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Case Report

Leishmania donovani infection mimicking ulcerative colitis in an immuno-competent patient

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ABSTRACT

We share a case of a 54-year-old Caucasian immune-competent male with a suspected long latent visceral leishmaniasis presenting primarily with parasitic colitis, splenomegaly, and pancytopenia. Due to histopathologically and endoscopically mimicking ulcerative colitis, the patient was initially treated for UC, until the parasites were identified and eradicated with liposomal Amphotericin B.

Case presentation

A 54-year-old male Caucasian patient from Bavaria, Germany presented himself to the emergency department with vomiting, diarrhea, and nausea, suspicious for viral gastroenteritis.

Two days later, the nausea and vomiting stopped, still complaining about increased bloody stool-frequency. He also reported a weight loss of 15 kg, fever up to 39.5°C, night sweats as well as shivering and chills in the following weeks leading to another visit in the emergency department approximately 10 weeks later. Patient history did not report any underlying conditions or chronic diseases. Upon further questioning the patient reported undulating fever with a daily peak in the evening. The social and travel history was remarkable for two cats in the household as well as visits to Kenia in 2016, Nevada/USA, Southern Tyrol/Italy, and Tuscany/Italy in 2022.

Physical examination revealed a 3/6 systolic heart murmur with propagation into the axillary vessels. Endocarditis was ruled out by echocardiography and four sets of blood cultures which remained sterile. Abdominal ultrasound revealed hepatosplenomegaly. Further diagnostics showed pancytopenia (Platelets 90/nl, RBC 3.57/pl, WBC 3.87/nl), slightly elevated serum concentrations of inflammation markers (CRP 10.1 mg/l, PCT 0.32 ng/ml), and elevated serum concentrations of sIL-2R (2680 U/ml), ACE (97.9 U/l), Ferritin (3769 ng/ml), liver enzymes (AST 91 U/l, ALT 114 U/l), as well as an increased LDH (643 U/l) without signs of hemolysis.

Due to the abdominal symptoms a gastroscopy and colonoscopy was performed due to suspected inflammatory bowel disease. Here high-grade ulcerative inflammation of the large bowel from the caecum to the rectum with decreasing inflammation level was shown (Figure 1a and b). The histopathological work-up of colonic biopsies revealed ulcerative pancolitis with signs of mucosal remodeling befitting a chronic inflammatory bowel disease or a chronic infectious disease. Stool samples showed a physiologic colon microbiome without evidence of pathologic bacterial species, as well as an increased calprotectin of 990 mg/kg. Therefore, as no infectious cause was identified, these changes were attributed to ulcerative colitis as befitting by endoscopy, histopathology, and clinical findings.

An immunosuppressive therapy with budesonide and mesalazine was initiated. This led to only a mild improve-

Abbreviations: ACE, Angiotensin converting enzyme; AIDS, Acquired immunodeficiency syndrome; ASTMH, American Society of Tropical Medicine and Hygiene; CL, Cutaneous leishmaniasis; CMV, Cytomegalovirus; CRP, C-reactive protein; CT, Computer tomography; EBV, Epstein-Barr-Virus; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme linked immunosorbent assay; ER, Emergency room; FDG, Fluorodeoxyglucose; GOT, Glutamic oxaloacetic transaminase; GPT, Glutamic-pyruvate transaminase; HIV, Human immunodeficiency virus; IDSA, Infectious Diseases Society of America; IFN, Interferon; IIFT, Indirect immunofluorescence test; LDH, Lactate dehydrogenase; PCR, Polymerase chain reaction; PCT, Procalcitonin; PKDL, Post-Kala-Azar-dermal Leishmaniasis; sIL-2R, Soluble interleukin 2 receptor; SUV, Standard uptake value; TNF, Tumor necrosis factor; UC, Ulcerative colitis; VL, Visceral leishmaniasis; WBC, White blood cell count; WHO, World Health organization.

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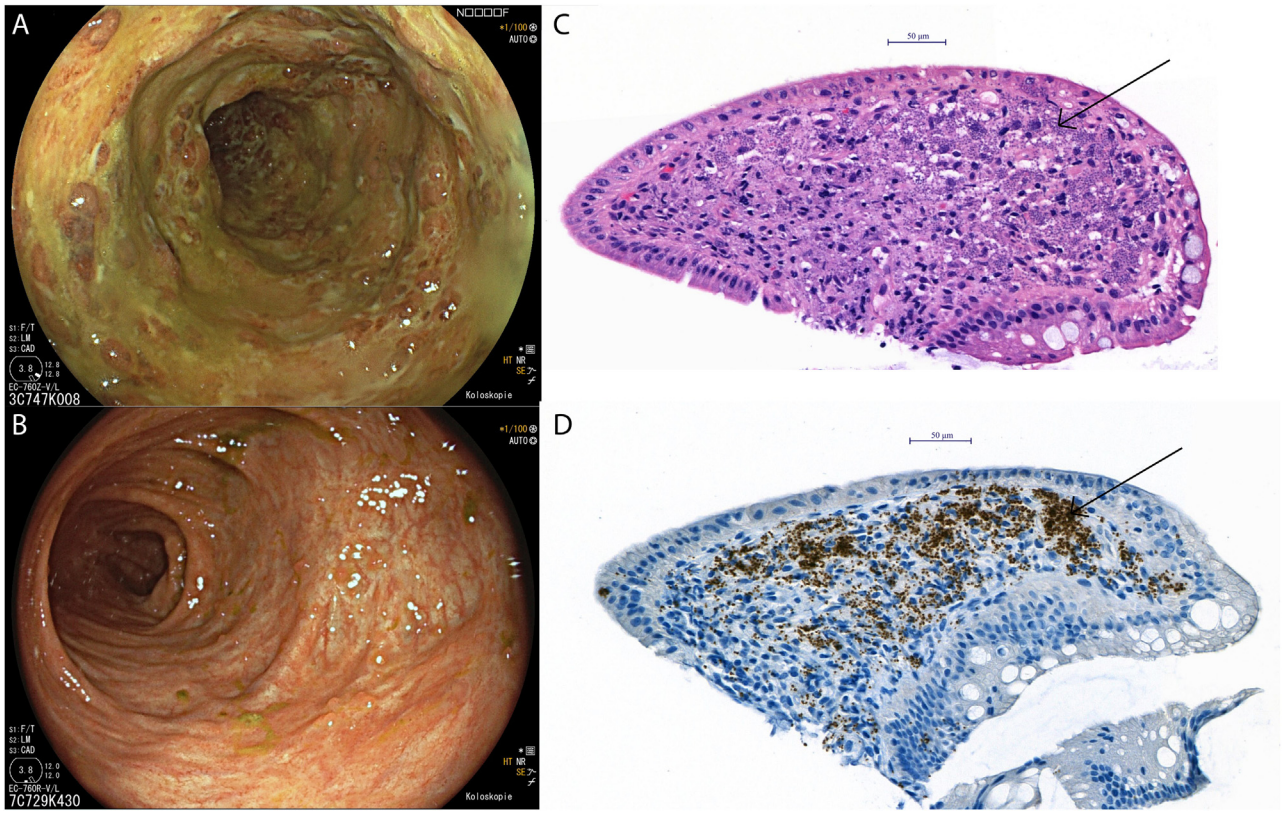

Figure 1. Initial colonoscopic findings in (a) showing a massive ulcerative inflammation with fibrin strands with decreasing inflammation from the caecum to the rectum, (b) showing the colonoscopy after eradication therapy with a much-reduced inflammatory activity in the sense of a remission and successful eradication, (c) hematoxylin-eosin staining of samples after vedolizumab initiation: colonic mucosa with crypt architectural disorder and moderate lymphocytic infiltrate. In addition, round to oval organisms (2-4 µm) are present intracellularly in histiocytes in the mucosa representing amastigotes of *Leishmania spp.*, marked by arrow. (d) CD1a staining: amastigotes are positive for CD1a (black oval structures). Biopsies taken during follow-up colonoscopy were clear of parasites.

ment of symptoms, whereas the calprotectin in the stool increased to 1397 mg/kg. Therefore, therapy with vedolizumab was initiated. This led to an initial remission of the bloody stool, and fever, and the frequency of diarrhea decreased.

Upon relapse of the symptoms further hematological and infectious diseases work up was performed. A CT of the abdomen showed a thickening of the ascending colon as well as consolidations of the left lower lung lobe attributed to atypic pneumonia. Serology for toxoplasmosis, CMV, EBV, Parvo-B19-Virus, coxiellosis, brucellosis, rickettsiosis, hepatitis-A/B/C/E virus, HIV, anaplasmosis, ehrlichosis, francicellosis, bartonellosis, as well as treponema remained negative. The PCR from the peripheral blood for malaria, tuberculosis, and leishmaniasis (whole peripheral EDTA-blood) remained negative as well. Therefore, a consensus was reached to perform bone marrow biopsy as well as a ^{18}FDG-PET-CT.

The bone marrow biopsy showed a hypercellularity with few dominant T-cell-subclones while electrophoresis showed free monoclonal light-chains of the kappa-type in urine. Light-chains of the lambda-type were positive in serum. The bone marrow also demonstrated a shift towards granulopoiesis as well as toxic granulations. No signs of *Leishmania* infiltration, other infections, or blood derived neoplasms were seen. The hyperreactive bone marrow was attributed to be reactive to chronic inflammation.

PET-CT showed splenomegaly with increased focal uptake of FDG, bone marrow activation, as well as diffuse tracer uptake of the entire colon. The native CT again showed a thickening of the colon wall as well as a diffuse lymphadenopathy. Due to increased FDG uptake of the colon another colonoscopy with biopsies was performed demonstrating recession of inflammation with remaining inflammatory activity in the right and transverse colon. Colonic biopsies confirmed remission of chronic inflammation alongside macrophages containing parasites resembling the amastigotes of *Leishmania spp*.

The samples of colonic mucosa with visible amastigotes tested PCR-positive for *Leishmania spp*. Further sequencing of the cpb-gene showed a 99% match with *L. donovani.* A PCR of an EDTA-blood sample remained negative, while an ELISA, immunoblot, and an IIFT (1:1280) were positive for *Leishmania spp.* Upon further questioning, the patient revealed that he was bit by a fly-like insect on the beach in Kenia which left a mark visible still today.

The patient started on a course of i.v. liposomal amphotericin B at 5 mg/kg/day, with a de-escalation to 3 mg/kg/day due to acute kidney injury as measured by an increased serum creatinine concentration. In total, the patient received a dosage of 46 mg/kg over 14 days.

In the first follow-up colonoscopy after 3 months no active inflammation and signs of mucosa healing were demonstrated. The *Leishmania*-PCR remained negative while the IIFT showed a significant decrease (1:320). Therefore, visceral leishmaniasis was considered as treated successfully. Further follow-up examinations after another 2 months confirmed no post-kala-azar-leishmaniasis, complete remission of pancytopenia and colitis, and normal serum creatinine level allowing to discontinue all medication without further relapse in follow-up appointments.

Discussion

We present the case of a patient with suspicion of long-latent visceral leishmaniasis which manifested in the colon mimicking ulcerative colitis and diagnosed by PCR out of colonic biopsies.

The very long incubation period can be explained by a successful suppression of the parasites without successful clearance. We suspect long-latent visceral leishmaniasis due to the sequencing demonstrating *L. donovani* which is not endemic in Italy, but in Kenia, Sudan, and India [1]. We consider Kenia as the most likely location for the primary infection.

It is of note that throughout the course of disease of this patient the PCR out of whole blood remained negative for leishmaniasis despite a meta-analysis reporting a pooled sensitivity of 93% with no difference between PCR performed out of the bone marrow versus the peripheral blood in immunocompetent patients [2]. According to the IDSA/ASTMH guidelines on visceral leishmaniasis a molecular assay out of the bone marrow aspirate should have preferentially been performed [3].

This case also highlights the importance of serology in addition to molecular assays. As a multimodal approach is suggested, serology could have been an important tool to diagnose this patient after the initial PCRs had turned out negative. In this patient, the appropriate diagnostic approach would have been to include the serology initially after the PCR, bone marrow microscopy, and blood smear for VL were negative, as recommended by the IDSA/ASTMH [3].

While a PCR performed out of the colonic mucosa is no common diagnostic method for leishmaniasis, it was the molecular tool allowing for the identification of the species due to the confirmed infiltration in this patient. Even after the initiation of vedolizumab only the PCR performed out of the colonic mucosa demonstrated a positive result. This highlights a very important issue: while we suspect the patient of having long-latent leishmaniasis for approximately 7 years, it was very difficult to diagnose, also due to the atypical manifestation in the colon.

Leishmania infections of the bowel are typically seen in immunocompromised patients with severe forms of AIDS or other exogenous immunosuppression [4]. This infiltration, however, mostly affects the duodenum with very few cases affecting the colon [5]. In this case, the patient was immune-competent until the locoregional immunosuppression with vedolizumab was started causing an increase in the multiplication rate of the parasites [6].

Conclusion

To the authors' knowledge, this is the first case of colonic visceral leishmaniasis mimicking an inflammatory pattern even on a microscopic level of ulcerative colitis. Splenomegaly, pancytopenia, and fever were symptoms pointing towards leishmaniasis, but PCR was initially negative. Correct diagnosis of leishmaniasis was established by PCR from colonic biopsies. Thus, serological tests and tissue PCR should be ordered to allow for adequate diagnosis and antiparasitic medical treatment.

Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to data privacy but are available from the corresponding author on request.

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Institutional review board statement

This study was approved by the Ethics Committee of the University of Regensburg, Regensburg, Germany. Registration: 24-3687-104.

Informed consent statement

Written informed consent to publish was obtained from the patient.

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Author contributions

J.B., S.S., M.M.: Study concept, design, and drafting of the manuscript. A.K., K.U., J.B., L.D.: Acquisition of data. K.U., J.B., A.M., S.S., M.M.: Analyses and interpretation of data. J.B., S.S., V.P., M.M.: Writing and critical revision of the manuscript for important intellectual content. M.M., S.S.: Supervision. All authors have read and agreed to the published version of the manuscript.

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