



Case report

Successful treatment of *Enterocytozoon bieneusi* gastrointestinal infection with nitazoxanide in a immunocompetent patient



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ABSTRACT

Microsporidia are organisms that are known to cause opportunistic infections in immunocompromised individuals. The gastrointestinal tract is the most common affected organ. *Enterocytozoon bieneusi* is the most common species that infect humans. There are no known established guidelines for the treatment of this particular microsporidium. A 72-year old immunocompetent female presented to our hospital with diarrhea for four weeks. She had failed outpatient oral antimicrobial treatment for suspected traveler's diarrhea and *Clostridium difficile*. Initial stool cultures were negative but given her persistent symptomatology, stool PCR was sent to rule out microsporidia and was positive for *Enterocytozoon bieneusi*. Patient failed treatment with albendazole. She was then subsequently treated with nitazoxanide and achieved successful infection resolution. This case demonstrates the importance of considering atypical infections in patient with persistent symptoms and suggest that nitazoxanide is effective in treating infection caused by *Enterocytozoon bieneusi* microsporidia.

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Introduction

Microsporidia are unicellular organisms which infect both animal and humans [1]. They were originally known as parasites, but now they are classified as fungi or related to fungi [2]. Infection usually occurs through ingestion or inhalation of spores [1]. Spores have a glycoprotein outer layer that provides environmental protection [1]. Microsporidia can affect multiple organ systems including intestinal, ocular, muscular, pulmonary, and renal. Currently, there are fourteen different organisms reported to infect humans with the two most common being the *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* [3].

In general, microsporidia are opportunistic infections with most cases reported in HIV positive and immunocompromised individuals [4]. There are a few cases reported in immunocompetent individuals. The most common clinical manifestation is diarrhea which is the result of malabsorption caused by reduced height and surface area of the intestinal villous [5]. Other rare clinical manifestations include pulmonary, ocular, and muscular [1].

The diagnosis is made by detection of spores in stool. Staining technique by Trichrome has only 63.8 percent sensitivity [6]. Polymerase chain reaction (PCR) stool assays has 100 percent

sensitivity and 97.9 percent specificity [6]. Albendazole is generally used for treatment however it is not very effective against *Enterocytozoon bieneusi* [7]. We report a case of a 72-year old immunocompetent female that presented with *Enterocytozoon bieneusi* gastrointestinal infection who was successfully treated with nitazoxanide.

Case report

A 72-year old female, with past medical history of hypothyroidism, hypoglycemia and *Clostridium difficile* colitis, presented with diarrhea ongoing for four weeks. Patient reported the start of her diarrhea after a camping trip to Milwaukee, Wisconsin, USA. She admitted to drinking water from the campsite. Patient reported ten liquid bowel movements per day with associated subjective fevers, chills, nausea, and malaise.

Approximately ten days prior to admission, patient was treated outpatient with oral sulfamethoxazole/trimethoprim and metronidazole by her primary care doctor for presumed *Clostridium difficile*/traveler's diarrhea. Clinically, patient's diarrhea continued to worsen and she presented to the hospital for further evaluation. She was admitted and started on oral vancomycin and metronidazole. Review of outpatient stool studies demonstrated negative *C. difficile* screen.

Laboratory analysis revealed normal white count (5900 per cubic millimeter); hypokalemia (2.1 mmol); hypophosphatemia (2.1 mg/dL); mildly elevated aspartate aminotransferase (47 U/L);

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acute kidney injury (creatinine 1.06 mg/dL); normal TSH (0.527 uIU/ml); gram stain demonstrated few fecal leukocytes, few yeast and absence of coliform flora; negative Shiga toxins; negative *Clostridium difficile* screen (GDH antigen and toxins); negative *Giardia lamblia* and cryptosporidium; negative rotavirus antigen; negative serum norovirus 1 and 2 by PCR; negative transglutaminase antibody (IgA and IgG); negative *Entamoeba histolytica* serology; negative serum HIV 1&2; normal serum immunoglobulins (IgA 346 mg/dL, IgM 80 mg/dL, IgG 1020 mg/dL); normal CRP (<0.15 mg/L), normal calprotectin fecal (<16 ug/g).

The patient was treated symptomatically with intravenous fluids, antidiarrheal and cholestyramine, however, her diarrhea remained uncontrolled. CT scan of the abdomen and pelvis with intravenous contrast was within normal limit. The gastroenterology service performed colonoscopy to the terminal ileum. Endoscopy revealed non-specific pancolitis with mild terminal ileum erythema and moderate pancolonic diverticulosis. Biopsies of the colon and terminal ileum revealed no morphologic abnormalities.

The patient had prolonged hospital stay. Repeat stool cultures were negative. Given her persistent diarrhea and camping history, stool PCR was sent to specialty lab to rule out cryptosporidium. *Enterocytozoon bieneusi* by PCR was detected. Infectious disease team recommended treatment with albendazole 400 mg twice daily. Patient received six doses but the medication was discontinued secondary to concern of its effectiveness. The patient continued to have severe diarrhea and she was eliminating the tablets undigested in her stool. Crushing albendazole tablets failed to make a difference in the clinical response.

At this time and after literature review, decision was made to start patient on nitazoxanide with reported successful treatment in case reports. She was started on 500 mg by mouth twice daily for fourteen days. Few days after initiating therapy, her stool started to form and became less frequent and she was discharged home. A week later, patient returned to the hospital secondary to decreased oral intake related to nausea which she attributed to nitazoxanide. She was admitted and treated supportively. Repeat PCR testing for microsporidia seven days on therapy was negative. She was started on rifaximin 550 mg by mouth twice daily for possible post-infectious irritable bowel. Patient completed fourteen days of nitazoxanide. PCR testing was repeated 14 days after treatment was completed and remained negative.

Discussion

There are over one thousand species of microsporidia and about fourteen of those can infect humans [8]. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common that infect humans [3,8]. Though it more commonly infects immunocompromised individuals (HIV positive, organ and bone marrow recipients), infection has also been described in immunocompetent hosts [9]. In a study involving about two hundred patients in Iran, microsporidia were detected in fourteen percent of immunocompromised patients (n = 20/199) and one and half percent of the immunocompetent patients (n = 1/68) [9]. The most common clinical symptoms were diarrhea and abdominal pain. In another study in Cameron, one-hundred and eighty one patient were studied and the prevalence of microsporidia in immunocompetent patients (n = 126) were surprisingly found to be sixty-seven percent [10]. In this study, patients were asymptomatic suggesting patients developing tolerance to the chronic infection. The mode of transmission is not fully understood and could be waterborne, food-borne, or zoonotic [4]. In a study in China, the rate of microsporidia infection was found to be higher in people that drink unboiled water than those with other sources suggesting water as a potential source of transmission [11].

Our patient was ultimately diagnosed with *Enterocytozoon bieneusi* when stool was sent for PCR testing for microsporidia as repeat "routine" stool studies were negative. In general, microsporidia are treated with albendazole however this medication is not very effective against the *E. Bieneusi* [12]. The current recommendation is to use Fumagillin in the treatment of infections due to *E. Bieneusi* in HIV-infected people [12]. Unfortunately, fumagillin is not available in the United States and its use limited elsewhere secondary to toxicity [13]. Our patient was tried on albendazole without success as she was eliminating the tablets undigested. There has been two cases of *E. bieneusi* reported in the literature (both in immunocompromised patients) successfully treated using nitazoxanide one-thousand milligram twice daily for sixty days [14,15]. Given the failure to respond to albendazole and after discussion with patient, we decided to trial nitazoxanide 500 mg by mouth twice daily for fourteen days. A few days post therapy, her diarrhea improved, and stool started to form. PCR testing in the stool were negative to detect microsporidia at day seven of treatment. They remained negative at day fourteen post treatment. Two-year follow-up with patient revealed no infection relapse.

In conclusion, intestinal infection due to the microsporidium *E. bieneusi* in immunocompetent patients has been reported. A clinical suspicion for atypical infection should be included in the workup specially if symptoms do not self-resolve. Obtaining PCR in the stool is the best method for detection. Management and treatment represent a clinical challenge specially for *E. bieneusi* species as the drug of choice (fumagillin) is not available in the United States and its use is limited secondary to side effects. The literature review revealed two cases of successful treatment using nitazoxanide. Our case illustrates that importance of considering microsporidial infection even in immunocompetent patients when symptoms fail to self-resolve. Our case suggests that nitazoxanide is effective in eradicating this strain of microsporidium and trials needed to further assess its role.

CRedit authorship contribution statement

Zaid Saffo: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing - original draft. **Najab Mirza:** Validation, Formal analysis, Writing - review & editing.

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