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Case Report

The Emergence of Co-Infection of Visceral Leishmaniasis in an Iranian Child with Chronic Granulomatous Disease: A Case Report

Mohammad Reza ABDOLSALEHI¹, Mehdi MOHEBALI^{2,3}, Hossein KESHAVARZ^{2,3},
Shima MAHMOUDI⁴, *Setareh MAMISHI^{1,4}

1. Department of Infectious Diseases, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
3. Center for Research of Endemic Parasites of Iran (CREPI), Tehran University of Medical Sciences, Tehran, Iran
4. Pediatric Infectious Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran

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***Correspondence**

Email:

smamishi@sina.tums.ac.ir

Abstract

Chronic granulomatous disease (CGD) described as an essential immunodeficiency problem of phagocytic cells resulting in a phagocyte dysfunction and inability to kill a spectrum of bacteria and fungi. Despite the fact that CGD patients are more susceptible to intracellular infections, visceral leishmaniasis has been reported rarely in these cases. Here, we report an uncommon case of visceral leishmaniasis in a child with CGD. An 8-yr old boy with CGD presented to the infectious disease ward, Children's Medical Center, Tehran University of Medical Sciences, Iran after the onset of 20 days fever with chronic crusted ulcer approximately 3 cm × 3cm on the left upper limb and a small ulcer measuring 0.5 cm × 0.5 cm on the right knee with moderate secretion. Bone Marrow Aspiration (BMA) and Bone Marrow Biopsies (BMB) of fragmented samples were performed and polymorphic population of hematopoietic cells, Megakaryocytes and Leishman bodies were seen. The patient was treated with meglumine antimoniate (Glucantime[®]) 20 mg/kg for 28 days and after partial improvement patient discharged and continue the treatment at home. Amphotericin B lipid complex (Ambisome[®]) (3–5 mg/kg per dose once) was administered every 3–4 weeks for 18 months as secondary prophylaxis that was well tolerated and effective.



Introduction

Chronic granulomatous disease (CGD) is described as an essential immunodeficiency problem of phagocytic cells resulting in a phagocyte dysfunction and inability to kill a particular range of microorganisms (1). Five genetic defects were found in CGD cases, each hindering one of five fundamental subunits of the phagocyte NADPH oxidase generating reactive oxygen species. A deficiency of NADPH oxidase renders the patient vulnerable to repeated life-threatening infections by a variety of bacteria and fungi (2).

Patients with CGD suffer from serious recurrent bacterial and fungal infections of body surfaces including skin, airways, and intestines, and lymph nodes (2). CGD has prompted another comprehension of the significance of metabolism for intra and extracellular host defense (3, 4). Although CGD patients are more susceptible to intracellular microorganism infections such as *Leishmania* parasites, visceral leishmaniasis (VL) has been reported rarely in children (5-7). VL is a vector-borne parasitic disease that is endemic in some parts of the world like the northwest and southeast of Iran (8-11).

Here, we report here a rare case of VL in a patient with CGD.

Case presentation

An 8-yr old boy with CGD presented to the Infectious Disease Ward, Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran after the onset of 20 days fever with chronic crusted ulcer approximately 3 cm × 3 cm on the left upper limb and a small ulcer measuring 0.5 cm × 0.5 cm on the right knee with moderate secretion.

Informed consent was taken from the patient's guardians and the study was approved by the local Ethics Committee.

A large ulcer with size 4cm x 5cm on the left leg having swelling, erythematous, mild secretion and central necrosis was seen (Fig. 1).



Fig. 1: A large ulcer with size 4cm x 5cm on the left leg having swelling, erythematous, mild secretion, and central necrosis

The ulcer was crusted slowly and the 4th finger possess swollen and redness (Fig. 2). The patient had been suffering from vomiting and mild abdominal pain, he showed mild distress but the oxygen saturation was normal.



Fig. 2: The fourth finger of the right hand possess swollen and redness

The patient was born at term, as he was the second child of healthy non-consanguineous parents and one of his siblings died due to CGD. The patient had a history of treatment for tuberculosis infection 6 months ago. He

has been using chemoprophylaxis drugs including itraconazole, trimethoprim-sulfamethoxazole, and interferon-gamma since 7 years ago.

On physical examination, his body weight was 20 kg. The child was pale, with hepatosplenomegaly (7 cm below the costal margins). Neither lymphadenopathy nor signs and symptoms of bleeding were seen.

The laboratory findings showed severe anemia and leukopenia (White blood cell count: $3.12 \times 10^9/L$, hemoglobin: 5.7 mg/dl, hematocrit: 18.4%, Mean corpuscular volume (MCV): 51 fL, reticulocytes: 0.58%). The CRP and ESR levels were 65mg/dl and 44 mm/h,

respectively. Viral serological markers for Epstein-Barr virus (EBV), Cytomegalovirus, *Toxoplasma*, and human immunodeficiency viruses (HIV) were negative. The wright and 2ME Tests were negative. In addition, blood culture and anti-*Leishmania* antibodies detection using the Direct Agglutination Test (DAT) was negative (1:100)(12).

Bone Marrow Aspiration (BMA) and Bone Marrow Biopsies (BMB) of fragmented samples were performed and a polymorphic population of hematopoietic cells demonstrated. Megakaryocytes and Leishman bodies were also seen (Fig. 3).

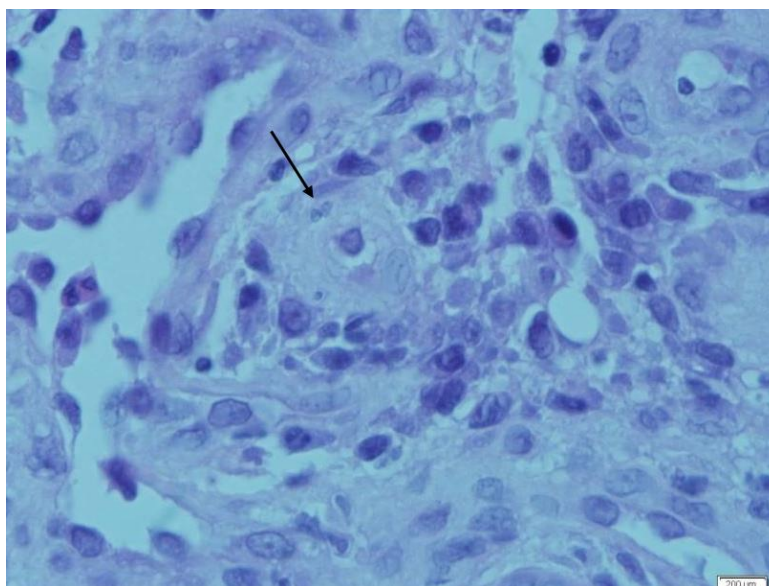


Fig. 3: Microphotograph showing Leishman bodies in BMA from a patient with visceral leishmaniasis with high magnification (1000X)

Pathological reports showed pseudoepitheliomatous hyperplasia with dense mixed inflammatory cells infiltration consistent with chronic infection. Few Leishman like bodies were seen in Giemsa staining. Three-phase bone scans scintigraphy showed no active bone lesion or active inflammatory process throughout the skeleton.

A report of endoscopic reveals mild chronic gastritis and mild congestion in esophageal mucosa.

The patient was treated with meglumine antimoniate (Glucantime[®]) 20 mg/kg for 28 days and after partial improvement patient discharged and continue the treatment at home (13). Amphotericin B lipid complex (Ambisome[®]) (3–5 mg/kg per dose once) was administered every 3–4 weeks for 18 months as secondary prophylaxis that was well tolerated and effective.

Discussion

CGD is an inherited primary immunodeficiency disease, which increases the susceptibility to infections caused by certain bacteria and fungi. Leishmaniasis is a complex of vector-borne diseases caused by > 20 trypanosomatidae protozoan species of the genus *Leishmania* (14).

The occurrence of visceral leishmaniasis in CGD children is rare. We report here visceral leishmaniasis in a case with CGD. Previously, Finocchi et al (6) reported the first description of visceral leishmaniasis infection in a 3-year old child with CGD. Moreover, Al Aayed et al reported a case of a 6-month-old infant with disseminated *L. donovani* and CGD (7).

Our case has been suffering CGD at birth and he was infected recently, while in previous studies (6, 7), CGD was diagnosed after detection of Leishman bodies.

Fever and splenomegaly at the onset of the disease were similar to previous reports (15). Among laboratory findings, pancytopenia and elevated ESR were seen which is considered as common findings among pediatric visceral leishmaniasis (15).

Among laboratory findings, leukopenia (3.12 cell/mm²) was not in agreement with previous reports (6, 7). In our study, the diagnosis was confirmed by detecting of the Leishman bodies in BMB and BMA at the first time, while in a previous report, the diagnosis was confirmed by direct microscopic demonstration of rare amastigotes of *Leishmania* spp. in a second BMA. This case had leukocytosis presented with indolent fever and multiple skin lesions on the face, neck, limbs and skin biopsy. Moreover, the bone marrow aspirate showed amastigote forms of *L. donovani* (6).

Microscopy of BMA is considered as the validated diagnostic approach for pediatric patients (16). Additionally, serological tests including direct agglutination, enzyme-linked immunosorbent assay, and indirect immunofluorescence are considered sensitive for the

diagnosis of visceral leishmaniasis among immunocompetent patients (16, 17). Although in Abdinia et al study that evaluated pediatric visceral leishmaniasis in the northwest of Iran, DAT was positive in more than 90% of cases (15), in our study, DAT was negative. A study in Iran has estimated the sensitivity of the observation of Leishman bodies from 35% to 67% (15); however, in this case, we found Leishman bodies in the bone marrow aspirate.

Conclusion

Despite the fact that the relationship of leishmaniasis with CGD and the killing of *Leishmania* spp. by human mononuclear phagocytes has not been described (18), the risk of infection with leishmaniasis in a patient with CGD living in an endemic area for leishmaniasis cannot be dismissed.

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Conflict of interest

The authors declare that there is no conflict of interests.

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