CASE REPORT

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Visceral leishmaniasis in a patient with ulcerative colitis – A case report

Visceralna lajšmanioza kod bolesnice sa ulceroznim kolitisom

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Abstract

Introduction. There is a rise of visceral leishmaniasis in immunocompromised patients due to increased availability of immunomodulatory drugs. In order to point at the occurrence of visceral leishmaniasis in patients with inflammatory bowel disease (IBD), we reported a case of female patient with a travel history to European Mediterranean countries, who was on immunosuppressive treatment due to ulcerative colitis. **Case report.** A 29-year-old female patient was admitted to hospital due to severe relapse of ulcerative colitis. Corticosteroid therapy was administered in addition to previous longterm azathioprine, with clinical response to the treatment. During the course of the disease she had recurrent high-grade fever with marked hepatosplenomegaly and pancytopenia. The diagnosis of leishmaniasis was established by positive serology tests and microscopic finding of amastigotes in bone marrow smears. The disseminated infection was responsive to treatment with liposomal amphotericin B, but therapy had to be discontinued due to urticarial rush. Subsequent therapy with antimony was administered, but it had to be stopped too due to liver toxicity. No further treatment for leishmaniasis was initiated as the clinical and laboratory data suggested that the patient had responded to the treatment. She was discharged from hospital in IBD remission and without signs of the infection. **Conclusion.** Visceral leishmaniasis should be considered in IBD patients with fever of unknown origin and relevant travel history in order to achieve favorable disease outcome.

Key words:
colitis, ulcerative; diagnosis; immunosuppressive agents; leishmaniasis; risk assessment; serology.

Apstrakt

Uvod. Visceralna lajšmanioza je u porastu kod imunokompromitovanih bolesnika zbog povećane dostupnosti imunomodulatornih lekova. Da bi ukazali na mogućnost postojanja visceralne lajšmanioze kod bolesnika sa zapaljenskom bolesti creva, prikazali smo bolesnicu sa ulceroznim kolitisom lečenu imunosupresivnom terapijom, koja je prethodno boravila u evropskim, mediteranskim zemljama. **Prikaz bolesnika.** Bolesnica, starosti 29 godina, primljena je u bolnicu sa teškim relapsom ulceroznog kolitisa. Pored dugogodišnje terapije azatioprinom primenjeno je i lečenje kortikosteroidima na koje je dobijen klinički odgovor. U toku lečenja bolesnica je bila visokofebrilna sa izraženom hepatosplenomegalijom i pancitopenijom. Dijagnoza lajšmanioze postavljena je serološkim testovima i mikroskopskim nalazom amastigota u sternalnom punktatu. Na terapiju lipozomalnim amfotericinom B dobijen je povoljan odgovor, ali je lečenje moralo biti prekinuto zbog generalizovane urtikarije. Potom je primenjeno lečenje preparatom petovalentnog antimona, ali je i ono moralo biti prekinuto zbog hepatotoksičnosti. S obzirom na to da je kod bolesnice već dobijen terapijski odgovor, dalje lečenje lajšmanioze nije primenjivano. Na otpustu iz bolnice ulcerozni kolitis je bio u remisiji i nije bilo znakova lajšmanioze. **Zaključak.** Kod bolesnika sa zapaljenjskom bolesti creva i febrilnošću nejasnog uzroka, koji su prethodno putovali u endemske krajeve, treba razmotriti i postojanje visceralne lajšmanioze u cilju postizanja povoljnog ishoda bolesti.

Ključne reči:
kolitis, ulcerativni; dijagnoza; imunosupresivi; lajšmanioza; rizik, procena; serologija.

Introduction

Leishmaniasis is an infectious disease caused by protozoan parasites of the genus Leishmania predominantly transmitted via the bite of an infected phlebotomine sand fly [1]. The most severe form is visceral leishmaniasis (VL) (kala-azar) where some of the internal organs of the body such as bone marrow, liver, spleen, etc. are affected. The

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global rise of VL cases is due to increasing numbers of immunosuppressed patients who have a history of travel to endemic countries [2]. Without adequate therapy severe cases of VL usually have unfavorable outcomes [1]. Thus, it is important for clinicians to be aware of this rare and potentially fatal disease [3]. Ulcerative colitis (UC) is not a rare disease [4], but reports of VL in patients with UC are scarce [5, 6]. We presented a case of a patient with inflammatory bowel disease (IBD) in whom VL occurred.

Case report

A 29-year old woman with 8-year history of UC and primary sclerosing cholangitis was admitted to the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia in Belgrade with frequent bloody stools, high-grade fever, abdominal pain, anorexia, fatigue and weight loss, that occurred for several days before hospitalization. Due to extensive, corticosteroid dependent UC she was treated with azathioprine 2 mg/kg/24 h for several years. Three months prior to hospitalization she had traveled on vacation to Montenegro sea coast and Greece (region of Athens) for 3 weeks. On physical examination she was undernourished (37 kg), Mayo score was 8, and she had a fever (38.3°C). Laboratory tests showed high C reactive protein level [44.3 mg/L (normal levels are bellow 3.0 mg/L)], high erythrocyte sedimentation rate (ESR) [78 mm/h (normal range under 20 mm/h)], mild elevation of alkaline phosphatase [167 IU/L (normal range 37–116 U/L)], and low serum albumin concentration [26 g/L (normal range 35–55 g/L)]. Immunological analyses showed elevation IgG [18.7 g/L (normal range 7–16 g/L)] and positive pANCA 1 : 256 (reference range < 1 : 40 titer). The stool culture and microscopy on enteric pathogens were negative. Urgent flexible rectosigmoidoscopy confirmed the presence of active colitis with continuously inflamed mucosa, complete loss of vascular pattern, granular appearance, friability and multiple erosions. Gastroscopy revealed mild chronic gastritis and reflux oesophagitis grade A. Chest x-ray at admission was normal. A 40 mg dose of prednisolone was administered with subsequent disease activity response. Due to recurrent fever chest X-ray was repeated after two weeks of hospitalization. The result showed round infiltrate in left hilar zone, and treatment with ceftriaxon and ciprofloxacin was administered. High fever subsided and computed tomography (CT) chest scan revealed regression of inflammation. However, after 3 days high fever recurred (39.5°C) and progressive hepatosplenomegaly (spleen 30 cm on CT scan) and pancytopenia [hemoglobin 78 g/L (normal range, 115–165 g/L), white blood count (WBC) 1.0×10^9/L (normal range 4–11 $\times 10^9$/L), platelets 40×10^{12}/L (normal range 150–450 $\times 10^9$/L)] were observed. Blood, sputum and urine cultures on several occasions were negative, as well as angiotensin-converting enyzme (ACE), hepatitis B surface antigens (HBsAg), anti-hepatitis C virus (HCV), polymerase chain reaction (PCR) Koch's bacillus (KB), skin tuberculin test and sputum KB analyses. Antibodies to Epstein-Barr virus (EBV), *Pneumocystis* pneumonia (PCP), cytomegalovirus (CMV), HIV, and *Mycoplasma pneumonia* were also negative. Ultrasound examination of the heart was normal. Ultrasound of thyroid gland showed two nodal changes in the left lobe that had benign characteristics, and thyroid hormone levels were within normal range. Doppler ultrasonography of the portal system showed no presence of thrombotic masses. Bone marrow (BM) aspiration demonstrated mildly hypercellular smears without the presence of parasites. In search for the fever etiology, leishmanial serology for determination of specific antibodies in the serum was proposed. Both the qualitative rapid dipstick rK39 test and the quantitative indirect hemagglutination assay were positive (a titer of 1 : 128). Because of positive leishmanial serology and negative reevaluation for parasites in previous bone marrow smears, BM aspiration was repeated. Direct microscopic examination of Giemsa-stained BM smears revealed only a few amastigotes of *Leishmania* spp. which were released from destroyed macrophages in the extracellular area (Figure 1).

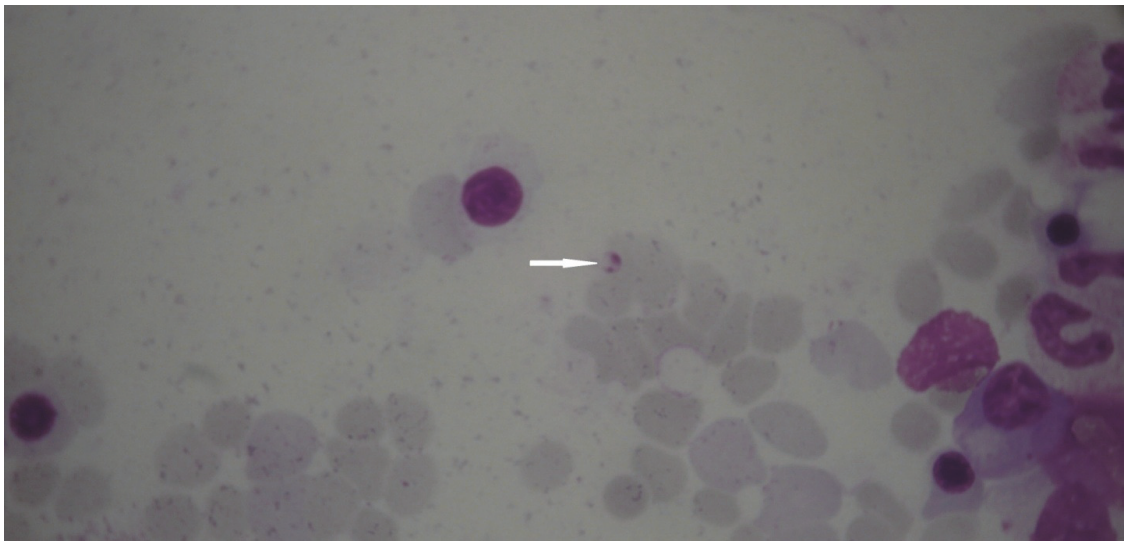

Fig. 1 – *Leishmania* sp. amastigote in the extracellular area (arrow) in Giemsa-stained bone marrow aspiration smear under oil immersion (× 1000).

Treatment with lyophilized amphotericin B in a dose 3 mg/kg was administered and fever disappeared after four days of the therapy, while inflammatory markers decreased. However, on the 5th day of the therapy urticarial rush developed so the treatment with amphotericin was discontinued. This therapy was considered too short for complete treatment, so another therapy with pentavalent antimony was started. However, on the 7th day of antimonial therapy, elevated serum transaminase levels [aspartate aminotransferase (AST) 203 IU/L (normal ranage 8–40 U/L), alanine aminotransferase (ALT) 76 IU/L (normal ranage 19–25 U/L)], as well as alkaline phosphatase [238 IU/L (normal ranage 37–116 U/L)], and gamma glutamyl transferase (γGT) (238 IU/L) were observed and the therapy was stopped. During the next several days laboratory findings continued to improve and returned to normal values. At discharge from hospital the patient was afebrile and UC was in clinical and laboratory remission, which was maintained at follow-up examinations during the following year.

Discussion

Immunosuppression is an established risk factor for VL [2, 7, 8]. The immunology and pathogenesis of leishmaniasis are complex [9]. Immunosuppressive conditions that predispose patients to VL can arise from many different causes; the exact mechanisms are not perfectly understood [8]. The rise of VL in immunocompromised patients due to increased availability of immunomodulatory and immune-ablative drugs offers new clinical challenges [10]. Patients previously treated with more than two immunosuppressive drugs are at particular risk for opportunistic infections [11]. Opportunistic infections have been increasingly reported in anti-tumor necrosis factor (TNF)-treated patients [12], but publications on Leishmania infections in patients treated with TNF inhibitors are still not frequent [11, 13, 14]. In the presented case VL occurred in an immunocompromised malnourished patient with severe relapse of autoimmune disease treated with two immunosuppressants. A combination of these factors contributed to the development of VL.

Leishmaniasis can have a number of diverse clinical variations with atypical and severe presentations in immunocompromised patients [8]. Latent infection can become clinically apparent within years to decades after exposure of people who become immunosuppressed [1]. The typical clinical symptoms are fever and splenomegaly. Leucopoenia and anemia are the most frequent hematological disorders [7]. These findings occur in a setting of complex clinical manifestations of underlying disease. In the presented case VL was suspected because of prolonged febrile state with progressing splenomegaly and pancytopenia, as well. Diagnosis of VL may be made with microscopic visualization of the parasite in infected tissue (such as bone marrow, liver, lymph node, colon mucosa or blood), with positive serological tests (DAT and k39 antibody) or with identification of *Leishmania* DNA [3, 10]. Light microscopy accurately detects *Leishmania* amastigotes in stained tissue samples even in immunocompromised patient. If the first procedure does not identify parasites but the clinical index of suspicion is high, repeated sampling is recommended [15, 16]. Serology also appears to be useful for supportive evidence for the diagnosis of VL in immunocompromised patients, but some comparative studies of different serological tests showed conflicting results [7, 17, 18]. Our case confirmed that the best diagnostic approach is the use of combination of methods, as the negative result of one test does not exclude the presence of VL.

Treatment is the prerequisite for good outcome of VL. Liposomal amphotericin B is the drug of choice for VL [1]. Pentavalent antimonials are also well established treatment for leishmaniasis, although there has been evidence of increased resistance in the recent decades [19]. Published trials showed that therapy with either antimonials or amphotericin B provided similar cure rates, but toxicity was higher with antimonials [7, 8, 20, 21]. This was confirmed by meta analysis of 17 studies in HIV infected individuals as the main difference among treatment regimens was in higher mortality rate with antimony use [18.4%, 95% confidence interval (CI) 13.3–25%)] [22]. Published cases of fatal toxicity related to antimonials include severe toxic hepatitis and pancreatitis [7], fatal arrhythmia [23], and unexpected sudden death [20]. In pediatric patients, a recent trial showed that N-methylglucamine antimoniate (n = 51) and amphotericin B deoxycholate (n = 50) had similar cure rates (94.1% vs. 94%, respectively) and serious adverse events (SAE) incidence was similar in both groups [24]. Treatment may be complicated with drug interactions between antileishmanial and other administered medications and their coinciding toxicity [21]. In the presented case both administered medications led to drug toxicity, but additional effect of their successive use had favorable outcome. Recently, an oral agent miltefosine became approved for the treatment of VL. In meta analysis of 2 trials with 523 participants (majority from India) miltefosine was as effective as amphotericin B deoxycholate in achieving VL definitive cure (relative risk 0.99, 95% CI 0.95–1.03) [25]. However, there is limited available evidence to support its use in southern Europe and Latin America or in immunocompromised patients with VL [26].

The lack of an effective vaccine or drugs to prevent infection emphasizes that prevention is crucial to break the global rise of leishmaniasis [26, 27]. Measures to prevent sand fly bites are advised for immunocompromised patients travelling to endemic areas [1, 28].

The reason for the uncommon published cases of VL in patients with UC might be due to their different geographic distribution. Leishmaniasis is native to a variety of developing countries [26]. Occasional cases of VL in Europe have been imported mostly from the Mediterranean region where the prevalence of latent infection is high [7, 10, 29]. On the contrary, IBD is more common in the industrialized world, particularly Western Europe and North America [30]. Incidence of VL is currently on the rise in nonendemic regions due to increased international travel and migration [27]. In our case travel history to Mediterranean endemic regions supported suspicion of VL.

The first report of VL in a patient with IBD was on a 27-year-old woman who was not exposed to *Leishmania* sp.

for over 20 years [5]. She was receiving 5 week corticosteroid therapy for UC presented after spontaneous abortion in the seventh month of her first pregnancy. The persistent fever was attributed to documented pyogenic infection. During week 2 progressive marked hepatosplenomegaly occurred. She died 5 weeks after diagnosis. At necropsy, histology showed *Leishmania donovani* organisms in the liver, spleen, bone marrow and lymph nodes [5].

Another reported case was a patient with UC and sepsis with pancytopenia persisting after colectomy due to colonic perforation. Bone marrow biopsy showed an infiltration with *Leishmania* bodies in macrophages, while DNA sequencing confirmed infection [6]. He had history of travel to Mallorca 1.5 years previously. Administration of liposomal amphotericin B cured the patient. Surprisingly, histological examination of the resected colon revealed the presence of an immunoblastic B-cell lymphoma suggesting major immune disturbance [6].

TNF-α inhibitors are potent immunomodulator drugs with growing use in IBD. Juzlova et al. [23] reported a case of 44-year-old man with Crohn's disease treated successfully with infliximab, who developed VL with cutaneous symptoms [23]. He was treated with antimony with a regression of the local findings, but on the 24th day after his admission, the patient suddenly expired due to fatal arrhythmia as a side effect of the treatment with antimony. In a recent report three cases of Catalan coast residents who were treated with TNF inhibitors for Crohn's disease, developed atypical cutaneous lesions of leishmaniasis [13]. In none of the cases *Leishmania* was detected microscopically; diagnosis was confirmed by PCR of skin samples, serology testing and response to treatment. They received systemic treatment with liposomal amphotericin B because of the lack of response to antimony intralesional treatment in 2 patients and because of hepatosplenomegaly in the third [13].

Conclusion

Published data showed that VL is uncommon in patients with UC. Unfavorable prognosis of untreated cases has been reported in the literature. The presented case suggests that VL should be considered in patients with UC if prolonged febrile state with progressing splenomegaly and pancytopenia occur in a patient with travel history to endemic regions.

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