

## Not Just a Fluke

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The large immigrant population and increasing international travel by North Americans mean that family physicians commonly see patients with diseases once considered exotic or rare on this continent. Liver fluke infestation, a problem that can persist for decades after immigration to the United States, has major associated morbidity and mortality. It can be asymptomatic or can cause vague or confusing symptoms and signs. The purpose of this report is to increase physician awareness of liver fluke infestation as a common problem among immigrants from China, Korea, Southeast Asia, and Japan.

### Case Report

A 35-year-old man, a new patient to a family physician, had a chief complaint of abdominal pain. He described his abdominal pain as "like a needle," located in the midepigastric area and radiating to the substernal area, occasionally associated with vomiting. He denied hematemesis, melena, and hematochezia. The patient had tried antacids and had been prescribed histamine<sub>2</sub>-receptor blocker agents by another physician, but had minimal relief of pain. He reported a history of similar abdominal pain approximately 9 years earlier, which had resolved until it recurred during the past 2 to 3 years. He had undergone upper gastrointestinal contrast radiograph studies and been tested for serum antibodies to *Helicobacter pylori*. The patient reported both of these were negative.

The patient's medical history was otherwise unremarkable. He denied use of alcohol, tobacco, or caffeine. His family history was notable only for colon cancer diagnosed in his father at the age of 54 years. The patient was a native of Canton province, China. He had been living in the United States for approximately 12 years. He had not eaten

steamed or raw fish since moving to the United States but recalled having done so previously.

His physical examination was unrevealing except for mild midepigastric tenderness to deep palpation. He had no organomegaly or masses. Rectal examination was not performed. The patient was given a prescription for omeprazole 20 mg/d, and referred for upper gastrointestinal endoscopy. Endoscopic findings were notable for mild esophagitis thought to be consistent with esophageal reflux.

The patient subsequently saw a third physician, and although he had decreased epigastric pain, he complained of new onset of cramping bilateral low abdominal pain and watery diarrhea without hematochezia. Examination findings at that time, including abdominal and rectal findings, were unremarkable. His stool tested negative for occult blood by guaiac test. Stool culture and examination for ova and parasites were negative. He was thought to have irritable bowel syndrome and was treated with bulk-forming agents; his diarrhea resolved but not the low abdominal pain. As a result of persistent symptoms and the patient's anxiety about colon cancer in view of his family history, colonoscopy was performed; findings were normal except for hemorrhoids.

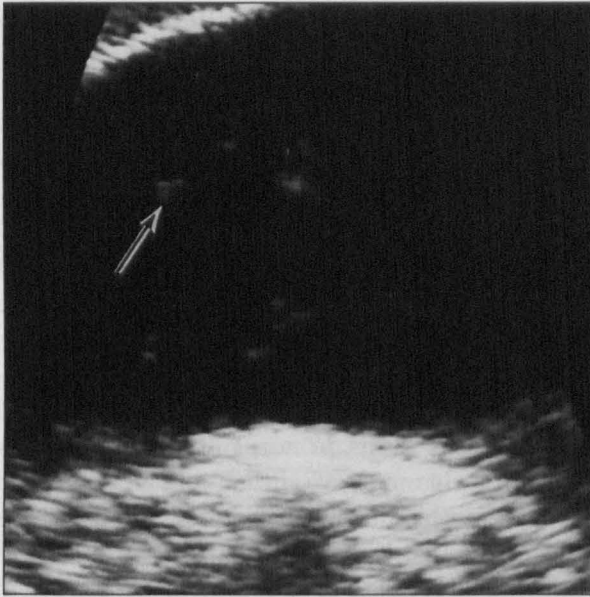
The patient then returned to the family physician complaining of headaches, difficulty sleeping, fatigue, and decreased libido, energy, and concentration. He was thought to be depressed, and fluoxetine was prescribed in addition to omeprazole and stool bulk-forming agent. The patient's symptoms improved, and he discontinued all medications. Six months later his epigastric pain and depressive symptoms recurred. He was restarted on omeprazole and fluoxetine, which relieved his depressive and epigastric symptoms; however, after meals he developed right lower quadrant pain associated with pain in his right shoulder.

An abdominal sonogram was obtained, which showed increased echogenicity of the portal triads throughout both lobes of the liver and diffuse dilatation of the intrahepatic biliary ducts, but normal size of the extrahepatic bile duct. The gall-

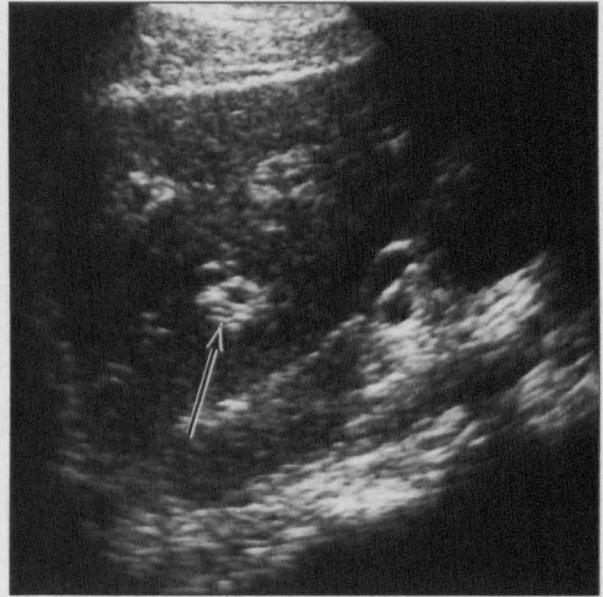
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**Figure 1.** Abdominal sonogram showing echogenic, nonshadowing objects in the gallbladder (arrow) thought to be flukes.



**Figure 2.** Abdominal sonogram showing increased echogenicity of portal triads (arrow).

bladder wall was of normal thickness, and no echogenic stones were seen. Numerous curvilinear echoes, however, were found in the bile (Figures 1 and 2). A magnetic resonance cholangiogram showed dilated intrahepatic bile ducts and a normal extrahepatic bile duct (Figure 3). A complete blood count was normal except for a white cell count of 9500/ $\mu\text{L}$  (normal 3600 - 9000/ $\mu\text{L}$ ), 16.4 percent eosinophils (normal 0.0 - 6.0 percent) and an absolute eosinophil count of 1600/ $\mu\text{L}$  (normal 0 - 700/ $\mu\text{L}$ ). Stool was subsequently obtained to test for ova and parasites, which revealed eggs of *Clonorchis sinensis*.

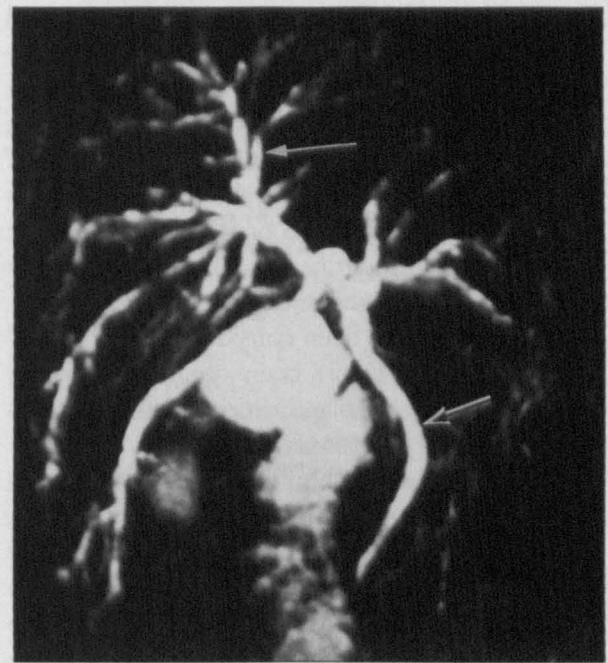
Following treatment with praziquantel, his epigastric and substernal pain resolved, his eosinophil count returned to normal, and three stool specimens were negative for ova and parasites. Nevertheless, he continued to complain of mild intermittent right upper quadrant pain and depression.

### Discussion

This patient had several problems, including esophageal reflux, irritable bowel syndrome, depression, and *C sinensis* infection. Some of his symptoms could have been caused by the *C sinensis*, but others persisted despite treatment for the liver fluke infestation.

Clinically the patient's condition and course posed several challenges common in family practice. The patient had ill-defined and changing

symptoms simultaneously attributed to several common and one uncommon cause. The example illustrates how the physician should make evaluation and management decisions based on the most likely clinical probabilities in the practice type and setting, while remaining alert to clues that other problems might be contributing to the patient's



**Figure 3.** Magnetic resonance cholangiogram showing normal extrahepatic bile duct (outline arrow) and dilated intrahepatic bile ducts (solid arrow). Contrast is also seen within the small intestine.



distress. This task can be made more difficult by discontinuous care, as with this patient. The diagnostic challenge can be compounded by communication difficulties, including limited English language skills and possible cultural biases toward reporting symptoms.

Nonetheless, the key to sorting out this patient's multiple diagnoses was to reevaluate his problems when they failed to resolve or when he developed new symptoms. The patient had positive findings of problems common in family practice (irritable bowel syndrome, depression, and esophagitis) that required evaluation and treatment. Although symptoms of these problems might have overlapped with or been exacerbated by those of the fluke infestation, they did respond to ordinary management and did not resolve completely with treatment of the *C sinensis*. Thus, these problems were thought, even in retrospect, to co-exist with the fluke infestation. The clue that ultimately led to the diagnosis of *C sinensis* was the new onset of right shoulder pain along with his abdominal pain, which suggested gallbladder disease.

The diagnosis of *C sinensis* might have been made earlier via stool tests for ova and parasites. The result of an initial stool test was negative; however, the patient had submitted only one specimen, which raises concern about a false-negative result. Clinical laboratories generally recommend three specimens for ova and parasite testing to reduce the risk of false negatives. In addition, despite the initial negative stool test for ova and parasites, none of the physicians explicitly considered *C sinensis*. Had they done so, they would perhaps have been more likely to order multiple repeat stools tests and identify the fluke infestation by that means. Although the diagnosis of parasitic infection might have been considered had an early complete blood count been obtained showing eosinophilia, no clear indication for this test was recognized early in this patient's course.

Family physicians should consider the possibility of liver fluke infestation in patients from Korea, China, Southeast Asia, or Japan who have vague abdominal complaints, jaundice, or pyogenic cholangitis. Flukes are parasitic trematodes, with species generally grouped by the major organ they infect. *C sinensis* is one of four major species of flukes that infect the biliary tract and are known as liver flukes.<sup>1</sup> Other flukes infect blood, intestine, or lung. Adult *C sinensis* are flat, leaf-shaped, her-

maphroditic organisms from 10 to 25 mm long and 3 to 5 mm in diameter.

*C sinensis* is endemic in Vietnam, Korea, Japan, Taiwan, Hong Kong, and China. It has been a subject of intensive study in Korea,<sup>2</sup> where an infestation rate of 80.3 percent has been reported in one village.<sup>3</sup> Men have higher infestation rates and parasite burdens than women,<sup>4</sup> perhaps because of different social customs in which men eat more uncooked fish. In regions of China where adults eat large amounts of raw fish, infestation rates increase with age. In other regions children eat small raw fish, but adults do not, and infestation rates peak in early teenage years.<sup>5</sup> Up to 26 percent of immigrants from China to the United States have been found to be infected with *C sinensis*,<sup>6</sup> and pathogenic parasites of various types were found in 11 percent of Southeast Asian refugees, including hookworm (4.5 percent), *Strongyloides stercoralis* (2.5 percent), and *C sinensis* (2.0 percent).<sup>7</sup> Notably, among the refugees, sex and years since immigration had no correlation with rate of infestation.

Adult *C sinensis* can survive 20 years or more. They produce eggs that are passed in the bile and then feces. Freshwater snails eat the eggs. In the proper snail host, the eggs undergo metamorphosis and release cercariae into the water. The cercariae penetrate scales and skin of specific freshwater fish, where they form cysts in the flesh. If a human eats undercooked or raw fish, the metacercariae excyst after reaching the duodenum, and the larvae travel through the ampulla of Vater to the bile duct. There they mature to adults and begin releasing eggs in about a month, thus completing the life cycle of the organism. Dogs, pigs, rats, cats, and other fish-eating mammals can also serve as hosts and are therefore reservoirs for subsequent human infestation.<sup>1,8</sup> Necessary snail hosts are not found in North America; therefore, the disease is limited to persons who have eaten undercooked fish in or from endemic areas.

In the biliary tract the flukes cause epithelial desquamation, adenomatous hyperplasia, fibrosis, dysplasia, and, eventually, cholangiocarcinoma.<sup>9,10</sup> The obstructive process can also lead to formation of stones in the intrahepatic bile ducts. The stones are composed of bilirubin and can precipitate recurrent pyogenic cholangitis.

Although acute infestation might occasionally be recognized,<sup>11</sup> most infestations are chronic and have relatively minimal or nonspecific symptoms.

Most infestations have fewer than 100 flukes and are asymptomatic. With increasing age and continued reinfection, persons in endemic areas can have increasing numbers of parasites. Most symptomatic patients are more than 30 years old. With moderate numbers (100 to 1000) of flukes, patients typically have intermittent nonspecific abdominal pain in the epigastric area or right upper quadrant, nausea, anorexia, and diarrhea. Large infestations can cause persistent pain and an enlarged gallbladder and can progress to biliary obstruction, portal cirrhosis, and hepatic failure.<sup>8</sup> The other major complications of clonorchiasis are recurrent pyogenic cholangitis and cholangiocarcinoma.<sup>9,12</sup>

The diagnosis is made by identification of eggs in stool or of adult flukes in the biliary tract. It is not uncommon for the diagnosis to be made at the time of surgery for biliary tract disease, at which time the parasites are seen in the gallbladder or bile ducts.

As in our patient, the infestation might be suspected as a result of findings on a transabdominal sonogram. Ultrasonic examination might show dilated intrahepatic, but not extrahepatic, bile ducts and thickening of bile ducts, along with nonshadowing echogenic masses in the gallbladder. The latter are thought to represent intracystic organisms. The curvilinear echoes seen in Figure 1 represent the flukes. In fact, subtle movement of the organisms could be seen on real time sonography. Sonographic evidence of flukes in the gallbladder is seen in 29 percent of cases. With ultrasonic examination, computed tomography, or cholangiography, the flukes can also be seen as multiple filling defects and intrahepatic (but not extrahepatic) ductal dilatation. Radiographic and sonographic imaging can reveal biliary tract calculi.<sup>13</sup> Newer diagnostic tests under development include ELISA-inhibition tests using *C sinensis* monoclonal antibodies.<sup>14</sup> Intradermal antigen tests have also been used in epidemiologic studies.

Treatment consists of praziquantel 25 mg/kg per dose for three doses on 1 day. It is highly effective in eliminating the organisms. Side effects of treatment are generally mild, consisting of headache, drowsiness, dizziness, myalgia, abdominal pain, nausea, and diarrhea. After treatment, repeated complete blood counts and stool tests for ova and parasites can confirm cure of the fluke infestation. Sonographic studies might not return to normal after treatment.<sup>15</sup> It is presumed, but has

not been proved, that treatment reduces risk of subsequent cholangiocarcinoma.

In conclusion, physicians should consider *C sinensis* infestation in the differential diagnosis of patients from China, Korea, Southeast Asia, and Japan who complain of abdominal symptoms, even if the patient has not been in the country of origin for many years. Symptoms referable to *C sinensis* can mimic and coexist with other common problems seen in family practice.

## References

1. Liu LX, Harinasuta KT. Liver and intestinal flukes. *Gastroenterol Clin North Am* 1996;25:627-36.
2. Rim HJ. Clonorchiasis in Korea. *Kisaengchunghak Chapchi* 1990;28(Suppl):63-78.
3. Hong SJ, Lee YH, Chung MH, Lee DH, Woo HC. Egg positive rates of *Clonorchis sinensis* and intestinal helminths among residents in Kagye-ri, Saengbiryang-myon, Sanhong-gun, Kyongsangnam-do. *Korean J Parasitol* 1994;32:271-3.
4. Chung DI, Kim YI, Lee KR, Choi DW. Epidemiological studies of digenetic trematodes in Yongyang County, Kyunpook Province. *Kisaengchunghak Chapchi* 1991;29:325-38.
5. Fang YY. Epidemiologic characteristics of *Clonorchis sinensis* in Guangdong Province, China. *Southeast Asian J Trop Med Public Health* 1994;25:291-5.
6. Kammerer WS, Van der Decker JD, Keith TB, Mott KE. Clonorchiasis in New York City Chinese. *Trop Doct* 1977;7:105-6.
7. Buchwald D, Lam M, Hooton TM. Prevalence of intestinal parasites and association with symptoms in Southeast Asian refugees. *J Clin Pharm Ther* 1995;20:271-5.
8. Lin AC, Chapman SW, Turner HR, Wofford JD Jr. Clonorchiasis: an update. *South Med J* 1987;80:919-22.
9. Ona FV, Dytoc JN. Clonorchis-associated cholangiocarcinoma: a report of two cases with unusual manifestations. *Gastroenterology* 1991;101:831-9.
10. Parkin DM, Oshima H, Srivatanakul P, Vatanasapt V. Cholangiocarcinoma: epidemiology, mechanisms of carcinogenesis and prevention. *Cancer Epidemiol Biomarkers Prev* 1993;2:537-44.
11. Ip M, Leung N, Cheng AF. Acute clonorchiasis. *Scand J Infect Dis* 1995;27:645-6.
12. Schwartz DA. Cholangiocarcinoma associated with liver fluke infection: a preventable source of morbidity in Asian immigrants. *Am J Gastroenterol* 1986;81:76-9.
13. Lim JH. Radiologic findings of clonorchiasis. *AJR Am J Roentgenol* 1990;155:1001-8.
14. Yong TS, Im K, Chung PR. Analysis of *Clonorchis sinensis* antigens and diagnosis of clonorchiasis using monoclonal antibodies. *Kisaengchunghak Chapchi* 1991;29:293-310.
15. Hong ST, Park KH, Seo M, Choi BI, Chai JY, Lee SH. Correlation of sonographic findings with histopathological changes of the bile ducts in rabbits infected with *Clonorchis sinensis*. *Korean J Parasitol* 1994;32:223-30.