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English title: Terminal ileum resection as a trigger for overwhelming strongyloidiasis and ensuing serial sepsis in a patient with complicated Crohn's disease: a case report

Second language title: Strongyloidiasis nach Dünndarm- Resektion beim Patienten mit Morbus Crohn

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Abstract

Nematode Strongyloides stercoralis, outside tropics and subtropics present in small endemic foci, can cause an infection after direct skin contact with contaminated soil containing infective filariform larvae and, rarely, after intimate interhuman contact or after transplantation of an infected solid organ. Following skin penetration, migration, and maturation through several stages, a small number of invasive filariform larvae can develop anew in the gut lumen, perpetuating new cycles of penetration, tissue-migration, and multiplication, without leaving the host. In a state of immunosuppression, autoinfection can progress to life-threatening hyperinfection and/or infection disseminated through virtually any organ.

In developed countries, the most frequently recognized risk for severe hyperinfection is corticosteroid therapy, but it has been also described in malnourished, alcoholic, cancer, and transplant patients. Due to the frequent need for immunosuppressive therapy, patients suffering from inflammatory bowel disease (IBD) are susceptible to developing overwhelming strongyloidiasis. Strongyloidiasis can be easily overlooked in clinical settings and in many European regions there is poor insight into the epidemiological burden of this disease.

We present a case of overwhelming strongyloidiasis which triggered three successive episodes of sepsis caused by gut flora in a young patient suffering from stenotic form of Crohn's disease. S. stercoralis hyperinfection occurred in the corticosteroid-free period, shortly after the terminal ileum resection which was probably the trigger for the overwhelming course. The patient was successfully treated with 10-day albendazole therapy.

Disease pathogenesis in our patient is discussed, as well as the epidemiological features of strongyloidiasis in Europe, therapeutic options, and possible diagnostic strategies in patients affected by IBD.

Key words: Crohn's Disease, overwhelming strongyloidiasis, hyperinfection, eosinophilia, sepsis, immunosuppression, ileum resection

Abstract in German

Strongyloides stercoralis, der Zwergfadenwurm, der außerhalb der Tropen und Subtropen in kleinen endemischen Regionen vorkommt, kann nach direktem Kontakt der Haut mit kontaminiertem Boden,- der die infektiösen, filariformen Larven enthält oder selten durch intimen zwischenmenschlichen Kontakt oder Transplantation eines infizierten Organs,- eine Infektion verursachen. Nach der Hautpenetration, Migration und Reifung über mehrere Stadien kann sich eine kleine Anzahl von invasiven, filariformen Larven im Darmlumen entwickeln und weiter einen neuen Zyklus der Gewebseinwanderung und Vermehrung fortsetzen, ohne den Wirt zu verlassen. Im Stadium einer Immunsuppression kann sich eine solche Selbstansteckung in eine lebensbedrohliche hyper/disseminierte Infektion entwickeln.

In hochentwickelten Ländern stellt die Therapie mit Kortikosteroiden das häufigste bekannte Risiko für eine ausgeprägte Hyperinfektion dar. Aber sie wurde auch bei unterernährten, alkoholabhängigen und Krebspatienten, sowie bei transplantierten Patienten beschrieben. Wegen der oftmaligen Notwendigkeit einer immunsuppressiven Therapie bei Patienten mit einer chronisch-entzündlichen Darmerkrankung (CED) sind diese anfällig für die Entwicklung einer verheerenden Strongyloidiasis. In vielen europäischen Regionen besteht wenig Verständnis für die Epidemiologie dieser Erkrankung und kann daher im klinischen Alltag leicht übersehen werden.

Wir stellen den Fall einer schweren Strongyloidiasis-Hyperinfektion bei einem jungen Patienten mit einer stenosierenden Form eines Morbus Crohn vor, bei dem durch die Darmflora drei aufeinanderfolgende Schübe einer Sepsis ausgelöst wurden. Die Hyperinfektion mit *S. stercoralis* hat sich in einer kortikoidfreien Zeit entwickelt, kurz nach der Resektion des terminalen Ileums, die vermutlich der Auslöser des verheerenden Verlaufes war. Der Patient wurde erfolgreich mit einer 10-tägigen Albendazol-Therapie geheilt.

Wir haben die Pathogenese der Erkrankung bei unserem Patienten besprochen und auch die epidemiologischen Besonderheiten der Strongyloidiasis in Europa, die Therapiemöglichkeiten

und die möglichen Diagnosestrategien bei Patienten mit CED.

Schlüsselwörter: Morbus Crohn, Strongyloidiasis, Hyperinfektion, Eosinophilie, Sepsis, Immunsuppression, Darmresektion

Case report

Due to acute exacerbation of chronic obstructive ileus in a 37-year old male patient with stenotic and fistulizing form of previously therapeutically neglected Crohn's disease, a resection of the terminal ileum was performed in September 2015.

The patient, who lived in sanitated urban conditions in continental Croatia, was diagnosed with Crohn's disease at the age of 25. It progressed to an advanced stenotic and fistulizing form by the age of 35 despite a lingering, but unsettled, mesalazine and methylprednisolone therapy. The disease was also complicated by an ischemic cerebellar stroke at the age of 36, and by arterial occlusions of the lower extremities, which led to consecutive bilateral transtibial leg amputations in March and April 2015. During May and July 2015, the patient was institutionally rehabilitated with the aim of adopting prosthetic legs, and he was continuously confined to an indoor home and hospital environment.

Preoperative imaging evaluation revealed multiple ileal stenoses, up to 2 mm, prestenotic dilations, up to 7 cm, with radiological signs of chronic ileus accompanied by several enteroenteral/colic fistulas, which enabled normal enteral passage. Esophagogastroduodenoscopy (EGD) with pathohistological diagnosis (PHD) of gastric and duodenal mucosa samples yielded normal findings, and colonoscopy revealed stenotic valvula Bauchini.

At hospital admission, the patient with legs amputated was symptom-free and afebrile, but extremely malnourished. Reported laboratory findings were: serum protein level 34 g/L, albumin 13.3 g/L, RBCs 2.73x1012/L, Hb 111 g/L, MCV 105.9 fL, Tr 550x109/L, L 14.2x109/L with 1% eosinophils (EO) in differential count. Beside slightly decreased serum iron, calcium, phosphorus and magnesium levels, as well as C-reactive protein (CRP) of 8.9 mg/L, other routinely performed laboratory tests were unremarkable. Corticosteroid therapy (methylprednisolone 12 mg/day), was discontinued and intensive combined parenteral and enteral nutrition was introduced.

On the 20th in-hospital day, clinical and radiological signs of complete enteral passage obstruction urged a surgical treatment. A resection of 63 cm of terminal ileum, cecum and appendix was performed with strictureplasty and formation of unipolar stoma.

Postoperative fever with an increase of CRP to 196.2 mg/L, but without bacterial isolates, was empirically treated with a combination of meropenem, ciprofloxacin, and metronidazole, which ultimately led to resolution.

On the 6th postoperative day, clinical and MSCT signs of diffuse peritonitis developed. After relaparotomy, lavage, and drainage, many EO were seen in ascetic fluid. Blood, urine, and ascites cultures remained sterile and empirical therapy with meropenem was continued. However, during 6 weeks following peritonitis, the patient's condition deteriorated. Peripheral blood eosinophilia developed and reached continuously high levels, up to 6480 EO/µl. The almost continuously febrile patient had to be subjected to targeted antibiotic/antifungal therapy thrice, due to serial bouts of severe, presumably enteral sepsis, with Enterococcus faecium, Candida albicans and Escherichia coli proven by blood cultures, respectively.

In the critically ill, severely hypoalbuminemic patient with continuous weight loss, an EGD was performed after 6 weeks of clinical deterioration. PHD of gastric and duodenal bioptic samples revealed rich eosinophilic infiltration of lamina propria, and worm-like structures matching morphological characteristics of Strongyloides stercoralis (Figure 1). Blood serology (qualitative ELISA test # 9450 Strongyloïdes ratti, Bordier, Switzerland) was positive for S. stercoralis, but stool samples remained negative thrice for ova and parasites, by flotation methods and staining, microscopy of direct wet smears, and agar plate culture.

After initiation of a 10-day albendazole therapy in a dose of 15 mg/kg/day, the patient´s condition rapidly improved; symptoms resolved, and eosinophilia receded. One month later, ileostomy occlusion was performed and the patient was discharged without immunosuppressive therapy.

On follow-up visit, three months after albendazole therapy, the patient´s stool samples

remained negative for parasites, and peripheral blood eosinophilia resolved completely. The symptom-free patient fully recovered, but further colonoscopy revealed a relapse of Crohn's disease in neoterminal ileum. Because of the patient´s intolerance to cytostatics, infliximab therapy was introduced in May 2017, which was followed neither by clinical nor laboratory signs of strongyloidiasis reactivation. Unfortunately, the patient has not showed up for further parasitological controls.

Discussion

Although multiple predisposing factors for reactivation of chronic strongyloidiasis were present in our patient, namely the four weeks earlier discontinued corticosteroid therapy, severe malnutrition, and chronically disturbed gut passage, we believe, based on clinical symptoms sequence and laboratory signs, that ileal resection triggered the overwhelming strongyloidiasis in our patient. To our knowledge, such a case has not been previously described in literature.

Impaired gut motility has been recognized as one of the predisposing factors for reactivation of strongyloidiasis. Inversely, cases were described, where an overwhelming strongyloidiasis precipitated gut obstruction - in cases of acute primary hyperinfection, and those involving a reactivation of chronic infection in immunocompromised host [1-3].

Although usually penetrating colonic mucosa and perianal skin, the massive penetration of gastric and duodenal mucosa has also been described in patients with ulcerative colitis [4,5]. Normal EGD and PHD findings during preoperative evaluation suggest our patient being in an asymptomatic steady state with a low parasite burden.

Translocation of bacteria due to transmural migration of parasitic larvae has been proposed as a mechanism of death in immunocompromised patients [6]. Among 27 solid organ transplant recipients with donor-derived strongyloidiasis, the presence of sepsis was a predictor of mortality, as it was seen in all 9 patients who died (100.0%) and in 4 patients who survived (23.5%; $P < .001$) [7]. Despite targeted treatment of three septic episodes, each caused by

enteric flora, definitive improvement in our patient was achieved eventually by antiparasitic treatment, which supports the importance of transmural larval migration in their pathogenesis.

The prevalence and incidence of S. stercoralis infection in Croatia is unknown. Even in endemic regions, strongyloidiasis is one of the most overlooked helminthiasis among the neglected tropical diseases. Scarce studies regarding areas in European countries reveal strongyloidiasis prevalence in hospital settings: Italy 1.8%, Spain 1.9, Austria 5.2%, France 31.1%, Romania 48.8%; in community-based studies: Spain 14.8%, United Kingdom 12.7%, northern Italy 1%; and among refugees and immigrants: Sweden 1.0%, Italy 3.3%, Spain 4.2%, and France 5.6% [8,9]. In Germany, S. stercoralis infection is recognized as a parasitic professional disease in miners [10]. In Europe, there have been sporadic cases of reactivated strongyloidiasis in immunocompromised patients, reported from Belgium, Netherlands, Spain and Italy [11-14].

Peroral ivermectin is the first-line therapy for severe, overwhelming strongyloidiasis, with a reported eradication rate of approximately 80% [15], albendazole being the second-line therapy, due to its reported failure rate of up to 50% [13]. In comparison to ivermectin, its absorption from gastrointestinal tract is poorer and half-life is shorter (8-12 h vs. 16-28 h, respectively) [16]. However, unlike ivermectin, it does cross the blood-brain barrier, which makes it suitable for treating cerebral form of strongyloidiasis, and it binds less to serum proteins (70% vs. 93%, respectively) [16]. We believe that profound serum hypoproteinemia can enhance the efficacy of albendazole by increasing serum albendazole concentration which might have contributed to a rapid clinical cure with a single 10-day course in our patient, who was treated with albendazole because of its immediate availability.

Preventive parasitological examination of stool samples before starting immunosuppressive therapy, especially corticosteroids, in patients with IBD, has been proposed in the early 1980s [17]. This was followed by the recommendation for serological screening in patients from endemic areas, and those with unspecific GI symptoms or eosinophilia, before solid organ or hematopoetic transplantation [7,18,19].

Absence of eosinophilia in some symptomatic cases [20], and low sensitivity of parasitic stool sample examinations in patients with strongyloidiasis, not exceeding 46% even after 3 stool examinations, suggest the use of serological testing for diagnostics in symptomatic patients, whereby the sensitivity by ELISA can exceed 95% [21]. In patients with impaired gut passage and suspected severe strongyloidiasis, the examination of duodenal aspirate or a biopsy sample, in which the yield can be very high during hyperinfection, is a more appropriate direct diagnostic test.

We can conclude that gut resection should be considered as a potential trigger for overwhelming strongyloidiasis in chronically infected patients. Besides several parasitic stool examinations, we suggest serological screening in patients with IBD who might be exposed and in whom abdominal surgical treatment is planned. However, when eosinophilia and/or clinical symptoms develop in a postoperative period, an early EGD procedure with analysis of duodenal aspirate and biopsies could contribute to a rapid diagnosis in those patients.

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Figure 1. Bioptic sample of the duodenum with Strongyloides larvae visualized close to the mucosal surface and rich eosinophilic infiltration of lamina propria