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Fascioliasis: sonographic abnormalities of the biliary tract and evolution after treatment with triclabendazole

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Summary Diagnosis of infection with the liver fluke *Fasciola hepatica* is usually difficult. Ultrasonography (US) might be a useful diagnostic alternative, and we assessed the value of sequential US in the diagnosis and monitoring of fascioliasis in 76 patients at baseline and for 60 days after treatment with triclabendazole. At baseline, biliary abnormalities were observed in 52 patients. Crescent-shaped parasites were seen in 11 patients; in 2 cases parasites were spontaneously moving and in 4 patients parasites were motionless. Postprandial examination revealed parasites adhering to the gallbladder wall in a further 5 cases. In 3 further cases, gallbladder contents were mobile but did not sediment downwards after patients changed position. Non-specific abnormalities were: impaired gallbladder contractility ($n = 23$), gallbladder tenderness ($n = 19$), debris ($n = 6$), calculi ($n = 5$), wall thickening ($n = 2$) and bile duct dilatation ($n = 12$). During day 1–7, *Fasciola*-like crescents in the gallbladder or passing through the bile duct were detected in another 15 patients, impaired gallbladder contractility in 16, gallbladder tenderness in 16, and bile duct dilatation in an additional 28 patients. Thirty-two patients with these US abnormalities experienced colic-like abdominal pain accompanied by increased alkaline phosphatase in 25 cases. During day 30–60, abnormalities regressed completely in 45 patients; 2/6 triclabendazole failures were evident by detection of living parasites. Biliary tract abnormalities are frequently observed by US, but the detection-rate of *Fasciola hepatica* is disappointingly low despite the parasite's relatively large size. US findings must therefore be interpreted together with other clinical measurements. The visualization of parasites being expelled through the dilated common bile duct allowed the causal interpretation of post-therapeutic abdominal pain and increase of liver enzymes. When triclabendazole is given on suspicion, visualization of worm expulsion and bile duct dilatation by US may be used to confirm diagnosis.

keywords ultrasound, triclabendazole, benzimidazoles, biliary colic, biliary obstruction, *Fasciola hepatica*

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Introduction

Cases of human fascioliasis are reported from many areas around the world including Europe, epidemic outbreaks mainly from Asia, the Caribbean and South America (Chen & Mott 1990). Diagnosis of infection with the liver fluke *Fasciola hepatica* is usually difficult. In chronic infection parasite eggs are frequently undetectable in stools even with optimized parasitological techniques, because low worm fecundity results in scanty and irregular egg excretion. Obtaining duodenal fluid for egg detection requires laborious and/or invasive procedures usually not well accepted by the patients. Serological tests are limited by cross-reactivity with other trematodes, and since antibody titres regress only slowly after therapy, these tests do not permit assessment of cure (Arjona *et al*. 1995; Haswell-Elkins & Elkins 1996). Innovative immunodiagnostic tests to detect *Fasciola* excretory-secretory antigens which reflect active infection require sophisticated laboratory equippment and skills and

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are thus not yet applicable in the field (Espino & Finlay 1994).

Ultrasonography (US) is an imaging method which due to its relative economy is becoming more widely available in regions of the world where *Fasciola hepatica* infection occurs most frequently. Portable devices permit its application even in remote geographical areas (WHO 1985). Due to the sporadic nature of the disease in developed areas of the world, current knowledge concerning the use of imaging techniques for the diagnosis of fascioliasis is limited to reports on a small number of patients (Bassily *et al.* 1989; Bassiouny *et al.* 1991; Pulpeiro *et al.* 1991; Fawzy *et al.* 1992; Arjona *et al.* 1995; El Shabrawi *et al.* 1997). The aim of this study was therefore to investigate systematically the value of US for the diagnosis of *Fasciola hepatica* infection and for the monitoring of patients after treatment by sequential follow-up US examinations.

Patients, materials and methods

An outbreak of fascioliasis had occurred in the town of La Palma in the Pinar del Rio province of Western Cuba, and 81 patients, presumably infected 9–11 months prior to the investigation, were enrolled in a clinical trial to investigate the safety and efficacy of triclabendazole (TCZ). Five patients who had undergone cholecystectomy were excluded from the analysis of the ultrasound (US) study and considered separately. Results regarding 76 patients (49 females, 28 males; age range 15–81 years, median 41) are presented. Prior to enrolment all patients had received at least one unsuccessful course of antiparasitic therapy. All therapy courses had ceased at least one month before entry into the study (Bassiouny *et al.* 1991; Millán *et al.* 1999).

Clinical investigations and treatment

Standard investigations performed in all patients included: physical examination; chest X-ray; clinical chemistry and haematology measurements; stool examinations; and determination of *Fasciola*-specific antigens and antibodies (Espino & Finlay 1994). All patients received TCZ at a dose of 20 mg/kg given as two oral postprandial doses of 10 mg/kg 12 h apart on day 0 of the study only (Millán *et al.* 1999). This dosage was chosen in order to assess the efficacy and tolerability of TCZ in symptomatic patients with fascioliasis refractory to therapy with other anthelminthics (Apt *et al.* 1995).

Ultrasound examination

A complete abdominal ultrasound examination was done using a portable scanner (Fukuda UF-4500, Tokyo, Japan) with a 3.5-MHz curved array and a 5-MHz linear real-time transducer. Examinations were performed by two examiners (J.R. and S.F.) and followed a standardized protocol. The first 35 patients were examined by both examiners together, the last 41 by one examiner only (S.F.). Before examination, patients had fasted and abstained from drinking fluid and smoking for at least 8 h. Examination was initiated with the patient lying supine. To mobilize possible pathological contents, the patients' position was reversed during examination. Since data on the variation of gallbladder wall thickness with body size are scarce and adjustment did not vary greatly in one previous study (Richter *et al.* 1992a), a gallbladder wall was considered thickened when it exceeded 3 mm in all patients irrespective of height (Braun 1983; Cooperberg & Gibney 1987; Pickhut 1993).

Examinations were repeated 45–60 min after a fatty meal to detect possible wall-adherent contents and to investigate gallbladder contractility. The latter was considered impaired if postprandial reduction of its volume remained $< 50\%$ (Braun *et al.* 1983). A gallbladder was considered distended when the organ was longer than 10 cm, wider than 4 cm, and its contraction was impaired (Braun *et al.* 1983; Cooperberg & Gibney 1987; Pickhut 1993). The sonographic Murphy sign, i.e. gallbladder tenderness under US-guided palpation, was systematically searched for (Ralls *et al.* 1982; Cooperberg & Gibney 1987). Diameters of the biliary radicals up to 2 mm, of the intrahepatic common bile duct, the hepatic duct, up to 5 mm, and of the extrahepatic common bile duct up to 6 mm were considered normal (Braun *et al.* 1983; Pickhut 1993). Liver and spleen measurements were performed and adjusted to body height as described by Dittrich *et al.* (1983). For monitoring, sequential US examinations were repeated according to a standardized schedule, i.e. daily from day 1–7, and on days 15, 30 and 60 post-therapy.

Statistics

Statistical significance was calculated using χ^2 analysis with Yates' correction.

Results

Of the 82 patients initially enrolled, 6 were excluded from the analysis for the following reasons: 4 had undergone cholecystectomy and were considered separately (data not shown); and two others failed to return for follow-up assessments. Results for the remaining 76 patients are presented here. Biliary colics occurred in 40 patients between day 2 and 7. A transient rise in alkaline phosphatase was observed in 38 patients. Efficacy and safety results of treatment are described in detail elsewhere (Millán *et al.* 1999). All but 6 patients were considered to have been cured by TCZ, since stool examinations were negative, *Fasciola* antigen levels in

faeces normalized, symptoms regressed, and no parasites were detected by US.

Ultrasonography results

Abnormalities detected are listed in Table 1. Spontaneously moving *Fasciola* parasites were found in only 2 cases (Figure 1). Characteristically crescent-shaped contents in the biliary tract was seen in another 4 patients. In 5 cases wall-adherent crescents could only be seen when patients were re-examined postprandially, when the gallbladder wall became less echogenic and the contrast between the wall and the hyperechoic crescents increased. In these cases the higher image resolution of the 5 Mhz transducer proved particularly useful (Figure 2). In a further 3 patients gallbladder contents was seen with a definite but not crescent-like shape, which was easy to mobilize inside the gallbladder but did not sediment downwards when the patient was asked to sit up (Figure 3). The same occurred in 2 patients with light gallbladder debris. Typically sedimenting concrements (rolling stone phenomenon) were seen in 4 patients. In 2/4 cases concrements were only partly calcified; the shape and size of calculi suggested that dead *Fasciola* parasites acted as nucleus of calcification, as observed in another patient with a similar finding who had undergone cholecystectomy (Figure 4). Other biliary abnormalities seen included gallbladder tenderness and impaired contraction and sedimenting sludge. Twenty-four patients had no biliary abnormalities, 21 patients had no US abnormalities at all.

From day 1–15 the signs of extrahepatic biliary obstruction in the study group as a whole increased, including dilatation of the bile duct and tenderness and impaired contraction of the gallbladder. Consequently, the number of patients who still had no biliary abnormalities decreased to only 8. Bile duct dilatation (40 patients) was usually accompanied by both biliary colic ($n = 32$; $P < 0.0001$) and increase in alkaline phosphatase levels ($n = 25$, $P < 0.05$). In another 10 patients a minor (≤6 mm) reversible bile duct enlargement was seen after TCZ.

Conversely, all but 8 patients who had experienced biliary colics had a dilated common bile duct; in 5 of the latter a minor transient bile duct increase was seen. Visualization of

Table 1 Sonographic findings in 76 patients with latent or chronic *Fasciola hepatica* infection before and after treatment with TCZ

	Number of patients				
Finding	Day 0	Day 1–7	Day 15	Day 30	Day 60
Total patients	76	76	75	75	76
Spontaneously moving parasites					
in gb*	2	1	2	2	2
in bd*	0	2	0	0	0
Motionless freely-floating crescents					
in gb*	3	6	2	1	1
in bd*	1	12	0	0	0
Gb* wall-adherent crescents	5	0	0	0	0
Formed 'weightless'gb* contents	3	3	1	0	0
'Weightless' gb*debris	2	2	2	1	1
Sedimenting gb* sludge	4	5	3	2	2
Abnormal bd* contents	0	3	0	0	0
Partly or completely calcified gb*concrement†	4	4	4	4	4
Positive US Murphy‡	19	35	9	8	15
Impaired gb function§	23	39	ND	ND	9
Gb* hydrops¶	0	1	0	0	0
Gb wall thickening†	1	6	2	1	1
Enlarged bd‡	12	40	12	11	8
Enlarged biliary radicals(	2	4	0	0	0
Pathological findings + +	55	71	24	25	31
Biliary tract abnormalities	52	68	21	22	29

*gb, gallbladder, bd, bile ducts; † associated to sludge in one case, to 'excluded' gallbladder in another case; ‡ tender gallbladder under ultrasound guided palpation; § reduction of gallbladder volume after fatty meal less than 50%, ND, not done; ¶ hydrops, i.e. gb length > 10 cm, width > 4 cm, associated with impaired contraction or paradox postprandial volumen increase; † gallbladder wall > 3 mm; ‡ diameter of intrahepatic common bile duct or hepatic duct: > 5 mm, of extrahepatic common bile duct > 6 mm; + diameter of biliary radicals > 2 mm; + + including abnormalities of the biliary tract, liver and spleen (latter two not listed) more than one finding may occur in the same patient.

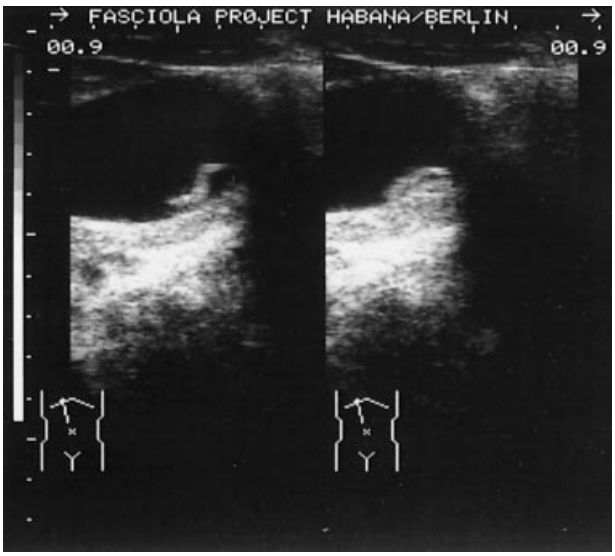

Figure 1 Two subsequent scans (left and right) of the gallbladder made at an interval of a few seconds show a liver fluke moving inside the gallbladder.

parasites by US became easier when crescent-shaped contents was expelled through the dilated bile ducts (Figure 5). In 2 patients actively moving parasites were seen in the gallbladder: in one patient, 4 parasites showed vivid movement but remained attached to the gallbladder wall by one end. All parasites ceased active movement by day 6 after therapy and were not seen again until examinations on day 15, 30 and 60; in the second case one parasite continued active movement throughout the study period. In two cases actively moving parasites were seen in the bile duct only on day 3 post-therapy.

By day 60 post-therapy US findings had normalized completely in 45 patients. Changes of the biliary tract remained in 29 cases, especially calculi and sedimenting sludge. Interestingly, there was no significant difference between the frequency of abnormalities of the biliary tract among the patients considered parasitologically cured (26/70) and treatment failures (3/6). Two of the therapy failures could be diagnosed by the sonographic demonstration of actively moving parasites alone, in one patient the persistence of motionless *Fasciola*-like crescents raised the suspicion of therapy resistence, which was confirmed by parasitological stool examination.

Findings unrelated to the biliary tract included liver texture abnormalities in 3 cases, i.e. slightly hyperechoic bands and increased echogenicity of hepatic ligaments. One patient had undergone US during the acute stage of infection, and the localization of the bands corresponded to former anechoic areas during this stage of the disease. Hepatomegaly was evident in 7 patients at baseline. After treatment a transient increase of liver size was observed in another 3 patients. Slight splenomegaly was seen in 8 patients at baseline, and a transient increase between days 3 and 15 in a further 3 patients. On day 60, only 3 patients still had an enlarged spleen.

Discussion

Ultrasound is a well-established noninvasive diagnostic tool (WHO 1985) which has proved valuable for diagnosing many helminthic diseases such as cystic, polycystic and alveolar

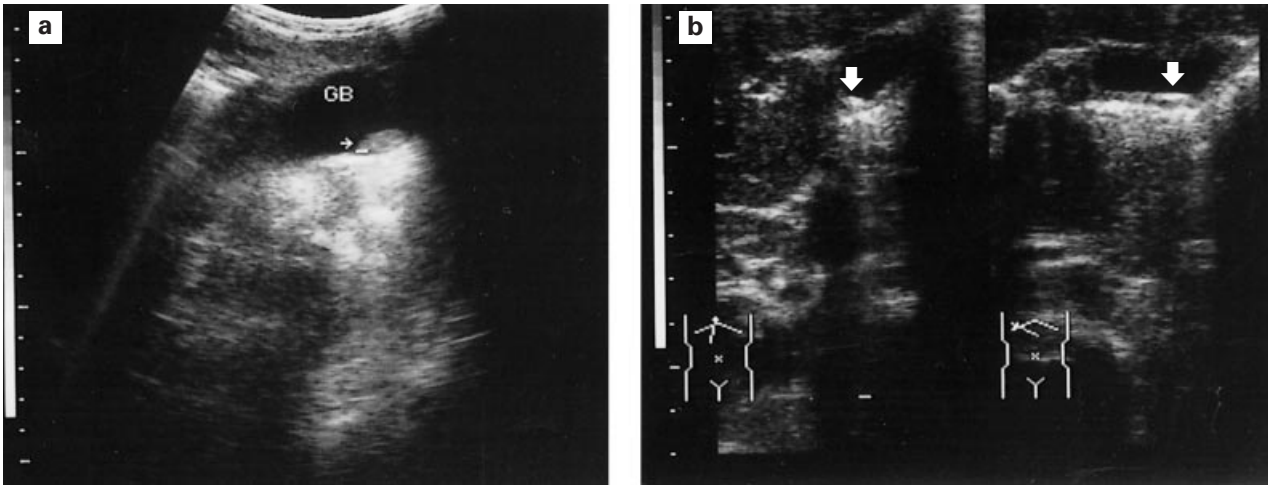

Figure 2 Two patients (a,b), where only examination repeated postprandially enabled the detection of the parasite (arrows) attached to the gallbladder (gb) wall.

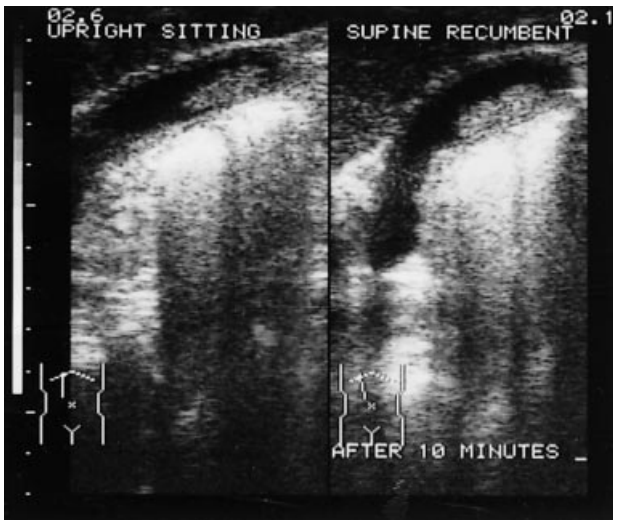

Figure 3 Formed 'weightless' content inside the gallbladder: This content, though freely moving inside the gallbladder, did not sediment downwards after patient changed position (left and right).

Figure 5 Scan revealing a *Fasciola* parasite in the dilated extrahepatic common bile duct (CBD) in a patient experiencing acute abdominal pain 4 days after treatment with triclabendazole.

echinococcosis, schistosomiasis, filariasis, clonorchiasis, and opistorchiasis (Gharbi *et al*. 1981; Didier *et al*. 1985; Lim *et al*. 1989; Mairiang *et al*. 1992; Richter *et al*. 1992b; Amaral *et al*. 1994; D'Alessandro 1997). However, knowledge on the value of US in the diagnosis and monitoring of *F. hepatica* infection is still limited. In Europe, human fascioliasis is most common in France and on the Iberian peninsula, related to the more frequent consumption of wild watercress in these countries. Thus, unsurprisingly, the first case reports on US findings in patients with fascioliasis were published by French and Spanish authors (Eisenscher & Sauget 1980; Vives *et al*. 1982; Houry *et al*. 1983; Messner *et al*. 1983; Bonniaud *et al*. 1984; Karabinis *et al*. 1985; Cauquil *et al*. 1986). Only few studies on a larger number of cases have been published (Pulpeiro *et al*. 1991; Bassiouny *et al*. 1991; Fawzy *et al*. 1992; Arjona *et al*. 1995; El Shabrawi *et al*. 1997).

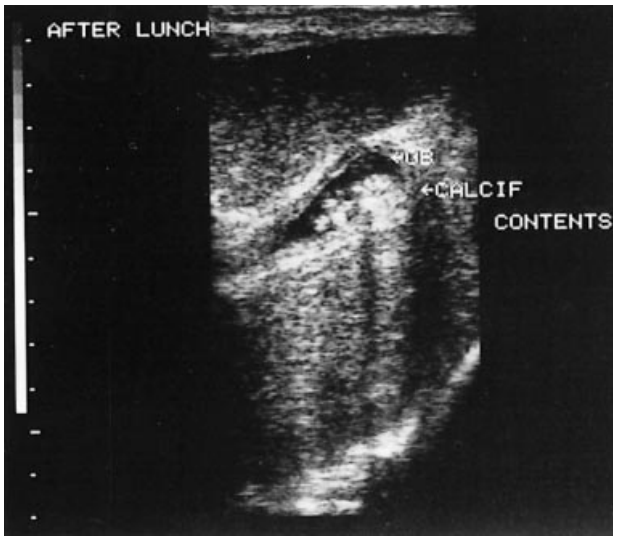

Figure 4 Partly calcified gallbladder concrement.

During the acute invasive stage of the disease, hypoechoic areas inside the liver, sometimes expanding into the peritoneal cavity, and splenomegaly are typically observed. In the latent and chronic stages of the disease, abnormalities essentially affect the biliary tract (Messner *et al*. 1983; Karabinis *et al*. 1985; Cauquil *et al*. 1986; Hodler & Meier 1989; Criado *et al*. 1989; Van Beers *et al*. 1990; Bechtel *et al*. 1992; Fawzy *et al*. 1992; Han *et al*. 1993; Arjona *et al*. 1995; El Shabrawi *et al*. 1997). Our study for the first time assessed the value of US in these later stages of fascioliasis, because the number of patients included exceeds the total number of patients on whom such data are currently available in the literature; and because all study patients were examined applying a standardized examination methodology and repeatedly re-examined after therapy according to a standardized schedule.The study design did not allow for assessment of the true sensitivity of US because because a gold standard for diagnosis does not exist and only patients where ova in stools had been detected were enrolled. Compared to parasitological means the detection rate of parasites by US was disappointingly low, although all patients were examined using both a 3.5 Mhz and a high resolution 5 Mhz transducer.

Since *F. hepatica* is a relatively big parasite (1.5 cm long,

3 mm wide, 1–2 mm thick) it is easily visualized *in vitro* (J. Richter 1994 unpublished) and when jutting into the gallbladder lumen. The low detection rate may be due to the fact that adult *F. hepatica* are not visible either when lodging in areas close to the bowel where intestinal gas hampers US visualization or when firmly attached to the gallbladder wall or to the wall of a bile duct. Indeed, the detection rate of *Fasciola*-like crescents increased considerably after therapy when parasites have become unable to adhere to the walls of the biliary tract. Moreover, the difference in echogenicity between the parasite and the walls of the biliary tract is minimal. Visualization of parasites adhering to the gallbladder wall becomes easier when patients are re-examined after a meal because the wall of the postprandially contracted gallbladder becomes less echogenic, thereby increasing the contrast between the gallbladder wall and the parasite. In this, the 5 MHz probe with a higher image resolution proved superior to the 3.5 MHz transducer.

The low number of spontaneously moving *F. hepatica* detected might also have been due to prior courses of antiparasitic therapy affecting their motility, although this is unlikely since therapies had been terminated for a period of at least one month prior to entry into the study, and based on pharmacological characteristics of the drugs used it would not be expected that a significant amount persisted in patients' serum or bile after this period. In addition, no sign of diminished worm load or activity had been observed by other clinical measures and none of the patients had reported the occurrence of dead parasites in his or her stools after any of these therapy courses.

In three patients apparently weightless, i.e. nonsedimenting contents with a defined but not crescent-like shape were seen: this type of contents corresponded to conglobated parasites in one of the patients who had undergone surgical intervention. The apparent weightlessness of these contents is consistent with the notion that *Fasciola* parasites have a similar specific weight as biliary fluid. Interestingly, despite their gross volume these formed contents disappeared by day 15–30, which is explainable if we assume that the conglobated worms fell apart and were subsequently expelled. At a second stage dead parasites may act as nucleus for calculi. One patient had partially calcified gallbladder contents. Calcified contents sediments downwards when the patient changes position.

US monitoring helped to elucidate the pathophysiology of the occurrence of biliary colic and the increase of liver enzymes observed during TCZ treatment in fascioliasis. In one patient where living worms were shown to be affected by treatment with TCZ, US demonstrated that it took 4 days until most parasites ceased to move completely. This interval is consistent with the time taken for the transformation of TCZ to its pharmacologically active metabolites and their subsequent absorbtion by the parasite (Bennett *et al*. 1986). Demonstrable expulsion of crescents through the dilated bile duct by US permitted differential diagnosis of these findings *vs*. drug-related toxicity. This is confirmed by the observation that biliary colics do not occur when TCZ is used for other indications such as lung worm infection (Ripert *et al*. 1992; Calvopiña *et al*. 1998).

In our study, US enabled the detection of transient bile duct dilatation also in patients not experiencing biliary colics. The frequency of biliary abnormalities increased to almost 90% on days 3–7 after therapy. Post-therapy US examinations might be especially useful when treating patients on suspicion with TCZ but other means do not yield evidence of active infection. US is also useful in diagnosing other complications of fascioliasis such as liver haematomas, obstructive pancreatitis, bile duct strictures and perforation of the bile duct (Gaucher 1981; Wong *et al*. 1985; Acuna-Soto & Braun-Roth 1987; Veerapan *et al*. 1991). US findings contributed to the interpretation of therapy failure in 2/6 patients: persistent live parasites at follow-up examinations in one case, and reappearance of live worms after only 11 days suggested that these were true treatment failures rather than reinfections. In an additional case treatment failure was suspected because the persistence of motionless crescents was confirmed by parasitology. Interestingly, in another patient a crescent passing through the dilated bile duct had been observed on day 4 after treatment, indicating that some but not all worms had been eliminated by TCZ.

In conclusion, the parasite detection rate by US was disappointingly low. Therefore, chronic *Fasciola* infection cannot be ruled out on the basis of normal findings by ultrasonography. US appears useful in monitoring adverse effects of treatment caused by the expulsion of parasites through the bile ducts. Since US detection rate increases after therapy, biliary abnormalities occurring a few days after TCZ therapy might also be used for retrospective confirmation of fascioliasis when TCZ is given on the grounds of clinical suspicion.

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