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Research Note

Unusual clinical course of trichinellosis with relapse

Z. PARALIČOVÁ[1], P. DUBINSKÝ[2], P. KRISTIAN[1], P. JARČUŠKA[1*]

[1]The Department of Infectology and Travel Medicine, Pavol Jozef Šafárik University, Faculty of Medicine and L. Pasteur University Hospital Košice, Rastislavova 43, Košice, E-mail: *infekcne@unlp.sk*; [2] Institute of Parasitology of the Slovak Academy of Science, Hlinkova 3, Košice

Summary

During an outbreak of trichinellosis in Eastern Slovakia in 2008, 16 people were hospitalized, including 10 patients having specific anti-*Trichinella* antibodies. The disease relapse was seen in a 68-year-old woman two weeks after her discharge from hospital, where she was treated with albendazole and prednisone for 10 days. Clinical symptoms of trichinellosis, eosinophilia, elevated CRP and LDH levels were observed again with recorded elevation of aminotransferase levels during the relapse. Herein we discuss a potential cause of unusual relapse of trichinellosis with liver damage in a female patient with type II diabetes mellitus.

Keywords: trichinellosis; outbreak; symptomatology; relapse

Introduction

Trichinellosis is a parasitic disease affecting various vertebrate species. Humans become hosts accidentally after consumption of insufficiently heat-treated meat that is infected with *Trichinella* larvae. Most infections are asymptomatic, however massive contaminations lead to the development of clinical symptoms that – in rare cases – may be severe or even life threatening. The intensity of symptoms depends on the amount of consumed live larvae, on causative species and host factors. The first stage of the disease caused by the presence of adult worms in the intestine is manifested by gastrointestinal symptoms. During the second week after infection, new larvae penetrate into the blood stream and systemic invasion occurs afterwards. Larvae settle preferentially in the striated muscles what is manifested by painful myositis. This is often accompanied by signs of fever, fatigue, periorbital edema, headaches and less frequently by exanthema. Among the most severe signs of trichinellosis are myocarditis, meningitis and pneumonia, which could lead to death (Kociecka, 2000; Dupouy-Camet *et al*., 2002; Gottstein *et al*., 2009).
Herein we present the case of a female patient with trichinellosis with a subsequent relapse two weeks after her discharge from hospital.

The outbreak

The outbreak of trichinellosis occured in Eastern Slovakia in 2008, after ingestion of pork meat from pig slaughtered at home. Meat products were prepared for a wedding dinner (Paraličová *et al*., 2009). Out of 55 persons participating on the wedding party, sixteen people, suspected of being infected, were hospitalized at the Department of Infectology and Travel Medicine (DITM), University Hospital in Košice. The causative agent of infection was confirmed to be *T. britovi*. Muscle larvae were confirmed in pork meat and smoked sausages investigated four weeks after the onset of the outbreak (Dubinský *et al*., 2008). Two patients exhibited the asymptomatic course of trichinellosis and the diagnosis was made on the basis of elevated eosinofils and epidemiological history. In 8 patients the course of the disease was mild and in 6 patients moderate. None of the patients had severe complicated course with organ damage. Anti-*Trichinella* specific IgG antibodies were detected by indirect enzyme-linked immunosorbent assay (ELISA) with ES antigens of *Trichinella spiralis* and *T. britovi*, according to a method published Havasiová & Dubinský (1994). Specific anti-*Trichinella* antibodies were confirmed in 10 patients (Tab. 1).

Case report

A 68-year-old woman with a history of arterial hypertension and type II diabetes mellitus participated actively in butchering where she had tasted raw meat. Three weeks after ingestion, first clinical signs of trichinellosis occurred: headaches, myalgia mainly in neck, thighs and shanks,

Table 1. Outbreak of trichinellosis in Eastern Slovakia in 2008

	Number
Patients	
Hospitalized	16
Serologically positive	10
Signs and symptoms	
Fever	14
Myalgia	13
Fatigue	11
Exanthema	6
Periorbital oedema	4
Diarrhoea	3
Elevated laboratory parameters	
Eosinophils	10
C reactive protein	9
LDH	5
Creatine kinase	4
Treatment	
Antihelminthic treatment	16
Prednisone treatment	6

fever up to 38.6 °C with shivers. The patient was taking antipyretics but the symptoms persisted; after two days exanthema spread on her chest and limbs and she developed periorbital edema. Three days after clinical signs occurred, she was admitted to DITM with suspicion of trichinellosis. Laboratory tests showed normal levels of leucocytes 7.5 x 10^9/l with 15 % eosinophilia (Tab. 2), eosinophilia progressed during hospitalization up to 27 %. The patient had elevated muscle CK enzymes (creatine kinase) 4.6 μkat/l and LDH (lactate dehydrogenase) 5.14 μkat/l. She had decreased levels of total proteins (62.8 g/l) with normal level of albumin (41.4 g/l), increased level of C-reactive protein (CRP) 40.3 mg/l and normal level of aminotransferases (AST 0.36, ALT 0.70, GMT 0.38 μkat/l). The albendazole treatment was started with the dose of 2x400 mg/day for 10 days. However, her clinical status did not improve (exacerbated exanthema and headaches), therefore prednisone was included with an initial dose of 50 mg/day. In the course of the treatment the patient's condition was gradually improving and after 14 days of hospitalization she was discharged from hospital, free of any clinical symptoms of trichinellosis, with normal laboratory findings.

The next two weeks the patient reported doing well; she stated that she did not ingest any contaminated meat anymore. However, afterwards she developed fever with shivers, chills and significant sweating, headaches and myalgia returned, accompanied by arthralgias, mainly in shoulders and knees and exanthema reappeared. After a week of self-treatment at home the symptoms persisted, therefore the patient visited the regional infectiology outpatient department in Rožňava where after laboratory examination the liver damage was confirmed and she was readmitted at DITM.

During second hospitalization, laboratory findings (Tab. 2) showed elevation of LDH (6.78 μkat/l), CRP (50.5 mg/l) and eosinophilia (17 % of total amount of leukocytes 9.5 x 10^9/l). Level of proteins was normal (72.3 g/l). Compared to first hospitalization we found elevated levels of aminotransferases: AST 5.6 μkat/l and ALT 9.8 μkat/l. Levels of GMT, ALP and bilirubin were normal (at the end of the first hospitalization all measured parameters were within normal range). Elevation of transaminases progressed to maximum values of AST 14.9 and ALT 27.9 μkat/l; another increase of LDH occurred up to 11.5 μkat/l. No other cause of liver damage was found in serological testing. The patient was treated by mebendazole with a dose of 1.0 g bid, for 10 days. Mebendazole was used in order to eliminate the potentially deficient effect of albendazole that was used during first course of therapy and its possible hepatotoxicity.

Table 2. Lab tests results of the patient at the first and second hospitalization

	1st hospitalization			**2nd hospitalization**		
Date	**19th June**	**25th June**	**30th June**	**25th July**	**4th Aug**	**19th Aug**
Lkc (x10^9/l)	7.5	12.0	10.8	9.5	10.9	12.2
Eoz(%)	17	27	2	17	19	2
FW	16/32	-	-	50/84	-	-
CRP (mg/l)	40.3	< 5	< 5	50.5	21	-
CK (μkat/l)	4.6	1.22	1.03	1.32	-	-
LDH (μkat/l)	3.46	5.14	2.87	6.78	11.5	-
AST (μkat/l)	0.36	-	-	5.6	14.9	0.5
ALT (μkat/l)	0.70	-	-	9.8	27.9	1.2
GMT (μkat/l)	-	-	-	0.85	-	1.46
Proteins (g/l)	62.8	-	-	72.3	-	-

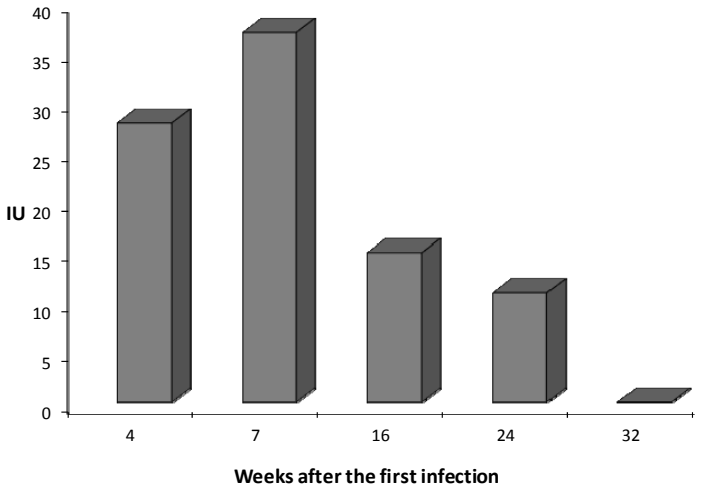

Fig. 1. Dynamics of anti-*Trichinella* antibodies detected by ELISA

In the course of the treatment, clinical symptoms and exanthema subsided, however levels of aminotransferases and eosinophilia worsened. Therefore prednisone with an initial dose of 60 mg per day was administered. During this therapy the clinical condition and laboratory findings gradually improved, only intermittent myalgias persisted.
Dynamics of anti-*Trichinellosis* antibodies (Fig. 1) had an interesting curve, reaching a maximum after finishing the first therapy with albendazole with a gradual decline.

Discussion

This is an unusual case when two weeks after finishing treatment for trichinellosis and discharging from hospital the disease relapse occurred and necessitated second hospitalization. The same clinical signs, as seen during first hospitalization, were observed. We have registered new attack of fever, headache, myalgias, intermittent exanthema and laboratory findings consistent with trichinellosis. Liver damage was manifested by elevated levels of aminotransferases.
Other cases reporting trichinellosis relapse in literature are scarce. Shimoni *et al*. (2007) report in their study a comparison of trichinellosis clinical courses in patients treated with anti-helminthic, either with (23 patients) or without prednisone (7 patients). In the non-prednisone group relapse occurred in 12 patients. Deterioration of the disease was most evident from day 4 till day 17, median of 9 days, from the treatment initiation. The most common symptoms were fever, myalgias, headache and abdominal pain. There was no repeated elevation of muscle enzymes. Symptoms subsided quickly during 24 hours of prednisone therapy. Aforementioned study supports the hypothesis that worsening of symptoms during treatment is common and that therapy with prednisone can prevent *Trichinella* relapse (Shimoni *et al*., 2007).
The relapse in our patient might be due to following reasons: 1) serial production of newborn larvae by *Trichinella* females; 2) higher reproduction capacity of *Trichinella* due to diabetes mellitus in our patient; 3) the dosing of albendazole was insufficient given the high BMI 4) hypothetically, the reinfection after the first hospitalization might have occurred.
In our patient, the relapse occurred despite prednisone treatment and not only clinical symptoms reappeared but also elevation of muscle enzymes and aminotransferase levels occurred. The causes of the relapse might be attributed to production of newborn larvae by *Trichinella* females still present in the intestine from the first episode or reinfection; however she did not admit repeated ingestion of contaminated meat.
Wakelin and Denham (1983) stated that adult *Trichinella* live in humans 6 weeks or more depending on species. Repeated signs of trichinellosis occurred 8 weeks after ingestion of contaminated meat. Their intensity and laboratory values were similar to those at the first hospitalization 4 weeks after infection, leading to conclusion of similar intensity as in our case. However, the patient was treated in the 6^{th} and 7^{th} week after infection with albendazole with a dose that was efficient in other patients infected during this outbreak and in no other case trichinellosis relapse was confirmed. Unlike others, this patient had type II diabetes mellitus. Concomitant diabetes mellitus and associated hyperglycemia could have influenced the number of adult worms in patient's intestine. Spaldonova *et al*. (1974) have found that in laboratory animals with alloxan-induced diabetes more muscle larvae were present. Spaldonova *et al*. (1974) and Pawlowski (1967) assume that with diabetes, more adult *Trichinella* develop in intestine.
Another explanation of alebendazole failure is that albendazole is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility. Albendazole concentrations are negligible or undetectable in plasma as it is rapidly converted to the sulfoxide metabolite prior to reaching the systemic circulation. The systemic anthelmintic

activity has been attributed to the primary metabolite, albendazole sulfoxide. Oral bioavailability appears to be enhanced when albendazole is co-administered with a fatty meal (estimated fat content of 40 g) as evidenced by higher (up to 5-fold on average) plasma concentrations of albendazole sulfoxide as compared to the fasted state (ZENTEL, Product Information, 2011). In general, patients with initial period of trichinellosis have poor food intake and expectable plasma level of albendazole is lower than plasma level in healthy subjects with normal food intake. There were no differences in plasma levels of albendazole in infected and in non-infected mice. The area under the blood concentrations to time curve (AUC) for albendazole sulphoxide was not significantly higher in infected mice than in control mice during the initial period of intestinal infection (Rodríguez *et al*., 2009).

According to a higher body mass index of our patient, the prescribed level of albendazole in muscles was lower than in patients with normal BMI during treatment with a standard dosage regimen of albendazole (400 mg twice a day).

The therapeutic effect of albendazole in our patient could have been also weakened by worsening liver disorder. Administered albendazole is metabolized in the liver and converted into albendazole sulphoxide efficient as antihelminthic agent. With suppressed liver function this conversion may be inhibited and is manifested by weaker effect of albendazole. Based on assumed weaker therapeutic levels of albendazole sulphoxide in this patient, the elimination of adult *Trichinella* from intestine was probably incomplete. Lower levels of therapeutically effective metabolite could have inhibited production of new-born larvae. Such parasitostatic effect of albendazole on parasite germinating cell is also known in *Echinococcus multilocularis*. After cessation of albendazole treatment, the growth of larvocysts is resumed (Reuter *et al*., 2000). When a 10-day-administration of albendazole was completed during the first hospitalization, similar regeneration of *Trichinella* females parasitizing in intestine could have occurred and the production of new born larvae might continue. Migration of these larvae into muscles caused relapse of trichinellosis.

Hypothetically, the trichinellosis relapse could also have been induced by reinfection after discharging the patient from hospital, although she denied this issue. Considering the fact that the portion of meat from infected pig has been processed into sausages in which up to 27.2±7.3 *Trichinella* larvae per gram were present (Dubinský *et al*., 2008), this food could have been the source of reinfection. More patients were infected particularly by sausages during this outbreak (Paraličová *et al*., 2009). This second option is supported by the fact that the clinical signs, eosinophilia, CRP and LDH levels were equal or even higher than those in the course of first infection. Only the CK values were lower. After mebendazole therapy, the clinical status of patient and eosinophilia values improved in short time.

Available literature addresses several cases of liver damage during trichinellosis. Januszkiewicz *et al*. (1970) have found hepatomegaly in patients who contracted trichinellosis. Remig and Fröscher (1987) presented collected data from trichinellosis outbreak in Germany where 3 out of 193 infected patients had intercurrent hepatitis. Similarly Turk *et al*. (2006) have confirmed hepatotoxic effect of *Trichinella* when during trichinellosis outbreak in Turkey out of 154 infected people 16% of patients had increased levels of AST. However, the rise of activity of aminotransferases may have occurred also due to action of albendazole which shows its negative effect on hepatic cells.

Levels of anti-T*richinella* antibodies in described patient showed an interesting course, reaching its maximum after finishing the first therapy and long term persistency up to 24 weeks after infection. During this period, the patient was treated at first with albendazole and then with mebendazole. Such course of seroconversion corresponds with findings of Schellenberg *et al*. (2003) that in people infected with *T. britovi* the decline of antibody levels occurs with delay, unlike in patients infected with *T. spiralis* where the specific antibodies disappear already in two weeks after efficient therapy (Pozio *et al*., 2001). In trichinellosis caused by *T. britovi*, the decline begins after six months and all patients become seronegative after three years (Pozio *et al*., 1993). Surprisingly, in cases of three other patients involved in the same trichinellosis outbreak and treated with albendazole, the high antibodies titers persisted even 32 weeks post infection (Paraličová *et al*., 2009).

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