Leishmania Viscerophila as the Cause of Fever of Unknown Origin in Children

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Citation

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Abstract: Fever of unknown origin (FUO) represents a challenging diagnostic dilemma in clinical pediatrics. In children, the differential diagnosis are led by infections. Causes of FUO may also differ geographically based on regional exposures, economic development and available diagnostic tools. Leishmaniasis is a disease caused by an intracellular protozoan parasite transmitted by the bite of a female sandfly. The clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to a mutilating mucocutaneous disease and even a serious, progressive, and potentially lethal systemic disease that affects the reticuloendothelial system (Visceral leishmaniasis). Onset of visceral disease can be insidious or sudden, it is characterized by the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia and hypergammaglobulinemia. In well-nourished children with intact immune system, full recovery from visceral disease is expected after treatment with appropriate medication, if left untreated death frequently occurs within 2 years. We report the case of a 20 months male patient hospitalized for FUO and resulting with Visceral leishmaniasis.

Keywords: Fever of Unknown Origin, Visceral Leishmaniasis, Fever, Hepatosplenumegaly, Pancytopenia

1. Introduction

Fever is a common presenting complaint in children and a persistently febrile child lacking an obvious source of fever put the parents and clinical pediatrics in a great stress. In 1961 Petersdorf and Beeson defined fever of unknown origin in adults (FUO) as a state of febrile illness for more than three weeks, with a body temperature greater than 38.3°C on several occasions and uncertain diagnosis after one week of study in hospital [1]. In 1991 Durack and Street recommended differentiating between four classes of FUO: classical FUO as originally defined by Petersdorf and Beeson, nosocomial FUO, neutropenic FUO, HIV-associated FUO [2]. They also proposed a minimum diagnostic evaluation of three outpatient visits or three days of in-hospital investigation, to allow for the time needed for incubating blood cultures and tuberculosis skin tests to become positive, before classifying a case as FUO. Knockaert and Vanderschueren updated the definition of FUO again by proposing to change the quantitative criterion of three days’ investigation after which no diagnosis has been made to a qualitative one, due to the advances in diagnostic methods, claiming for an “appropriate intelligent standard inpatient or outpatient workup”[3]. Even with modern advances in medicine, FUO remains a challenge and it may be a symptom of approximately 200 described cases [4-6]. Classical FUO is subdivided in four main etiological categories: infections, malignancies, non-infectious inflammatory diseases (NIID) and miscellaneous conditions [4]. Infections were the leading cause for classical FUO in most published studies, accounting for approximately one third of all cases: abscesses, endocarditis, tuberculosis, and complicated urinary tract infections dominate the group of infection-related FUO, regardless of the age of the patient. In the group of NIID, Still’s disease and systemic lupus erythematosus are as the most frequent causes seen in younger patients [7]. Among patients with neoplasms, FUO can be related to the tumor itself, or more frequently by complicating infections [8]. Etiology also clearly depends on geography, as in developing countries the percentage of infections is much higher than in developed countries, while for neoplasms and NIID it is the opposite [9-12].
2. Case Report

A 20-months-old male admitted to the University Hospital Center of Tirana with a classic case of fever of unknown origin (FUO). The major complaint was an intermittent fever up to 39.5°C with morning and afternoon pick which did not subsided despite 10-day treatment with antibiotics for broncho-pneumonia in a regional hospital. On physical examination the child appeared ill, pale with no apparent focus of infection. Laboratory investigations on admission revealed a blood cell count WBC 5400 cells/ml (84.2% lymphocytes, 6.9% monocytes, 8.9% granulocytes), RBC 4,600,000 cells/ml, hemoglobin level 9.3 g/dL, hematocrit value 27.1%, platelet count 138,000 cells/ml, aspartate aminotransferase AST 57U/L, alanin aminotransferase ALT 16U/L, lactate dehydrogenase LDH 399U/L, prothrombin time/international normalized ratio INR 1.470, blood urea nitrogen 20mg/dL, creatinin level 0.3mg/dL, serum total protein level 7.3g/dL. Chest radiograph was normal and abdominal ultrasonography showed hepatosplenomegaly. Serologic detection of antibodies to Leishmani Donovani antigen resulted positive 22.4 UI/ml (< 9 UI/ml). Soon after serologic results was initiated treatment with Liposomal amphotericin B (AmBisome) 5mg/kg in a five day regimen and one single dose on day 14 and 21. (Table 1). Fever subsided on the third day of treatment.

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>1</th>
<th>14</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC cells/ml</td>
<td>4,900</td>
<td>14,000</td>
<td>13,900</td>
</tr>
<tr>
<td>RBC cells/ml</td>
<td>3,650,000</td>
<td>4,230,000</td>
<td>4,930,000</td>
</tr>
<tr>
<td>HGB g/dl</td>
<td>7.1</td>
<td>9.0</td>
<td>10.7</td>
</tr>
<tr>
<td>Lymphocytes %</td>
<td>76.3</td>
<td>44.1</td>
<td>39.9</td>
</tr>
<tr>
<td>Granulocytes %</td>
<td>15.5</td>
<td>51.1</td>
<td>53</td>
</tr>
<tr>
<td>Platelet</td>
<td>77,000</td>
<td>453,000</td>
<td>500,000</td>
</tr>
<tr>
<td>PT HS %</td>
<td>51.8</td>
<td>69.5</td>
<td>82.5</td>
</tr>
<tr>
<td>Gama globulin %</td>
<td>39</td>
<td>33.5</td>
<td>16.5</td>
</tr>
</tbody>
</table>

3. Discussion

Leishmaniasis is a disease caused by an obligate intracellular protozoa parasite transmitted by the bite of a female sandfly (Phlebotomus species). It affects as many as 12 million people worldwide, with 900,000 to 1.3 million new cases each year. The global incidence of leishmaniasis has increased in recent years due to increased international leisure- and military-related travel, human alteration of vector habitats, and concomitant factors that increase susceptibility, such as infection with human immunodeficiency virus (HIV) and malnutrition. With the exception of Australia, the Pacific Islands, and Antarctica, the parasites have been identified throughout large portions of the world. The bite of one infected sandfly is sufficient to cause the disease, because a sandfly can egest more than 1000 parasites per bite. Traditionally divided between Old World and New World parasites, more than 20 pathogenic species of Leishmania have been positively identified about 30 of the 500 known phlebotomine sandfly species have been

Leishmania species exist as extra-cellular flagellated promastigotes in the guts of female sandflies, and transform to the amastigote form in animal and human hosts. The protozoa resist phagolysosomal enzymes and replicate within the macrophages, spreading so throughout the reticuloendothelial system of the host and living within the intra-cellular lysosomal organelle of macrophages. Pathogenesis appears related to T-cell cytotoxicity, and control of visceral leishmaniasis depends on the magnitude of T helper 1 and multicytokine responses early in the course of infection. During progressive Leishmania infection in mice, Th2-type CD4 T cells expand and secrete interleukin-4, resulting in polyclonal B-cell activation [16]. Fully established visceral leishmaniasis is associated with cellular anergy.

Onset of visceral disease can be insidious or sudden. The incubation period varies after infection (usually 3-6 mo, but can be months or years) and may depend on the patient's age and immune status as well as the virulence of Leishmania species, and the parasite burden. Infections may heal spontaneously or may progress to chronic disease. If spontaneous recovery occurs, the patient’s cell- mediated immunity increases. If the individual is unable to generate an appropriate immune response, the parasite disseminates in the reticuloendothelial cells of the body, or the parasite may remain dormant and not present itself until one’s immune system becomes compromised [17]. Acute onset is characterized by the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia. 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. Young malnourished children are most susceptible to developing progressive infection; those who present later in the course of the disease may present with edema caused by hypoalbuminemia, hemorrhage caused by thrombocytopenia, or growth failure caused by features of chronic infection. 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 [18-22].

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 [23-25]. Mediterranean VL affects primarily children as well as an increasing rate of immunocompromised and immunosuppressed adult individuals, such as HIV-infected and patients under any immunosuppressive therapies [26-28]. The disease is known to occur in Albania since 1938 typically as a childhood disease [29]. Migration, lack of control measures and HIV co-infection are the three main factors reported for driving the increased incidence of VL (30). Poverty and leishmaniasis are also strictly associated. Poor housing conditions and diet, poverty-related concurrent infections as well as proximity to infected dogs, are all specific factors related to zoonotic VL [31]. In developing countries, young malnourished children are extremely susceptible to develop progressive infection. In these areas, the disease has an insidious onset with pyrexia, which is continuous or remittent and becomes intermittent at a later stage.

From a retrospective review of 100 cases hospitalized as Fever of Unknown Origin (FUO) in the General Pediatrics Ward in the University Hospital Center of Tirana during a 5-years period 2012-2017, 17 cases (17%) resulted with Leishmania Visceralis. The total number of Leishmania Visceralis during this period is 178 cases. From this figures resulted that 10% of Leishmania Visceralis had insidious onset with prolonged fever and were hospitalized as FUO.

4. Conclusion
Fever of unknown origin (FUO) represents a challenging diagnostic dilemma in clinical pediatrics. The leading cause of FUO in children are common infections with atypical presentation. In Europe, physicians are sometimes ill-informed on the diagnosis and treatment of Leishmaniasis. The geographic distribution of Leishmaniasis has widened and the disease is reported in areas in which it was previously non endemic. The onset of Visceral Leishmaniasis may be insidious with prolonged pyrexia specially in young malnourished children. Visceral Leishmaniasis is a potential cause of FUO in children not only in endemic countries.

References


