, and tachycardia with elevated heart rate of 120 beats/min. The abdomen was soft, not distended, bowl sounds were present, liver and spleen were both enlarged o palpation.

Laboratory examination revealed : WBC 5,100 cells/mm^3 (1,800 neutrophils, 2,700 lymphocytes), RBC 3,750,000 cells/mm^3, Hemoglobin level 8.8g/dl, Hematocrit value 26.5%, Platelet count (PLT) 153,000 cells/mm^3, Erythrocyte sedimentation rate 22 mm/h (<15mm/h), Aspartate aminotransferase 48 U/L (21-44 U/L), Alanin aminotransferase 15 U/L (9-25U/L), blood Urea Nitrogen (BUN) 9.2 mg/dL (10.9-36 mg/dL), Creatinine 0.38 mg/dL (0.38-0.54 mg/dL), Lactate dehydrogenase enzyme (LDH) 640 U/L (192-321U/L), C reactive protein 2.76 mg/dL (<0.5mg/dL), Fibrinogen activity 455 mg/dL (160- 390mg/dL), Ferritin value 367.16 ng/mL (13.7-99.8ng/mL) [Tab.1].

Radiologic examination of thorax and abdomen revealed peribronchial inflammatory changes and increased liver and spleen. Serologic examination for Salmonellosis, Brucellosis, Tickettsiae, HIV, EBV, CMV, and Manthoux test were negative. Cultures of blood, urine and feces resulted in no bacterial growth. Serology for a recent infection of SARS-CoV-2 resulted positive for IgG anti SARS-CoV-2. Ultimately the diagnosis of MIS-C was performed and prednisolone 1 mg/kg daily was added to the therapy. Fever subsided in the following 24 hours and the child seemed playful, but after this short recovery in the next 24 hours ensued a recrudescence of high fever together with a deterioration of the general conditions. The imminent blood count analysis revealed; Leukopenia (WBC 3,200 cells/mm^3, Neutrophil 1,000 cells/mm^3, Lymphocyte 2,000 cells/mm^3), RBC 3,570,000 cells/mm^3, Hemoglobin 7.8 g/dL, Hematocrit 24,9%, PLT 124,000 cells/mm^3 [Tab.1]. Facing this clinic and laboratory scenario suspicion was raised upon the diagnosis of Visceralis leishmaniasis. Diagnosis was confirmed based on positive serologic results. Treatment with Ambisome was initiated, fever gradually abated and the general clinical conditions gradually improved.

Table 1 Laboratory values

Laboratory parameters	Day 1	Day 5
White blood cells	5,100 cells/mm³	3,200 cells/mm³
Lymphocytes	2,700 cells/mm³	2,000 cells/mm³
Neutrophils	1,800 cells/mm³	1,000 cells/mm³
Red blood cells	3,750,000 cells/mm³	3,570,000 cells/mm³
Hemoglobin	8.8 g/dL	7.8 g/dL
Hematocrit	26.4%	24.9%
Platelets	153,000 cells/mm³	124,000 cells/mm³
Erythrocyte sedimentation rate	22 mm/h	
Aspartate aminotransferase	48 U/L	
Alanine aminotransferase	14 U/L	
Blood urea nitrogen	9.2 mg/dL	
Creatinine	0.38 mg/dL	
C reactive protein	640 U/L	
Lactate dehydrogenase	2.76 mg/dL	
Fibrinogen	455 mg/dL	
Ferritin	367.16 ng/dL	

3. Discussion

Since the beginning of COVID-19 global pandemic in March 2020, it was clear that children were less affected or suffer mild to moderate disease with a few cases with severe disease that needed hospitalization. This was mostly contributed to their stronger immune innate system which is composed by a higher proportion of total lymphocytes and absolute numbers of T and B cells as well as natural killer cells. Children have a less pro-inflammatory cytokine response and are less prone to develop acute respiratory distress syndrome. They also have a more efficient trained immunity and healthier airways [9,10]. However despite this since May 2020, several highly endemic countries reported a novel syndrome in children and adolescents termed "Multisystem Inflammatory Syndrome in Children" (MIS-C), which seemed to develop after the infection rather than during the acute stage of COVID-19. Several case definitions were proposed, all included fever, elevated inflammatory parameters and organ dysfunction not attributed to other infectious causes [Tab.2] [11]. Pathophysiology of MIS-C is still unclear and possible mechanisms include viral mimicry resulting in autoantibodies production, formation of immune complexes which activate inflammation and viral super-antigen sequences which activate host immune cells [12].

The presenting child had a persistent fever for approximately 10 days which was unresponsive to antibiotics. She had pulmonary involvement with small inflammatory changes in both fields but without acute distress. Gastro-intestinal symptoms were reported (abdominal pain, nausea), and hepatomegaly and splenomegaly were observed. Work up to detect infectious diseases did not brought any accurate diagnosis as all cultures were negative and serologic tests for Salmonellosis, Brucellosis, Rickettcia, HIV, EBV and Tuberculosis were negative too. Increased inflammatory markers, involvement of two systems, fever unresponsive to antibiotics, and a positive serology for an imminent SARS-CoV-2 infection prompted to the diagnosis of MIS-C.

However the recrudescence of fever after a 48 hours fever-free following the administration of steroids made clear made obvious the co-existence of another condition. Meanwhile changes observed in blood count (leukopenia, anemia, thrombocytopenia), presence of hepato-splenomegaly, persistent high fever raised suspicion upon the presence of Visceralis Leishmaniasis, which was confirmed by positive serologic test. Administration of Ambisome together with the use of broad spectrum of antibiotics and steroids brought about the resolution of the fever and full recovery of the child.

Leishmaniasis affects as many as 12 million people worldwide. The World Health Organization reports endemic leishmaniasis in 98 countries and 3 territories on 5 continents (Africa, Asia, Europe, North America, South America), with an official estimated annual incidence of 0.7-1.3 million cases of cutaneous disease and 0.2-0.4 million cases of visceral disease [13]. Geographic distribution of leishmaniasis is generally restricted to tropical and temperate regions (natural habitats of the sandfly), and it is limited by the sandfly's susceptibility to cold climates. The global incidence of leishmaniasis has increased in recent years due to increased international travel and migration, human alteration of vector habitats, and concomitant factors that increase susceptibility, such as infection with human immunodeficiency virus (HIV) and malnutrition [14,15].

In areas with known animal reservoirs, such as the Mediterranean Basin, visceral leishmaniasis mainly affects children, with devastating outcomes as it is the most fatal form of the disease. The spectrum of illness ranges from asymptomatic infection or self-resolving disease to fulminant, severe, life-threatening infection; many subclinical cases occur and go unrecognized for each clinically recognized case. The extent and presentation of disease depend on several factors, including the humoral and cell-mediated immune response of the host, the virulence of the infecting species, and the parasite burden. Infections may heal spontaneously or may progress to chronic disease, often resulting in death from secondary infection [16]. Onset of visceral disease can be insidious or sudden. The incubation period varies after infection (usually 3-6 months, but can be months or years) and may depend on the patient's age and immune status as well as the species of *Leishmania*. If visceral disease is left untreated, death frequently occurs within 2 years which may be due to hemorrhage (secondary to infiltration of the hematopoietic system), severe anemia, immunosuppression, and/or secondary infections. The most important immunologic feature is a marked suppression of the cell-mediated immunity to leishmanial antigens. In persons with asymptomatic self-resolving infection, T-helper (Th1) cells predominate, with interleukin 2 (IL-2), interferon-gamma, and IL-12 as the prominent cytokines that induce disease resolution, although immune suppression years later can result in disease [17].

In Mediterranean countries, about 1,000 people are estimated to be affected by clinical disease annually, although asymptomatic or sub-clinical cases are by far more frequent [18]. The disease is known to occur in Albania since 1938 typically as a childhood disease [19]. Poverty and malnutrition play a major role in the increased susceptibility to leishmaniasis [20,21]. Its insidious beginning, distribution to the entire body by reticulo-endothelial system, devastating effects on bone marrow and immune system makes it difficult to differentiate from other systemic diseases associated with fever. The scenario of co-existing of Visceralis leishmaniasis with another systemic inflammatory disorder makes the appropriate diagnosis even more challenging. Ultimately the post COVID-19 era has enriched the diapason with a novel inflammatory systemic disorder in children. The probability of Visceral leishmaniasis co-existing with MIS-C is real even in non-endemic countries so a high index of suspicion should be maintained while valuating a child presenting features of each disorder.

Table 2 Centers for Disease Control case definition for MIS-C

(1) An individual aged < 21 years with:
(2) Clinical criteria: • A minimum 24-h history of subjective or objective fever≥38.0 ◦ C AND •Severe illness necessitating hospitalization AND •Two or more organ systems affected (i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological)
(3) Laboratory evidence of inflammation • One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
(4) Laboratory or epidemiologic evidence of SARS-CoV-2 infection • Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR • COVID-19 exposure within 4 weeks prior to onset of symptoms
(5) No alternative diagnosis
Abbreviations: CDC, Centers for Disease Control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

4. Conclusion

Co-existence of two serious and life threating conditions such as Visceralis leishmaniasis and Multisystem Inflammatory Syndrome in Children is a real probability. The devastating outcome of each disease while non-appropriately treated, makes imperative the accurate diagnosis. As these diseases have some similar clinical and laboratory features a high index of suspicion should be kept for both of them while valuating an ill child with fever and elevated inflammatory parameters.

Compliance with ethical standards

Acknowledgments

We thank the medical staff of the General Pediatric Ward for the precious support!

Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of informed consent

Consent was taken from the parents of the child included in the study, for using the data of the medical records, providing anonymity.

References

[1] World Health Organization. Leishmaniasis: the disease and its epidemiology. Available at http://www.who.int/leishmaniasis/disease_epidemiology/en/. Accessed: April 10, 2014.

[2] Centers for Disease Control and Prevention. Parasites home: leishmaniasis. Epidemiology & risk factors. Available at http://www.cdc.gov/parasites/leishmaniasis/epi.html. Accessed: April 11, 2014.

[3] Cardo LJ, Rentas FJ, Ketchum L, Salata J, Harman R, Melvin W, et al. Pathogen inactivation of Leishmania donovani infantum in plasma and platelet concentrates using riboflavin and ultraviolet light. Vox Sang. 2006 Feb. 90(2):85-91. [QxMD MEDLINE Link].

[4] Cardo LJ, Salata J, Harman R, Mendez J, Weina PJ. Leukodepletion filters reduce Leishmania in blood products when used at collection or at the bedside. Transfusion. 2006 Jun. 46(6):896-902. [QxMD MEDLINE Link].

[5] Zijlstra EE. Visceral leishmaniasis: a forgotten epidemic. Arch Dis Child. 2016 Feb 19. [QxMD MEDLINE Link].

[6] Keller DM. Novel noninvasive method for diagnosis of visceral leishmaniasis by rK39 testing of sputum samples. Medscape Medical News. February 7, 2013. Available at http://www.medscape.com/viewarticle/778974. Accessed: February 18, 2013.

[7] Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. N Engl J Med. 2010 Feb 11. 362(6):504-12. [QxMD MEDLINE Link].

[8] Tiuman TS, Santos AO, Ueda-Nakamura T, Filho BP, Nakamura CV. Recent advances in leishmaniasis treatment. Int J Infect Dis. 2011 Aug. 15(8):e525-32. [QxMD MEDLINE Link].

[9] Carsetti R, Quintarelli C, Quinti I, Piano Mortari E, Zumla A, Ippolito G, et al. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? Lancet Child Adolesc. Heal. Elsevier B.V.; 2020 [cited 2020 Jul 11]. p. 414–6. Available from: https://www.psychiatry. [PMC free article] [PubMed]

[10] Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: Why children fare better than adults? 2098 Available from: 10.1007/s12098-020-03322-y. [PMC free article] [PubMed]

[11] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. Elsevier ltd; 2020;395:1771–8. Available from: 10.1016/S0140-6736(20)31103-X. [PMC free article] [PubMed]

[12] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA - J Am Med Assoc 2020;1–11. [PMC free article] [PubMed]

[13] Centers for Disease Control and Prevention. Parasites home: leishmaniasis. Epidemiology & risk factors. Available at http://www.cdc.gov/parasites/leishmaniasis/epi.html. Accessed: April 11, 2014.

[14] Holaday BJ, Pompeu MM, Jeronimo S, Texeira MJ, Sousa Ade A, Vasconcelos AW, et al. Potential role for interleukin-10 in the immunosuppression associated with kala azar. J Clin Invest 1993; 92: 2626-32.

[15] Abramson MA, Dietze R, Frucht DM. Schwantz R, Kenney RT. Comparison of New and Old World leishmanins in an endemic region of Brazil. Clin Infect Dis 1995, 20: 1292-7.

[16] Dujardin JC, Campino L, Cañavate C, Dedet JP, Gradoni L, et al. Spread of vector-borne diseases and neglect of leishmaniasis, Europe. Emerg Infect Dis. 2008; 14: 1013–1018. [PMC free article] [PubMed].

[17] Biglino A, Bolla C, Concialdi E, Trisciuoglio A, Romano A, et al. Asymptomatic Leishmania infantum infection in an area of northwestern Italy (Piedmont Region) where such infections are traditionally nonendemic. J Clin Microbiol. 2010; 48: 131–136. [PMC free article] [PubMed].

[18] Xynos ID, Tektonidou MG, Pikazis D, Sipsas NV. Leishmaniasis, autoimmune rheumatic disease, and anti–tumor necrosis factor therapy, Europe. Emerg Infect Dis. 2009; 15: 556–959. [PMC free article][PubMed].

[19] Velo E, Bino S, Kuli-Lito G, Pano K, Gradoni L, et al. Recrudescence of visceral leishmaniasis in Albania: retrospective analysis of cases during 1997 to 2001 and results of an entomological survery carried out during 2001 in some districts. Trans R Soc Trop Med Hyg. 2003; 97: 288–290. [PubMed].

[20] Desjeux P. The increase in risk factors for leishmaniasis worldwide. Trans R Soc Trop Med Hyg. 2001; 95: 239–243. [PubMed].

[21] Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. Trends Parasitol. 2006; 22: 552–557. [PubMed].