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CASE SERIES

Two Cases of Siblings with Variation in Response to Standard Treatment of Visceral Leishmaniasis in Kenyatta National Hospital

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Abstract

Background: Visceral leishmaniasis is caused by a protozoan parasite of the genus Leishmania, transmitted by sandflies of the genus Phlebotomus. It is one of the neglected tropical infectious diseases, though it has been endemic in many countries around the world. High morbidity and mortality have been reported in Sub-Saharan Africa, including Kenya, attributed to misdiagnosis, late diagnosis, or medication lack. The cases we present, highlight the disease's characteristics and the variable individual to the conventional standard treatment.

Cases: This case series highlights two siblings in a family of 17 children; a 9-year-old boy and his 4-year-old brother. They presented with a history of progressive abdominal swelling for about five months for the younger brother and four months for the older. These symptoms were accompanied by fevers, easy fatigability, bilateral lower limb swelling, and a pruritic skin rash. Both siblings had pedal edema, massive Splenomegaly, and pancytopenia with severe anemia. The diagnosis of VL was made via a positive rapid test for VL. After which, both siblings were started on treatment with sodium stibogluconate and Paromomycin for 17 days. The 9-year-old gained full recovery, but his brother did not. So, the 4-year-old boy was started on therapy with liposomal amphotericin for six days, after which he gained full recovery. The father was tested and found negative for VL, while the rest of the family were then asymptomatic but not tested.

Conclusion: VL is treatable, especially if diagnosed and managed early enough. The serological tests' presence makes the diagnosis easy, and management started early, sufficient for better outcomes. Variation in response to treatment raises concern about whether we have a new species in this geographical area or drug-resistant organisms' development to the standard therapy. Importantly, screening family members in the same household and exposure is crucial, especially for children younger than five-years-old.

Abbreviations

VL: Visceral leishmaniasis; WBC: White Blood Cells; Hb: Hemoglobin; CRP: C-Reactive Protein LFTs: Liver Function Tests; RFTs: Renal Function Tests; SSG: Sodium Stibogluconate; LB: Liposomal Amphotericin B

Introduction/Background

Visceral leishmaniasis, also known as kala-azar, is one of the neglected tropical diseases worldwide but endemic in several countries worldwide. The World Health Organization has noted most cases occurring in Brazil, East Africa, and India. In 2018, more than 95% of new cases reported to WHO happened in 10 countries: Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan, and Sudan [1]. In Kenya, VL remains an issue of public health concern affecting more than 30 sub-counties. It is endemic in the Rift Valley and Eastern regions, with small foci in the North-Eastern area. In the Eastern Region, foci have been documented in areas including Kitui and Mwingi counties [2].

VL remains one of the top parasitic diseases with outbreak and mortality potential. If contracted has devastating and debilitating effects, including immune suppression, wasting, and severe illness, it can even lead to death. The parasite's inoculation precedes the infec-

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tion in humans by the bite of an infected sand fly into a healthy individual [3] in a few hours after inoculation of the organism, the obligate intracellular Leishmania parasite rapidly localizes in phagocytes to colonize its host. At this stage, Leishmania benefit from pro-inflammatory properties of the sand fly saliva that plays an essential role in the phagocyte chemo-attraction, being thus an important determinant of infection outcome. Among the common characteristic organs affected in the infection are the liver, spleen, vessels, and bone marrow [4].

Furthermore, household members of individuals with previously confirmed visceral leishmaniasis have been found to have a higher frequency of the disease [5]. Hence, the household members of infected individuals should be included in the risk group for visceral leishmaniasis. Serological screening should be performed to detect possible infection.

The treatments available in different parts of the world for Visceral leishmaniasis treatment include Sodium stibogluconate (SSG), Paromomycin, Liposomal Amphotericin B (LB), and Miltefosine. Currently, in East Africa, SSG and Paromomycin are recommended at first line for the disease [2]. However, although cheaper and been noted to have marked response in this part of the world, SSG, like the other anti-leishmanial medications, has been associated with side effects to the gastrointestinal and cardiac function, so this has to be monitored [6].

Variation in response to treatment has been reported in different geographical areas and different individuals partly due to drug resistance and different genetic composition of individuals [7].

In this case series, we highlight two young children with visceral leishmaniasis from Mwingi County in the Rift Valley region of Kenya. These cases we present put forward the disease's characteristics and the variable individual response to the standard treatment.

Case Presentation

The cases described here are; a four-year-old male (case 1) and his brother, nine-year 11-months-old (case 2). Both residing in Mwingi, Kitui County in Kenya, and referred to Kenyatta National Hospital, Kenya, for further evaluation and treatment. Their clinical presentation of both siblings is represented in Table 1.

Laboratory Investigations were done for both chil-

Table 1: Table showing clinical features at presentation.

	Symptoms	Signs
Case 1	Progressive abdominal swelling for five months, with a reduced appetite and abdominal pain; Bilateral lower limb swelling for the same period On and off fevers for two months. Easy fatigability and general body weakness.	Palmar and conjunctival pallor. Moderate Bilateral pitting lower limb edema; Grossly distended abdomen, Soft on palpation, Mild tenderness on deep palpation, Normal bowel sounds, and with Splenomegaly of 13 cm below the costal margin.
Case 2	Progressive abdominal swelling, which had started about four months prior. On and off fevers for four months; Bilateral lower limb swelling for three months; Easy fatigability.	Palmar and conjunctival pallor, Moderate Bilateral pitting lower limb edema; The abdomen was distended, soft, mildly tender on deep palpation, with Splenomegaly of 15 cm below the costal margin.

Table 2: Table showing the positive laboratory findings in both siblings plus the normal reference laboratory values.

Case 1	WBC **1.86 × 10^9**; Neutrophils **0.30 × 10^9**; Lymphocytes **1.26 × 10^9**; CRP 11.02; Platelets **57 × 10^9**; Hb **6.9 g/dl.** LFTs and RFTs were normal The Rapid test for VL (rK39) was **Positive.** Blood smear test for malaria was negative Peripheral blood film: **Rouleaux formation, normochromic anemia**; **leukopenia, reduced platelets** HIV test: **Negative**
Case 2	WBC **4.98 × 10^9**; Neutrophils **1.33 × 10^9**; Lymphocytes **2.46 × 10^9**; CRP 6.90; Platelets 173 **×** 10^9; Hb **6.7 g/dl.** LFTs and RFTs were normal: The Rapid test for VL (rK39) was **Positive.** Blood smear test for malaria was negative Peripheral Blood Film: **Rouleaux formation, normochromic anemia; leukopenia**, adequate platelets HIV test: **Negative**
Reference ranges	WBC: 3.00-15.00 **×** 10^9 ; Neutrophils: 1.50-7.00 **×** 10^9; Lymphocytes: 1.00-3.70 **×** 10^9 ;CRP: 0-6; Platelets: 150-450 **×** 10^9; Hb: 12-18 g/dl

Table 3: Table showing the response to treatment during and after Sodium stibogluconate and Paromomycin.

Case 1	He was spiking fevers throughout the 17 days of treatment and persistence of symptoms. He then was started on second-line therapy with amphotericin B targeted for six doses. This well-tolerated, he showed significant improvement, with fevers' resolution and the marked reduction in spleen size plus no side effects to any of the drugs were noted.
Case 2	Tolerated the medications well and showed significant improvement, with fevers' resolution and marked reduction in spleen size. No side effects to the drugs were noted.

dren, and the results are summarized in Table 2.

VL's standard first-line treatment in Kenya was initiated for both children with a combination of Sodium stibogluconate and Paromomycin for a 17-day course of therapy. Both children also received packed red blood cell transfusions to manage the anemia, plus intravenous ceftriaxone and oral paracetamol for pyrexia and nutritional support. There was no previous infectious disease diagnosed in both children. The response is summarized in Table 3.

Immediately after their last day of treatment, each child was re-examined, and the results are shown in Table 3. After the younger sibling's recovery, both children were discharged for follow- up at Mwingi Level IV hospital in Mwingi county, close to their home area.

Their parents are both farmers, the patients being the 11th born (case 1) and 9th born (case 2) of 12 children from his mother. All children live together in the same homestead, and there was no family history of chronic medical illness.

The father who stayed with them in the hospital upon admission as their direct caretaker was tested negative for VL with the Rapid test. Unfortunately, due to logistical reasons, the rest of the family members were not tested. Follow up of the family was recommended at Mwingi Level IV hospital.

Discussion

Visceral leishmaniasis, even though it is rare, in Kenya has been known for many years to be endemic in the Eastern part of the country and the Rift Valley region. This distribution may be explained by challenges in complete control of both the vector and the animal reservoirs, as noted in other areas of the world [8]. In 2018, Diba, et al. [9] reported a surge in visceral leishmaniasis cases in Kenya, where males were more affected than females. However, all age categories were affected; most of the patients were older males between 15 and 44 years [9]. The cases described here were children below 12 years of age, and all coming from Mwingi in Kitui County in the Eastern Province of Kenya, a region known to be endemic.

The incubation period of leishmaniasis has been described to be between 6 weeks to 6 months. Still, it may extend from 10 days to 10 years [10]. Factors that determine progression from infection to disease are not fully understood, but most individuals remain asymptomatic [11,12]. The host's ability to mount a cell-mediated immunity has been highlighted as very important in controlling the infection [10].

In the cases we highlight here, the older child developed symptoms one month after the younger sibling's symptoms were already established. This difference can either be explained by the different onset of infection or even some immune system differences. There is also a very high likelihood that both children contracted the disease simultaneously. Therefore, there is a good chance that the younger brother's case would have been arrested if the diagnosis were made early and everyone in the family screened for VL after that. And this is because it has already been shown that family members of infected individuals are at risk and have a very likelihood of contracting the disease.

Important differential diagnoses that had to be excluded were acute leukemia and tropical malaria Syndrome. They all present with features of pancytopenia, Splenomegaly, and fevers, among other parameters [13]. However, epidemiological data and the patient's history can immensely assist in reducing misdiagnoses. In both cases described, the malaria tests were negative. Because of the endemic nature of this disease in the area, the presence of the rapid test for visceral leishmaniasis (rK39) makes the diagnosis of VL easy, and treatment started early, without the need for bone marrow, especially in these resource-limited settings, if an individual has clinical signs. And for these two children, having got the positive rapid test for VL, treatment was commenced, and with an excellent response to the medications, bone marrow aspirate was not done.

VL treatment depends on several factors, including concomitant pathologies, parasite species, and geographical location [1]. Other aspects to consider are whether the patient has primary Kala-azar, a relapse, or a concurrent medical condition, for instance, HIV, among others [2]. Treatment of VL needs an immunocompetent system. It involves both supportive therapies, including nutritional support, blood transfusion in severe anemia, and medicine of inter-current infections. The cases described here needed a blood transfusion plus antibiotics started on admission, nutrition support, and scabies treatment.

The first-line pharmacological treatment of VL in Kenya is a combination therapy of Sodium gluconate (pentavalent antimonial) at 20 mg/kg/day intramuscu-

larly or intravenously plus Paromomycin 15 mg/kg/day for 17 days. Monotherapy with Sodium Stibogluconate is still being used in endemic areas where Paromomycin is unavailable or contraindicated. On receiving the whole 17-day therapy, however, the younger child did not have the initial cure, still had fevers, Splenomegaly, and still was not feeding well. Hence switched to the second-line therapy with Liposomal amphotericin B at 3 mg/kg/day for six days. After this, he achieved recovery, with no fevers, regression in the spleen's size, increase in the White blood cell counts and hemoglobin, and normal appetite return.

There are multiple factors however, that have been defined to predispose an individual to severe disease and death, and these include; visit delayed more than 56 days, fever lasting more than 21 days, normal or low temperature (< 37.5 °C), hemorrhagic syndrome, hemoglobin rate < 5.5 g/dL, sedimentation rate < 25 mm, hypoalbuminemia < 30 g/L, age < 5-years-old, severe malnutrition, Jaundice, Total platelet count < 50,000/mm^3, Neutrophil count < 500/mm^3 and Dyspnea [14] And the presence of one or more of these factors appear to consider amphotericin as the first-line medication to treat the disease [15]. The younger child was more predisposed to have severe disease because of his age, thrombocytopenia, and Neutrophilia.

And remarking the difference in the neutrophil counts of both children, the low neutrophil count in younger sibling highlights the lowered immunological capability to fight off the infection compared to the older sibling and hence a difference in the therapeutic response.

However, even though the response to treatment varies depending on the parasite species and host factors, in 2 siblings with a close genetic makeup and in the same geographical area, it is intriguing to differ. A concern arises as to whether we have a new species in this geographical area or the development of drug-resistant organisms to standard therapy. However, being different individuals, siblings could still have a difference in response to certain medications. Charlotte, et al. report VL in 2 siblings who, after traveling to an endemic area, developed the disease 5 and 15 months after traveling; however, both responded to the same treatment [16]. We, however, did not find any study where two siblings reacted differently to similar treatment despite being in the same geographical area. In these cases, however, further tests, including molecular tests indicating the parasite load and species types, needed to be done to confirm whether we had different species in the two children, pointing to further studies that may need to be done in this regard.

Visceral leishmaniasis should be considered in all children with a history of fevers, pancytopenia, and Splenomegaly as a key differential diagnosis. It is treatable, especially if diagnosed and managed early enough. The serological tests' presence makes the diagnosis easy, and management started early, sufficient for better outcomes. Variation in response to treatment raises concern about whether we have a new species in this geographical area or the development of drug-resistant organisms to the standard therapy. Importantly, screening family members in the same household and exposure is crucial, especially for children younger than five-years-old.

Declaration

Ethics approval, consent to participate, and consent for publication: Informed consent was obtained from the legal guardians for participation and publication of this case report.

Availability of data and materials: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Competing Interest: Authors declare that they have no competing interest.

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