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Please cite this article: **VISCERAL LEISHMANIASIS IN A PATIENT WITH ULCERATIVE COLITIS. A CASE REPORT**

**VISCERALNA LAJŠMANIJAZA KOD PACIJENTKINJE SA ULCEROZNIM KOLITISOM. PRIKAZ SLUČAJA**


UDC:

DOI: [https://doi.org/10.2298/VSP180302076J](https://doi.org/10.2298/VSP180302076J)

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.

Goran Janković*, Lena Martinović*, Zorica Dakić †, Dragana Mijač*, Miloš Štulić*, Miodrag Krstić*

*Clinic for Gastroenterology and Hepatology, Clinical Centre of Serbia, School of Medicine, University of Belgrade, Serbia
† Department of microbiology, Clinical Centre of Serbia, School of Medicine, University of Belgrade Serbia

Corresponding author: Goran Janković
Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia, School of Medicine, University of Belgrade, Serbia
Address: Koste Todorovica 2 Street, 11000 Belgrade, Serbia
Telephone: +381-63-1467526
Fax: +381-11-3615587
E-mail: goran.jankovic.beograd@gmail.com

Goran Janković - obtaining, analysis, explanation and clarification of results; planning conception, creation and critical review of manuscript; design proposal and final adjustment of manuscript for publication
Lena Martinović - obtaining, analysis, explanation and clarification of results, creation and critical review of manuscript; design proposal of manuscript for publication
Zorica Dakić - obtaining, analysis, explanation and clarification of results
Dragana Mijač - obtaining, analysis, explanation and clarification of results
Miloš Štulić - planning conception, creation and critical review of manuscript; design and final modification of manuscript for publication
Miodrag Krstić - analysis and explanation of results; final revision of manuscript for publication
Abstract

**Introduction:** In order to point at the occurrence of visceral leishmaniasis in a patient with inflammatory bowel disease, we report 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 long-term azathioprine, with clinical response to 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 treatment. She was discharged from hospital in IBD remission and without signs of 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.
Apstrakt

Background

Leishmaniasis is an infectious disease caused by protozoan parasites of the genus Leishmania predominantly transmitted via the bite of an infected phlebotomine sand fly. 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 global rise of VL cases is due to increasing numbers of immunosuppressed patients who have a history of travel to endemic countries. Without adequate therapy severe cases of VL usually have unfavorable outcomes. Thus, it is important for clinicians to be aware of this rare and potentially fatal complication. Ulcerative colitis (UC) is not a rare disease, but reports of VL in patients with UC are scarce. The aim of this case report was to stress that VL may occur in a patient with inflammatory bowel disease (IBD) with particular clinical aspects.

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 Centre of Serbia 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 2mg/kg/24h 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 (37kg), Mayo score was 8, and she had a fever (38.3°C). Laboratory tests showed high C reactive protein level (44.3 mg/l), high ESR (78mm/), mild elevation of alkaline phosphatase (167 IU/l), and low serum albumin concentration (26g/l). Immunological analyses showed elevation of IgG (18.7 g/l) and positive pANCA 1:256. 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 40mg 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 CT chest scan revealed regression of inflammation. However, after 3 days high fever recurred (39.5°C) and progressive hepatosplenomegaly (spleen 30cm on CT scan) and pancytopenia (hemoglobin 78g/l, WBC 1.0 x10⁹/l, platelets 40x10¹²/l) were observed. Blood, sputum and urine cultures on several occasions were negative, as well as ACE, HBsAg, anti-HCV, PCR BK, skin tuberculin test and sputum BK analyses. Antibodies to EBV, PCP, CMV, HIV, and mycoplasma pneumonia were also negative. Ultrasound examination of the heart was normal. Ultrasound of thyroidal gland showed two nodal changes in the left lobe that had benign characteristics, and thyroid hormone levels were within normal range. Doppler ultrasonography of portal system showed no presence of thrombotic masses. Bone marrow aspiration demonstrated mildly hypercellular smears without the presence of parasites. In search for the fever etiology leishmanial serology for determination of specific antibodies in 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 (Fig. 1). Treatment with lyophilized amphotericin B in a dose 3mg/kg was administered and fever disappeared after four days of therapy, while inflammatory markers decreased. However, on the 5th day of 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 (AST 203 IU/l, ALT 76 IU/l), as well as alkaline phosphatase (238 IU/l), and gamma-GT (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-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 in people who become immunosuppressed \(^1\). The typical clinical symptoms are fever and splenomegaly. Leucopenia 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. Pentavalent antimonials are also well established treatment for leishmaniasis, although there has been evidence of increased resistance in the recent decades. Published trials showed that therapy with either antimonials or amphotericin B provided similar cure rates, but toxicity was higher with antimonials. 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%, CI 95% 13.3-25%). Published cases of fatal toxicity related to antimonials include severe toxic hepatitis and pancreatitis, fatal arrhythmia, and unexpected sudden death. 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 SAE incidence was similar in both groups. Treatment may be complicated with drug interactions between anti-leishmanial and other administered medications and their coinciding toxicity. 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). However, there is limited available evidence to support its use in southern Europe and Latin America or in immunocompromised patients with VL. The lack of an effective vaccine or drugs to prevent infection emphasizes that prevention is crucial to break the global rise of leishmaniasis. Measures to prevent sand fly bites are advised for immunocompromised patients travelling to endemic areas. 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. Occasional cases of VL in Europe have been imported mostly from the Mediterranean region where the prevalence of latent infection is high. On the contrary, IBD is more common in the industrialized world, particularly Western Europe and North America. Incidence of VL is currently on the rise in non-endemic regions due to increased international travel and migration. 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. 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 L donovani organisms in the liver, spleen, bone marrow and lymph nodes.

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. 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.

TNF-α inhibitors are potent immunomodulator drugs with growing use in IBD. Juzlova et al. reported a case of 44-year-old man with Crohn's disease treated successfully with infliximab, who developed VL with cutaneous symptoms. 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 disease, developed atypical cutaneous lesions of leishmaniasis. In none of the cases was Leishmania 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.

Conclusion

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


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