Case Report

Septic shock due to visceral leishmaniasis, probably transmitted from blood transfusion

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Abstract

A case of visceral leishmaniasis (VL) in a 77-year-old woman, with renal failure on haemodialysis, admitted in the intensive care unit (ICU) with vascular instability requiring vassopressor treatment, is presented. Initially, no co-infection could be detected. The patient initially responded well when liposomal amphotericin B was administered, after bone marrow demonstrated multiple intra-cellular Leishmania amastigotes and extra-cellular promastigotes. However, the patient died from uncontrolled septic shock from a secondary bacterial infection, the tenth day of admission.

To our knowledge, vascular instability has not been reported in VL. Moreover, non-vector transmission was also suspected in this case. The patient had undergone cholecystectomy three months earlier, during which two blood units had been transfused; IgG anti-Leishmania antibodies at a high titer were detected in one of the two healthy blood donors, later.

Key words: visceral leishmaniasis, shock, clinical findings, transmission, blood products

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Introduction

Visceral leishmaniasis (VL; kala-azar) encompasses a broad range of manifestations of infection. It may be asymptomatic or subclinical and self-resolving, but usually runs a subacute or chronic course and may be fatal without or despite treatment [1]. Death usually occurs because of severe secondary bacterial infections in advanced disease [1,2].

Patients with VL usually present with fever, abdominal pain, diarrhoea, epistaxis, hepatosplenomegaly (splenomegaly usually predominates), peripheral lymphadenopathy, pancytopenia (anaemia, thrombocytopenia, leucopenia with neutropenia, and marked eosinopenia, associated with a relative lymphocytosis and monocytosis), and hypergammaglobulinaemia [1]. Nevertheless, some cases of the infection present atypically and cases have been reported that affect the lungs, pleura, oral mucosa, larynx, oesophagus, stomach, small intestine and bone marrow [3]. Leishmaniasis, though a serious public health problem in developing countries, is a rather unusual cause of admission in an intensive care unit (ICU). Moreover, to our knowledge, the parasite has not been reported to cause cardiovascular dysfunction, as yet.

The disease is a vector-borne disease caused by obligate intramacrophage protozoa, transmitted by the bite of phlebotomine sand flies [1-3]. However, there is increasing evidence that the Leishmania parasite may be transmitted by blood transfusion [4-13].

Case Study

A 77-year-old woman, with renal failure on hemodialysis for the past year and a half, was admitted in our ICU just after her hemodialysis session because of vascular instability requiring vasopressors, despite adequate fluid resuscitation. She resided in the countryside and there was no history of recent travel to other countries. Her prior history included chronic atrial fibrillation, arterial hypertension, and cholecystectomy three months earlier; two blood units had been transfused during this surgery.

One and one half months prior to admission, the patient had fever, chills and sweats during hemodialysis and throughout the day later; occasional diarrhoea and weight loss of four kilograms were

also reported. Broad spectrum antibiotics and anti-tuberculosis medication (for 20 days), administered in a regional hospital, did not result in symptom relief; therefore, she was referred to our hospital. Laboratory investigation revealed pancytopenia [haemoglobin 6,4gr/dl, total leucocytes 3.7 x 10^3 c/dl (78% polymorphonuclears), platelets 80 x 10^3 c/dl]. The prothrombin, activated partial thromboplastin time, and fibrinogen were within normal range; D-dimers were mildly elevated. Total bilirubin was 3.5mg/dl; alanine aminotranferase: 131 IU/l; aspartate aminotranferase: 121 IU/l; albumin 2.9mg/dl. Mild splenomegaly was evident on computed tomography and 2-D echography (14 cm in its maximal diameter). Despite empirical treatment with vancomycin and ceftazidime, she was finally admitted in ICU on the tenth day (Apachee II score, 26) needing low dose of noradrenaline (5-8 μg/min); thereafter, in fact, the patient was suffering from hypotension requiring fluid volume or even mild vasopressor therapy, during or just after hemodialysis sessions the last few days.

Echocardiography revealed good right and left ventricular systolic function. Antibiotic treatment (imipenem-cilastatin, teicoplanin and amikacin), recombinant human activated protein C, and hydrocortisone in association with continuous veno-venous hemodialysis were also initiated. Serial cultures of blood, urine, sputum and bronchoalveolar lavage (BAL) failed to yield any significant growth. Mantoux and sputum test for acid-fast bacilli were negative. HIV test was also negative. Platelets dropped further up to 13 x 10^3 c/μl and bleeding diathesis emerged. A bone marrow aspirate was performed on the fourth day in ICU. Microscope slide examination (Giemsa stained) demonstrated multiple intra-cellular Leishmania amastigotes and extra-cellular promastigotes (Figure 1); peripheral blood smear showed no parasites. Liposomal Amphotericin B (200 mg/day) was immediately initiated. This led to a quick elevation of platelets although the need of hemodynamic support was still present. Unfortunately, the patient died after abrupt deterioration from severe septic shock (noradrenaline increased from 6 to 80 μg/min in a few hours), seven days after the initiation of Amphotericin B treatment, while being in a weaning process (platelets 85 x 10^3 c/dl). Blood cultures just before death revealed multiresistant *Acinetobacter baumannii*.

According to the clinical and laboratory progression of our patient, VL seemed to be the cause of admission in ICU, performing as a rather long-standing but gradually deteriorating septic shock. A thorough postmortem pathologic examination of the bile, in order to assess whether gastrointestinal symptoms before cholecystectomy could be due to VL, did not reveal any sign of Leishmania involvement. IgG anti-Leishmania specific antibodies at a high titer (1:512; immunofluoroscence method) were detected in one of the two healthy blood donors whose blood had been transfused during cholesystectomy, probably indicating a non-vector transmission of the parasite to the patient.

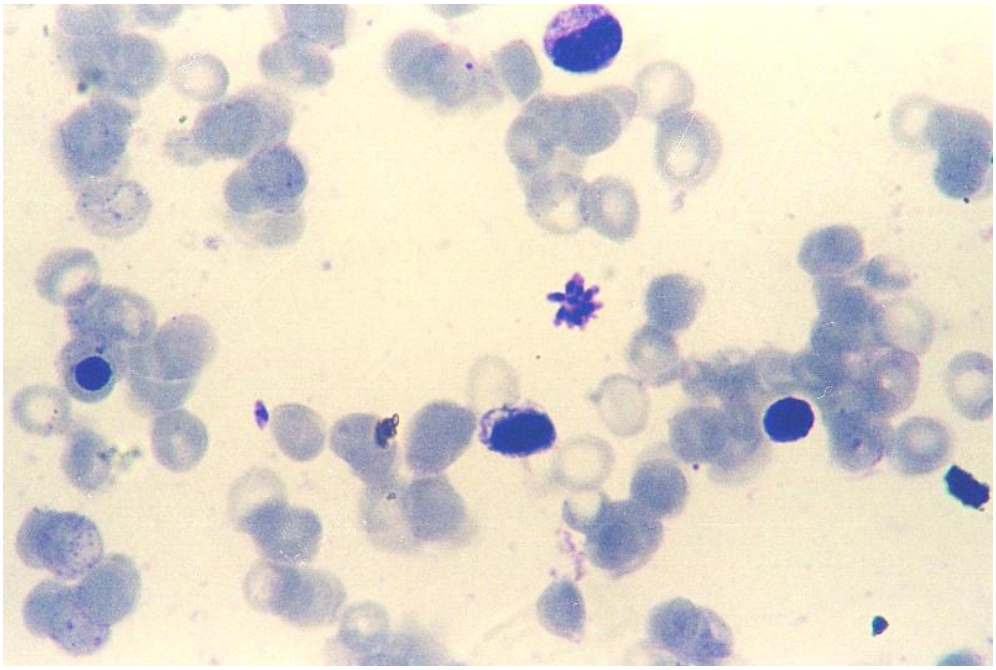
Discussion

Leishmaniasis is endemic in Asia and Africa (*L. donovani*), South America (*L. chagasi*) and Southern Europe, including Greece (*L. infantum*) [1-3]. It is a disseminated protozoan infection, typically transmitted by female sand fly bites [1-3]. Usually, VL has a history of long-term fever frequently going undiagnosed for months, finally developing pancytopenia with extreme splenomegaly [1-3]. The incubation period varies from three to eight months [3] (range 10 days [14] to 34 months [15]).

Seropositivity resulting from asymptomatic *L. infantum* infections [16,17], as well as healthy seropositive individuals with intermittent circulation of the parasite in peripheral blood (asymptomatic carrier), has been reported previously [17,18]. After Operation Desert Storm in the beginning of the nineties, blood products from US soldiers coming from Iraq showed Leishmania infection [19,20]. In addition, survival of the parasite in blood and blood products under blood storage conditions has been demonstrated [21]. Recently, anti-Leishmania antibodies were found in 11 of 1,449 blood donors from Agrigento district, Sicily, Italy (0.75% of cases), among which Leishmania DNA was detected from four (36.4%) [13]. Yet, anti-Leishmania antibodies were detected in 44 of the 1,437 blood donors (3.1%) from the Balearic Islands [17].

However, the donors' blood is not routinely examined for VL as the transmission of the parasite by blood transfusion is strongly suspected, but has not yet been provided. There are a few reports suggesting this mechanism of transmission although in most cases no donor could be identified [4-10]; all of them corresponded to patients who received blood units from donors resident in areas endemic for kala-azar. Yet, an indication that Leishmania can be transmitted by blood was shown by an outbreak of leishmaniasis among intravenous (IV) drug users in Spain [11]. Finally, the possibility that blood

Figure 1. Bone marrow aspirate (fourth day in ICU) indicating a "rosette" of extra-cellular promastigote Leishmania bodies (Giemsa stain).



transfusion might pose a risk of Leishmania transmission was also suggested by the significant increase in the prevalence of anti-Leishmania antibodies in hemodialysis patients in Brazil who received multiple blood transfusions [12]. The International Forum showed that in most European countries no specific measures are implemented to prevent TT-leishmaniasis [19]. Only Ireland and the USA defer donors for 12 months after they had visited Iraq. In Israel, visitors of endemic areas, mainly Iraq, are rejected [19].

In our case, blood transfusion from an infected asymptomatic donor was probably the way of transmission of the parasite in our patient. A probable large parasite load from the blood transfusion during cholocystectomy, in association with the renal failure related to immunosuppression, in an old debilitated patient, was probably the cause of the rather rapid presentation of the infection (with only mild splenomegaly) and the unexpected deterioration to cardiovascular instability needing vasopressor therapy, at last.

Current data indicate that vulnerability to VL is partly genetically determined [22]. Yet, the extent and presentation of the 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 [2]. Recently, Antinori *et al*. suggested that immunodepression seems to predispose to development of VL as Leishmaniasis is increased among organ transplant recipients (so far, the number of published cases has quadrupled since the beginning of the 1990s) [23].

The diagnosis of visceral leishmaniasis is usually based on microscopic detection of amastigotes in smears of tissue aspirates or biopsy samples. With sensitivity ranging from 55–97%, bone marrow aspiration smears and/or bone marrow biopsies are frequently recommended when VL is suspected. Lymph node aspirate smears (sensitivity 60%) or biopsy, and splenic aspirates (sensitivity 97%) may also be taken for diagnosis, although the splenic aspirates may give rise to life-threatening haemorrhage [1-3].

Leishmania antibodies may be detected with a sensitivity of 72% and a specificity of 94% [24]. However, traditional serologic assays (*e.g*., indirect immunofluorescent antibody testing) do not reliably distinguish past from current infections [1,2].

Most patients feel better and become afebrile during the first week of treatment [25]. Splenomegaly and biochemical abnormalities do not resolve for weeks to months in some cases [2,25]. Treatment is largely based on pentavalent antimonials [25].

Increasing resistance to antimonials is a major problem, and this is most evident in north Bihar, India, where the failure rate to this treatment is 50% [24,25]. Amphotericin B is an effective antibiotic used in Pentavalent antimony (Sb(V)) resistant patients. However, it is toxic and needs to be given for a prolonged period on an inpatient basis. The alternative is using the liposomal form, which is highly effective and less toxic, although up to now prohibitively expensive [26]. The trend in southern Europe is shifting towards using liposomal amphotericin B as the preferred treatment, even though the response rate is still around 90% for antimonials [23]. However, a recent trend in increasing resistance to Sb(V) in this area has been recorded, possibly attributed to using meglumine antimonate to treat infected dogs [27]. The effectiveness of short courses of this liposomal amphotericin B is resulting in improved cost benefits [26,28]. The dose of lipid formulations for VL is 2–5 mg/kg daily, for a total dose of about 5–40 mg/kg (varies by region, drug, and host status) [2]. We used a high IV dose of liposomal Amphotericin in our case, although in a 77-year-old woman with renal failure on hemodialysis, because of her severe clinical condition with shock. In fact, the kinetics of the drug is difficult to evaluate in the presence of shock and oedema. Probably a half dose would be appropriate, taking into account the renal failure. On the other hand, although the main adverse effect of liposomal Amphotericin is renal failure, we were not concerned about kidneys in this patient who would continue on hemodialysis if she had lived.

In conclusion, blood transfusion might pose a risk of Leishmania transmission. In endemic *L. infantum* areas, blood may be examined for Leishmania before transfusion, as recipients of blood products include critically ill or immunocompromised patients; in these patients, implementation of more effective anti Leishmania measures (prestorage leucodepletion) may be useful [29]. Yet, long-lasting vascular instability and/or mild septic shock-from VL, with no other obvious causative agent, must be in mind in the case of previous blood transfusions in debilitated and immunodeficient patients.

Summary of key points

We present a case of visceral leishmaniasis (VL) in an old woman, with renal failure on hemodialysis, who admitted in ICU with vascular instability, requiring vasopressors. In addition, non-vector transmission, through transfused blood units, was also probable.

- blood transfusion might pose a risk of Leishmania transmission; blood may possibly be examined for Leishmania before transfusion, in endemic *L. infantum* areas
- deteriorating vascular instability from VL, i.e. long-lasting mild septic shock, must be in mind in the case of previous blood transfusions in debilitated patients with no other obvious causative agent.

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