Giardiasis: report of a case refractory to treatment

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SUMMARY

Caused by the protozoan *Giardia lamblia*, giardiasis is one of the most common parasitic diarrheal infections affecting humans. Although a variety of antigiardial drugs are available to treat infections in humans, failure of conventional treatment with nitroimidazoles for giardiasis has been increasingly reported. We describe the follow-up of a patient with recurrent giardiasis refractory to nitroimidazoles. Despite the different therapies received, the symptomatology and parasitic forms of *G. lamblia* persisted in the patient. There is no standard treatment regimen for giardiasis refractory to nitroimidazoles. When treatment failure is confirmed, it is necessary to switch to second-line regimens.

Keywords: *Giardia*, giardiasis, nitroimidazoles, treatment failure, combination therapy.

INTRODUCTION

Giardiasis is a common gastrointestinal parasitic infection that affects humans worldwide, with a reported prevalence of up to 30% in low-income countries [1]. A lower prevalence is observed in high-income countries, where infections are usually associated with travel [2]. Infection occurs by ingestion of cysts in faecally contaminated food or water, or through person-to-person contact [3]. The clinical manifestations are quite heterogeneous, ranging from asymptomatic or with common symptoms such as steatorrhea and abdominal pain to systemic symptoms such as fever and weight loss [1,3]. The diagnosis of giardiasis in a clinical setting is based on visual recognition of *Giardia* cyst or trophozoites by light microscopy, using concentration techniques [3]. Several different therapeutic agents are available to treat giardiasis, but in some cases the complete parasitological cure is not achieved, which implies a failure of the treatment [4-7]. We present a case report of giardiasis refractory to treatment.

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CASE REPORT

We present a 39-year-old man with clinical manifestations of *Giardia* infection unresponsive to standard treatments.

In January 2015, the patient complained of watery diarrhea (three loose stools daily); diffuse abdominal pain of moderate intensity, bloating, nausea, abdominal distension, belching, weight loss, asthenia and adynamia. The diagnosis of giardiasis was confirmed by the detection of *G. lamblia* cysts and trophozoites in fecal smears. Initially, the patient received a 7-day course of oral metronidazole, 500 mg given t.i.d., but showed no signs of improvement. In March 2015, the patient was re-evaluated due to symptom persistence and *G. lamblia* cysts and trophozoites were still found in fecal samples. The patient received a 4-week course of oral metronidazole, 750 mg given b.i.d., followed by 500 mg of metronidazole administered b.i.d. for 2 weeks, resulting in a partial improvement of symptoms. After therapy discontinuation, all symptoms reappeared. Subsequent

Table 1 - Summary of all antigiardial drugs with dosage administered to the patient, 2015-2016.

Date	*Drug*	*Dosage*
14/01/15	Metronidazole	500 mg t.i.d. during 7 days
09/03/15	Metronidazole + Metronidazole	750 mg b.i.d. during 4 weeks + 500 mg b.i.d. during 2 weeks
05/06/15	Tinidazole + Albendazole	2 g as a single dose + 200 mg q.d. during 7 days
07/10/15	Furazolidone	100 mg q.i.d. during 7 days
06/11/15	Secnidazole	2 g as a single dose*
07/06/16	Nitazoxanide + Metronidazole	500 mg b.i.d. during 3 days + 500 mg t.i.d. during 7 days

*Patient presented an adverse effect to Secnidazole.
(q.d.): once daily; (b.i.d.): twice a day; (t.i.d.): three times a day; (q.i.d.): four times a day.

treatments with tinidazole, albendazole, furazolidone and secnidazole were also unsuccessful (Table 1). Transient improvement of symptoms was noted during treatment, but *Giardia* trophozoites where still present in stool samples (Table 2). The patient and his family denied having known risk factors for giardiasis, and the patient medical history did not suggest the presence of immunodeficiency. Fecal samples were examined for the presence of cysts and trophozoites of protozoa, and eggs and larvae of helminths by direct microscopy using 0.83% saline and 1% Lugol's iodine preparations. In addition, each stool sample was analyzed by the formol-ether concentration technique. Laboratory tests of blood samples showed the presence of eosinophilia and an increased average globular volume (Table 3).

In June 2016, the patient had similar complaints: nausea, belching, occasional watery diarrhea and weight loss. The physical examination revealed generalized mucocutaneous pallor, soft abdomen, mildly painful to palpation, with no signs of peritoneal infiltration, anus erythematosus and a weight of 58 kg (at the time of symptom onset, the patient's weight was 70 kg). Subsequently, the patient received a 3-day course of oral nitazoxanide, 500 mg given b.i.d., and metronidazole, 500 mg given t.i.d. for 7 days. After the treatment the symptoms improved, diarrhea resolved, and the patient remained healthy for the following 3 years. Results of stool samples for trophozoites became negative in August 2016 and the patient remained negative upon follow-up testing.

DISCUSSION

In the present report, we present the case of an immunocompetent patient with giardiasis who

Table 2 - Results of parasitological examinations of faecal samples between 2015-2019.

Date (d/m/y)	*Parasite morphology*	
	Cysts of G. lamblia	*Trophozoites of G. lamblia*
14/01/15	+	+
09/03/15	+	+
05/06/15	+	+
07/10/15	+	+
06/11/15	+	+
23/02/16	-	+
29/04/16	-	+
07/06/16	-	+
10/08/16	-	-
31/05/17	-	-
22/05/18	-	-
20/05/19	-	-

(d/m/y): day/month/year; (+): positive; (-): negative.

Table 3 - Results of laboratory tests of blood samples between 2015-2016.

Date (d/m/y)	*Leu (cells/mcL)*	*Eos (%)*	*Hgb (g/dL)*	*Hct (%)*	*ESR (mm/h)*
14/01/2015	5,900	8.2	15.6	46	110.4
09/03/2015	6,100	7.1	15.2	46	105.4
05/06/2015	6,300	6.9	15.2	43	94.2
07/10/2015	6,900	8.6	14.8	41	92.4
06/11/2015	7,200	7.9	14.9	39	90.1
23/02/2016	7,300	5.1	15.1	44	88.2
29/04/2016	7,500	3.3	15.3	45	88.1
07/06/2016	7,900	1.4	15.6	46	88.4

WBC: White blood cell count; Eos: eosinophils; Hgb: hemoglobin; Hct = hematocrit; ESR: erythrocyte sedimentation rate; mcL: microliter; dL: deciliter; mm/h: millimeters per hour.

did not achieve a complete parasitological resolution despite several standard courses of therapy for giardiasis. Despite initial improvement, the symptoms returned always after the treatments interruption, and Giardia trophozoites and cysts were still present in the stool samples [8].

Treatment-refractory giardiasis is an increasingly common problem in clinical practice and currently, little evidence is available to guide initial empiric therapy of refractory giardiasis and additional testing [7-11].

Although treatment-refractory giardiasis is a problem in clinical practice, most of the refractory cases can be cured due to the large number of alternative and combination regimens of antigiardial drugs [5, 6]. The most commonly used drugs for first-line treatment of giardiasis are the 5-nitroimidazoles, particularly metronidazole [5,8]. Other drugs used are tinidazole, albendazole, nitazoxanide, quinacrine and furazolidone [5].

Starting with a combination of drugs to improve clinical outcomes is a suggested strategy in cases of initial treatment failure [7]. A clinical observational study in Norway showed that metronidazole in combination with albendazole was effective in 30 (79%) out of 38 adult patients. Paromomycin was effective in three out of six patients and quinacrine in combination with metronidazole was effective in three patients [10]. Another study reported the results of a group of six immunocompetent and immunocompromised patients whose infections were cured after they received a combination of quinacrine and metronidazole [12]. In a case series of 10 patients with refractory giardiasis, clinical and parasitological cure was achieved in all patients who received a combination of two or more drugs with metronidazole, tinidazole, paromomycin or albendazole [13]. Another case series reported eleven pediatric patients with drug-refractory giardiasis, for whom therapy with a combination of secnidazole and albendazole resulted in cure for 9 of the 11 (82%) patients [14].

In this present case report, treatment-refractory giardiasis was documented by parasitological examinations. No susceptibility *in vitro* tests were performed. We evaluate the possible factors associated with therapeutic failure, such as adherence to drugs, the dosage administered, immunological status and reinfection [7, 8]. Given that there is no standard treatment regimen for giardiasis refractory to nitroimidazoles, we prolonged initially the monotherapy with a higher drug doses and successively combined different anti-giardial drugs regimens.

CONCLUSIONS

Treatment failure of *G. lamblia* infection is defined by the persistence of signs and symptoms and by the presence of parasites in stool samples. Limited data are available to guide treatment when nitroimidazole therapy has failed. The combination therapy with two or more anti-giardial drugs seems to be superior to monotherapy in the management of treatment-refractory cases. It would be important to obtain molecular epidemiological evidence on the genetic variability of circulating *G. lamblia* isolates in cases with refractory giardiasis.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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REFERENCES

[1] Fletcher S.M., Stark D., Harkness J., Ellis J. Enteric protozoa in the developed world: a public health perspective. *Clin. Microbiol. Rev*. 25, 420-449, 2012.
[2] Giacometti A., Cirioni O., Fortuna M., et al. Giardiasis: a parasitic disease of continued topicality. Study of prevalence among a selected adult population. *Infez. Med*. 8, 82-86, 2000.
[3] Minetti C., Chalmers R.M., Beeching N.J., Probert C., Lamden K. Giardiasis. *BMJ* 355, i5369, 2016.
[4] Leitsch D. Drug Resistance in the microaerophilic parasite *Giardia lamblia*. *Curr. Trop. Med. Rep.* 2, 128-135, 2015.
[5] Granados C.E., Reveiz L., Uribe L.G., Criollo C.P. Drugs for treating giardiasis. *Cochrane database Syst. Rev*. 12, CD007787, 2012.
[6] Escobedo A.A., Almirall P., Gonzalez-Fraile E., Ballesteros J. Efficacy of 5-nitroimidazole compounds for giardiasis in Cuban children: systematic review and meta-analysis. *Infez. Med*. 27, 58-67, 2019.
[7] Carter E.R., Nabarro L.E., Hedley L., Chiodini P.L. Nitroimidazole-refractory giardiasis: a growing problem requiring rational solutions. *Clin. Microbiol. Infect.* 24, 37-42, 2018.

[8] Lalle M., Hanevik K. Treatment-refractory giardiasis: challenges and solutions. *Infect. Drug Resist*. 11, 1921-1933, 2018.
[9] Nabarro L.E.B., Lever R.A., Armstrong M., Chiodini P.L. Increased incidence of nitroimidazole-refractory giardiasis at the Hospital for Tropical Diseases, London: 2008-2013. *Clin. Microbiol. Infect*. 21, 791-796, 2015.
[10] Morch K., Hanevik K., Robertson L.J., Strand E.A., Langeland N. Treatment-ladder and genetic characterisation of parasites in refractory giardiasis after an outbreak in Norway. *J. Infect.* 56, 268-273, 2008.
[11] Munoz Gutierrez J., Aldasoro E., Requena A., et al. Refractory giardiasis in Spanish travellers. *Travel Med. Infect. Dis*. 11, 126-129, 2013.
[12] Nash T.E., Ohl C.A., Thomas E., Subramanian G., Keiser P., Moore T.A. Treatment of patients with refractory giardiasis. *Clin. Infect. Dis*. 33, 22-28, 2001.
[13] Lopez-Velez R., Batlle C., Jimenez C., Navarro M., Norman F., Perez-Molina J. Short course combination therapy for giardiasis after nitroimidazole failure. *Am. J. Trop. Med. Hyg*. 83, 171-173, 2010.
[14] Escobedo A.A., Almirall P., Chirino E., Pacheco F., Duque A., Avila I. Treatment of refractory paediatric giardiasis using secnidazole plus albendazole: a case series. *Infez. Med*. 26, 379-384, 2018.