

Biliary Liver Flukes (*Opisthorchiasis* and *Clonorchiasis*) in Immigrants in the United States: Often Subtle and Diagnosed Years After Arrival

William M. Stauffer, Jonathan S. Sellman, and Patricia F. Walker

Background: Biliary liver flukes are extremely common parasites in some regions of the world where consumption of raw fresh-water fish is a cultural practice. *Clonorchis sinensis* and *Opisthorchis* spp. are the major biliary liver flukes associated with human disease. Some of these parasites are highly associated with cholangiocarcinoma. It was noted that several cases presenting at our center had been in the US for prolonged periods. This prompted us to retrospectively review cases of liver fluke infection diagnosed at our facility.

Methods: All cases of biliary liver fluke infection over a 6-year period were retrospectively investigated at a clinic serving international patients, to determine the prevalence and risk factors for infection in a nonendemic area. Cases were identified through review of stool ova and parasite (O&P) records maintained at Regions Hospital/HealthPartners microbiology laboratory. All O&P samples positive for *Opisthorchis* spp. or *Clonorchis sinensis* were included in the review.

Results: Seventeen cases were identified during the study period. Our center performed approximately 1,800 stool O&P examinations per year on approximately 1,100 individuals per year during the study period. Biliary liver flukes were uncommon, accounting for 1.3% of individuals infected with organisms considered to be potentially pathogenic. Infections were predominantly found in migrants from Laos, Cambodia and Thailand. Cases were also identified in migrants from the former Soviet Union and South America. It is of note that 25% of patients were detected after 5 years of residence in the US. Often, the only clinical clue to infection was a mild absolute eosinophilia (500 to 1000 μ L).

Conclusions: Although biliary liver fluke is an infrequent cause of infection in immigrants to the US, because of the potential long-term consequences of chronic infection, educational information highlighting routes of infection and the fact that asymptomatic infection is common and may eventually lead to cancer should be aimed at high-risk community members and those who have been visiting friends and relatives in endemic areas.

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The parasitic trematodes (flukes) *Clonorchis sinensis* and *Opisthorchis* spp. are the major liver flukes associated with human disease, termed clonorchiasis and opisthorchiasis respectively. These trematodes' natural reservoirs include cats, dogs, and other fish-eating mammals. The geographic distribution of these parasites corresponds to the range of the intermediate host snail (i.e., *Bithuynia* spp.) and fish (carp of the Cyprinidae and Anabatidae families). *Clonorchis sinensis* is primarily endemic in China, Taiwan, Vietnam, Korea, Hong Kong and Japan. *Opisthorchis viverrini* is endemic in Laos, Cambodia, and Thailand, whereas *Opisthorchis felineus* is found in parts of eastern Europe, Siberia, and parts of Asia. Humans are accidental hosts, and become infected upon ingesting raw fresh-water fish, the intermediate host, which contain the metacercariae encysted in muscle. There are an estimated 17 million infected individuals in developing countries, 9 million with *Opisthorchis viverrini*, 7 million with *Clonorchis sinensis*, and 1.5 million with *Opisthorchis felineus*.¹ Chronic infections may cause biliary thickening, cholangitis, cirrhosis and a predisposition to cholangiocarcinoma,²⁻⁴

although most patients are asymptomatic, complicating diagnosis. Cholangiocarcinoma is primarily associated with *Opisthorchis viverrini*, and infection has been estimated to increase risk of the disease by at least 5-fold; once the malignancy has been acquired, 2-year survival approaches 0%.⁵ Patients with symptoms often have vague and non-specific complaints. Intermittent right upper quadrant abdominal discomfort, typically occurring in the late afternoon, may be the initial symptom of infection. Patients may also develop diarrhea, flatulence, anorexia, fatigue, and low-grade fever.^{3,6}

Many individuals referred to our center for primary or consultative care were subsequently diagnosed with liver flukes. It was noted that a substantial number of these patients had migrated to the US many years prior to diagnosis. This prompted us to retrospectively review cases in which liver fluke was diagnosed.

Methods

Cases were identified through review of stool ova and parasite (O&P) records maintained at Regions Hospital/HealthPartners microbiology laboratory. Records were reviewed for the period 1 January 1993 to 31 December 1998. All O&P samples that were positive for *Opisthorchis* spp. or *Clonorchis sinensis* were included in the review. Data were abstracted from patient charts using a standardized form. The study design was reviewed and approved by the appropriate institutional review board.

Results

Seventeen cases were identified during the study period. Our hospital performed approximately 1,800 stool O&P examinations on 1,100 individuals per year during the study period. Biliary liver flukes were uncommon, accounting for 1.3% of individuals infected with organisms considered to be potentially pathogenic (Table 1). Patient ages ranged from 4 to 79 years, with a majority of patients being older than 50 years (Table 2). There were approximately equal numbers of men and women. The time since immigration was bimodal. Many cases were detected on immigrant medical screening within the first 3 months of arrival. Others were identified years after initial migration to the US (Table 2). The latter cases usually had stool examinations years after arrival as they presented to, or were referred to, our center with vague and nonspecific complaints, frequently accompanied by eosinophilia. It was also noted that several of these patients had visited their home country since their initial migration, adding the possibility that some infections may have been travel-related. A majority of cases were detected in individuals of Laotian and

Table 1 Number of Patients Infected with Individual Parasite Species

Potentially Pathogenic Species	No. (%) of Positive Specimens
<i>Giardia lamblia</i>	363 (28.1)
Hookworm spp.	297 (23.0)
<i>Strongyloides stercoralis</i>	139 (10.8)
<i>Trichuris trichiura</i>	132 (10.2)
<i>Ascaris lumbricoides</i>	115 (8.9)
<i>Entamoeba histolytica/dispar</i>	82 (6.4)
<i>Hymenolepis nana</i>	60 (4.6)
<i>Taenia</i> spp.	31 (2.4)
<i>Enterobius vermicularis</i>	23 (1.8)
<i>Opisthorchis</i> spp. and <i>Clonorchiasis sinensis</i>	17 (1.3)
<i>Schistosoma mansoni</i>	13 (1.0)
Other ^a	19 (1.5)
Total	1291 (100)

^a*Schistosoma hematobium* (n = 6), *Diphylobothrium latum* (n = 4), *Fascioloides* spp. (n = 4), *Paragonimus westermani* (n = 3), *Taxocara* (n = 1)

Table 2 Characteristics of Study Patients with Liver Fluke Infections

	Number of Cases (%)
Age	
0–18 years	1 (6)
19–50 years	5 (29)
51–80 years	11 (65)
Total	17 (100)
Time since immigration	
0–3 months	9 (53)
4 months to 5 years	4 (24)
5 years to 10 years	2 (12)
>10 years	2 (12)
Total	17 (100)
Absolute eosinophil count (per μ L)	
<500	2 (12)
500–1000	13* (76)
>1000	2 (12)
Total	17 (100)

*Six cases were reported as normal because they fell within normal laboratory limits when using percentages, rather than absolute counts, for white blood cell differential reporting.

Cambodian descent, which is not surprising, given that infection rates in some communities in these areas exceed 25%.^{1,7,8} This corresponds to the common practice in many parts of Laos, Cambodia, and parts of northern Thailand of eating raw fish. Popular local dishes consist of a combination of pounded raw fish and spices, including lemon and onion, and are present in the diet from infancy to old age (i.e., *Koi Pla*). More recent cases have occurred in individuals from the former Soviet

Union and from Latin America (*Opisthorchis quayaquilensis*), correlating with changing patterns of migration to Minnesota (Table 3).

Presenting signs and symptoms were diffuse and chronic in character and included headaches, nausea, abdominal pain and cramping, rashes, pruritis, anorexia, facial swelling, insomnia, arthralgias and dyspnea. The power of this study did not enable determination of which signs or symptoms were attributable to the liver fluke infection. Eighty-eight percent of the patients had eosinophilia (defined as an absolute eosinophil count greater than 500/ μ L) (Table 2). It is worth noting that most patients had a mild eosinophilia and that approximately 50% of the cases with an absolute count of more than 500/ μ L eosinophils had a normal white blood cell differential distribution by percentage. This is noteworthy, as many laboratories report white blood cell differentials by percentage, and these cases would not have been identified unless the absolute eosinophil count was calculated. No patients had elevated bilirubin or abnormal liver function test results, which are rarely associated with biliary liver flukes. Among those patients undergoing immigrant medical screening, many other potentially pathogenic organisms were also detected (Table 4). However, among patients who had

been in the US for a period of greater than 1 year, only two were found to have other potentially pathogenic organisms (*Strongyloides stercoralis* and *Entamoeba histolytica/E. dispar*).

Discussion

Clinicians often assume that patients who have been in the US for several years no longer harbor significant tropical infectious diseases, and tend to ignore the mild eosinophilia often seen in immigrant populations.⁹ Liver flukes have been known to infect the human host for longer than 20 years, and have been highly associated with cholangiocarcinoma, an almost uniformly fatal carcinoma.^{2-5,9,10} Approximately half of the cases in this series were detected months to years (up to 14 years) after immigration to the US. It is unknown if the patients seen on referral had initially received medical screening on arrival to the US.

Although *Opisthorchis* spp. and *Clonorchis sinensis* account for a small minority of infections detected on screening and diagnostic stool O&P examinations, the cases detected were clustered in older Laotian and Cambodians (frequently immigrating via Thailand). Laotian refugees have previously been described as being at high risk for biliary liver fluke infection.¹¹ More recent and sporadic cases found on new arrival screening are being detected in patients originating in eastern Europe and the former Soviet Union—corresponding to increased numbers of refugees arriving from these endemic areas.^{12,13} Given the potential consequences of chronic infection with biliary liver flukes, and the relative ease and effectiveness of treatment, targeted screening is suggested. The data suggest that any high-risk immigrants or refugees from endemic areas, particularly those of Laotian and Cambodian descent, be screened by having a stool O&P examination (preferably with formalin ether concentration or Stolls dilution method),¹⁴ regardless of the duration of residence outside the endemic region. In addition, it may be worthwhile considering screening of family members and perhaps community members, on the assumption that they have similar dietary patterns, particularly after people have returned to their home country to visit friends and relatives. This is particularly true in this higher-incidence population, as it is the same population who tend to harbor *Opisthorchis viverrini*, the biliary liver fluke most closely associated with cholangiocarcinoma. Educational information highlighting routes of infection and the fact that asymptomatic infection is common and may eventually lead to cancer should be aimed at high-risk community members and travelers who have returned to endemic areas to visit friends and relatives.

Table 3 Countries of Origin of Patients with Biliary Liver Fluke Infection

Country (Descending Order of Occurrence)
Laos
Cambodia
Thailand
Vietnam
Former Soviet Union
Ecuador

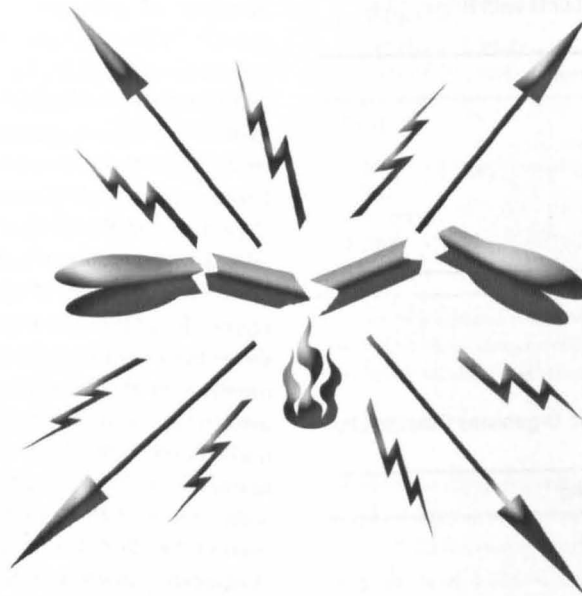
Table 4 Other Potential Pathologic Organisms Detected by Stool O&P

Other Organisms in Order of Frequency
<i>Trichuris trichiura</i>
<i>Ascaris lumbricoides</i>
Hookworm
<i>Strongyloides stercoralis</i> *
<i>Giardia lamblia</i>
<i>Entamoeba histolytica/dispar</i> *

*Coexisting organisms found in patients who had been in the US for over 1 year.

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