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Journal

American Journal of Tropical Medicine and Hygiene, 104(6)

ISSN

0002-9637

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Publication Date

2021

DOI

10.4269/ajtmh.20-0632

Peer reviewed

Am. J. Trop. Med. Hyg., 104(6), 2021, pp. 2065–2068
doi:10.4269/ajtmh.20-0632

Case Report: *Clonorchis sinensis* Infection Associated with Eosinophilic Pneumonia

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Abstract. *Clonorchis sinensis*, a trematode prevalent in East Asia, causes hepatobiliary infection. Exposure typically occurs through ingestion of raw or undercooked fish containing the encysted larval form of the parasite. Extrahepatobiliary disease has not commonly been described. In this case report, we describe an unusual case of *C. sinensis* infection associated with eosinophilic pneumonia. A middle-aged man from China presented with subacute cough and was found to have a bilateral diffuse eosinophilic pneumonia with associated peripheral eosinophilia. Stool microscopy revealed *C. sinensis* eggs, and the patient improved after treatment with prednisone and praziquantel. Pulmonary clonorchiasis should be considered in patients with eosinophilic pneumonia from areas highly endemic for this pathogen.

CASE PRESENTATION

An estimated 15 million people are infected with the trematode *Clonorchis sinensis* worldwide, the majority in East Asia.[1,2] Whereas chronic infection with *C. sinensis* is associated with hepatobiliary disease, reports of extrahepatobiliary manifestations are rare. Here we describe an unusual case of *C. sinensis* infection associated with eosinophilic pneumonia.

A 63-year-old man from China presented with 1 month of worsening cough and weight loss. The cough was dry with scant production of white sputum, without hemoptysis. His past medical history included hypertension, type II diabetes mellitus, and stroke. He reported similar symptoms approximately 20 years prior while living in China; he was diagnosed with pulmonary tuberculosis though did not recall specific treatment. He was born in the Guangxi Province of China and emigrated to the United States 4 years before presentation. He last visited the rural Guangxi Province one year prior. During that trip, he had eaten raw freshwater fish.

On presentation, the patient was in no acute distress. He was afebrile. Oxygen saturation was 94% on room air. Pulmonary examination was normal. His laboratory findings revealed a white blood cell (WBC) count of 11.5 cells × 10^9/L with 1.7% eosinophils (absolute eosinophil count of 0.2 cells × 10^9/L). Liver enzymes were normal. Chest X-ray showed bilateral airspace opacities, with focal consolidation in the right upper lobe and at the bases (Figure 1). Computed tomography of the chest with contrast showed multifocal reticular and ground-glass opacities, an 11-mm spiculated nodular mass within the left apex, and associated bulky mediastinal and hilar lymphadenopathy (Figure 2).

Serial acid-fast smears, tuberculosis PCR, and acid-fast bacilli (AFB) culture were negative. Over the next week, his WBC count increased up to 21.2 cells × 10^9/L with 24.6% eosinophils (absolute eosinophil count of 5.2 cells × 10^9/L). He developed respiratory distress requiring 6 L of oxygen via the nasal cannula. Further evaluation was initiated for parasitic infections. Serologic testing was negative for *Strongyloides stercoralis*, *Echinococcus* spp., *Trichinella* spp., and lymphatic filariasis. *Schistosoma mansoni* antibody by ELISA, expected to be cross-reactive with other *Schistosoma* species, was equivocal. Thin and thick peripheral blood smear examinations were negative for blood parasites.

The patient underwent bronchoscopy and ultrasound-guided transbronchial needle aspiration. Bronchoalveolar lavage (BAL) microscopy for parasites was negative. Lung biopsy with hematoxylin and eosin staining revealed focal organizing pneumonia and diffuse chronic inflammation with prominent eosinophilic infiltration, characteristic of nonspecific interstitial pneumonitis or hypersensitivity pneumonitis (Figure 3). Acid-fast bacilli and Gomori methenamine-silver stains were negative. Given the concern for eosinophilic pneumonia, prednisone 60 mg daily was initiated with rapid symptomatic improvement.

Stool microscopy for parasites revealed *C. sinensis* eggs in three samples (Figure 4). Stool microscopy was performed with concentrated wet mount, using the Apacor "Midi Parasep SF" fecal parasite concentrator system, and unconcentrated trichrome stain. The patient completed six doses of praziquantel 1800 mg every 5 hours, which he tolerated well. An abdominal ultrasound showed mild common bile duct wall thickening, but no evidence of obstruction or ductal dilation. Chest X-ray performed 3 days after initiating prednisone showed mild improvement in airspace opacities. On hospital day 21, he was discharged home without supplemental oxygen. Prednisone was continued with plans to taper.

DISCUSSION AND REVIEW OF LITERATURE

Clonorchis sinensis is not traditionally thought to be associated with pulmonary disease, although case reports have been described previously.[3–8] A comprehensive search was performed using the PubMed database from inception until February 2019. Search terms included "*C. sinensis*," "*Clonorchis*," and "clonorchiasis," combined with the terms "eosinophilic pneumonia" and "pulmonary eosinophilia." References in each manuscript were reviewed to identify additional cases.

In addition to the present case, we encountered six other case reports and series in the literature, describing a total of 14 cases of pulmonary disease associated with *C. sinensis* (Table 1).[3–8] The first recorded case was published in 1949.[3] The patients ranged in age from 23 months to 54 years. The descriptions were from China, Hong Kong, and Korea. Most patients had pulmonary symptoms, lasting from days to

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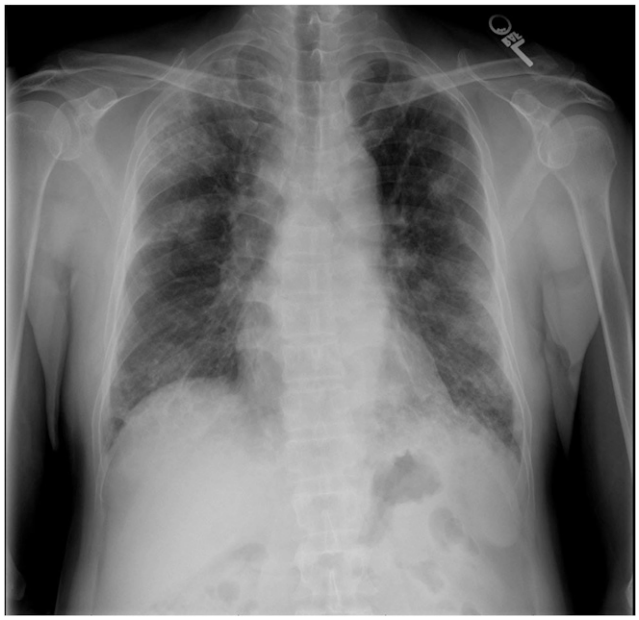

FIGURE 1. Chest X-ray. Initial chest X-ray showed bilateral airspace opacities with focal consolidation in the right upper lobe and at lung bases.

1 month before presentation. Two patients had no reported pulmonary symptoms; one presented with epigastric discomfort and fever, and the other with rash on the extremities.[5,7] All had transient pulmonary infiltrates on imaging. All were diagnosed with *C. sinensis* infection, 13 of the 14 cases by visualization of eggs on stool microscopy, but in one case by serum antibody testing.[8] Two patients had transbronchial lung biopsy showing eosinophilic pneumonia.[6,7] Treatment varied;

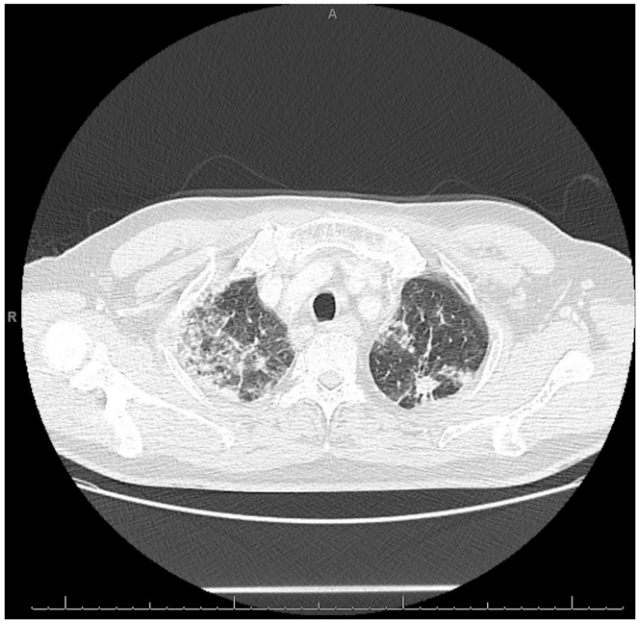

FIGURE 2. Computed tomography of the chest. Initial Computed tomography of the chest with contrast showed multifocal reticular and ground-glass opacities, an 11-mm spiculated nodular mass within the left apex, and associated bulky mediastinal and hilar lymphadenopathy.

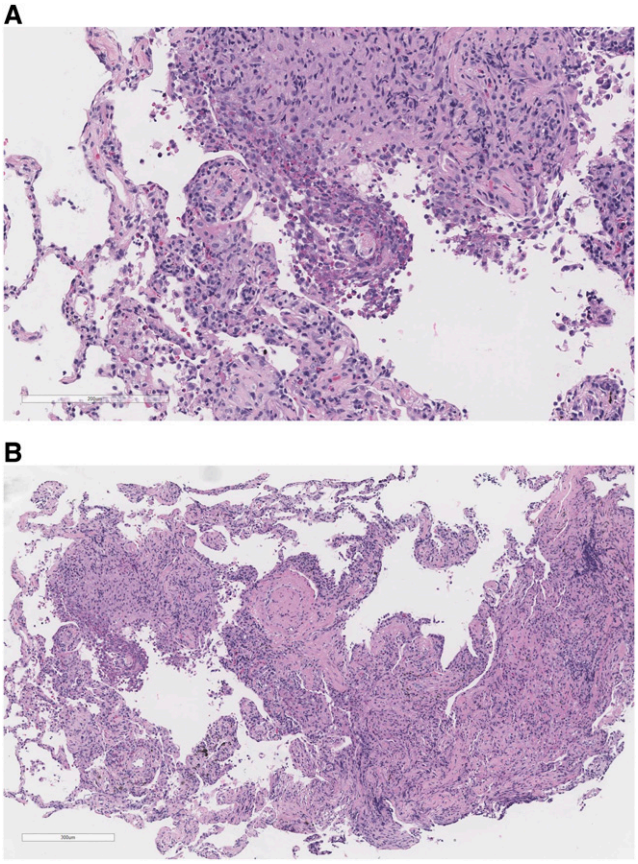

FIGURE 3. Pathology findings. Left lower lung tissue biopsy with hematoxylin and eosin staining revealed alveoli with focal organizing pneumonia and diffuse chronic inflammation with prominent eosinophilic infiltration, characteristic of nonspecific interstitial pneumonitis or hypersensitivity pneumonitis. This figure appears in color at www.ajtmh.org.

many received antiparasitic therapy, usually praziquantel, although nine patients in one case series received no therapy.[4] Only one patient received glucocorticoids.[6] All patients improved over time, ranging from days to months.

Clonorchis sinensis is a trematode prevalent in East Asia that infects the hepatobiliary system. There are an

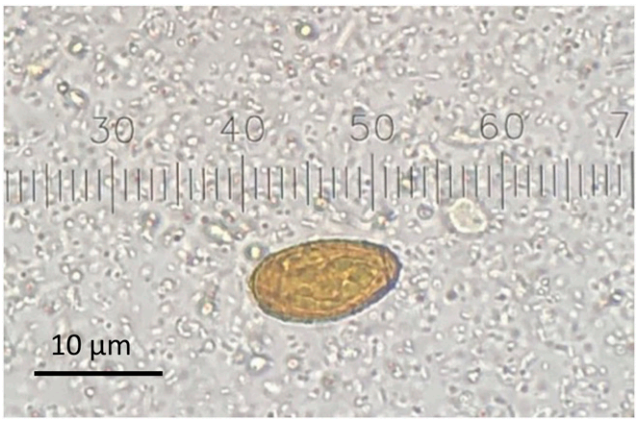

FIGURE 4. Stool microscopy for parasites. *Clonorchis sinensis* egg. This figure appears in color at www.ajtmh.org.

TABLE 1
Characteristics of cases reported in the literature of pulmonary disease attributed to *C. sinensis*

Author, year of publication	Patient age, gender	Geographic location	Exposure history	Symptoms	Maximum reported peripheral eosinophilia (%)	Imaging findings	Method of diagnosis of *Clonorchis* infection	Treatment
Cartwright, 1949[3]	21, male	Shanghai, China	Consumption of "poorly cooked native fish"	Fever, chills, productive cough	74	Transient bilateral pulmonary infiltrates	*Clonorchis* ova identified in stool	Mapharsen therapy
Engel, 1967[4]	20–50 (9 patients), male	Hong Kong	Unknown	Transitory hemoptysis	Unknown	Transitory infiltration (seen in two of nine cases)	*Clonorchis* ova identified in stool	No treatment
Mo, 1984[5]	36, male	China	Ingestion of raw freshwater fish and cooked crabs	Epigastric discomfort, fever, diaphoresis	76	Transient bilateral pulmonary infiltrates	*Clonorchis* ova identified in stool and bile	Praziquantel
Lee, 1998[6]	37, male	Korea	Unknown	Dyspnea, cough	71.4	Nodular pulmonary parenchymal infiltrates	*Clonorchis* ova identified in stool	Praziquantel, corticosteroids
Lee, 2003[7]	54, male	Korea	Ingestion of raw freshwater fish	Rash on extremities	35	Migrating pulmonary nodules and patchy densities	*Clonorchis* ova identified in stool, positive skin test for *C. sinensis*	Praziquantel
Sheng, 2017[8]	23 months, female	China	Ingestion of raw freshwater crayfish	Cough, wheezing	9.7	Bilateral ground-glass attenuation and reticular opacities	Identification of *C. sinensis*–specific IgG in serum	Praziquantel

C. sinensis = *Clonorchis sinensis*.

estimated 15 million people infected worldwide, with approximately 13 million in China.[1,2] Most infected persons are asymptomatic.[2,9] When present, most of the signs and symptoms are related to worm burden and associated with inflammation and obstruction of the biliary system.[1] When left untreated, infection may persist for up to 30 years, and can lead to hepatomegaly, cirrhosis, and cholangiocarcinoma.[9] Most infections occur in persons resident in, or who have travelled to, endemic areas. The main risk factor for infection is consumption of raw or undercooked fish.[9]

The life cycle of *C. sinensis* begins with freshwater snails, the first intermediate host, which ingest the embryonated eggs of *C. sinensis*.[9] Within the snail, eggs release miracidia which develop into sporocysts, rediae, and finally cercariae.[9] Cercariae are released from the snail, and enter freshwater fish or shrimps, the second intermediate hosts, and encyst, becoming metacercariae.[9] Definitive hosts such as humans and other carnivores including cats and dogs become infected by eating raw or undercooked fish containing these metacercariae.[2] After ingestion, metacercariae excyst in the duodenum, and then migrate to the hepatobiliary system, where they mature.[10] The mature trematodes release eggs which are passed from the bile into the stool of infected persons.[9] Excreted embryonated eggs are ingested by snails, resuming the life cycle.

We propose three potential pathophysiologic mechanisms by which *C. sinensis* could contribute to pulmonary disease. The first, and the likely mechanism in this case, is pulmonary eosinophilia resulting from an immunological hypersensitivity reaction. This mechanism has been well described in tropical pulmonary eosinophilia, a hypersensitivity reaction to lymphatic filarial parasites, which can manifest years after leaving the endemic area.[11] The robust immune response in tropical pulmonary eosinophilia is, in part, mediated by an expansion of IL-4 and IL-5 producing cells, promoting polyclonal expansion of eosinophils.[12] Although liver flukes are not typically thought to cause pulmonary disease, there have been reports of *Fasciola*, another liver trematode, causing lung involvement by this mechanism, lending biologic plausibility to this idea.[13,14] It is likely that *C. sinensis* infection similarly contributed to an immunological hypersensitivity reaction, resulting in pulmonary manifestations in the case described here.

A second less likely putative mechanism for pulmonary manifestations with *C. sinensis* is by direct pulmonary migration of the adult or larval parasite itself. Excluding the lung fluke *Paragonimus* which directly invades the pulmonary parenchyma, *Schistosoma* is one trematode known to migrate through the lung in the larval form.[11] *Schistosoma* and other helminths which transiently migrate in this way typically present with Loeffler syndrome, characterized by transient, migratory pulmonary infiltrates with pulmonary and peripheral eosinophilia.[15,16] A similar mechanism was considered with *C. sinensis*, although deemed very unlikely; if this mechanism were plausible, larval stages would be expected to migrate through the lungs early after infection; however, this patient had last visited China with potential exposure to *C. sinensis* 1 year prior to presentation. Moreover, neither BAL microscopy nor lung pathology showed *C. sinensis* larvae. A third mechanism was considered, similar to schistosomiasis causing portal hypertension and pulmonary vascular disease via migration of eggs from the

portal to pulmonary vasculature, but was deemed highly unlikely because of the absence of *Clonorchis* eggs on lung pathology, as well as the presentation of eosinophilic pneumonia rather than liver fibrosis with pulmonary hypertension.[17,18]

Clonorchis sinensis infection is typically diagnosed by microscopic identification of eggs in stool specimens. Eggs of *C. sinensis* are difficult to distinguish morphologically from those of *Opisthorchis* species, and generally, these infections are differentiated by epidemiological clues when possible.[9] The geographic origin of this patient's infection in China allows the diagnosis of clonorchiasis. In addition, determining whether *C. sinensis* eggs in stool represent the causative pathogen versus asymptomatic shedding in the setting of an alternative disease can be difficult. However, in this case, no alternative cause of pulmonary symptoms was found.

Treatment of *C. sinensis* infection involves praziquantel or albendazole, which are the antiparasitic therapies of choice.[9] On the other hand, treatment of eosinophilic pneumonia includes systemic glucocorticoid therapy, generally tapered over several weeks to months.[19] Of the 14 cases of this entity in the literature, only one patient received glucocorticoid therapy,[6] and most patients, although not all, received antiparasitic therapy. However, all were reported to show clinical improvement over time. The optimal therapy for eosinophilic pneumonia associated with *C. sinensis* infection is unclear based on the limited data; however, we suggest antiparasitic therapy with consideration of systemic glucocorticoids based on the severity of respiratory symptoms.

Received June 10, 2020. Accepted for publication January 10, 2021.

Published online May 3, 2021.

Acknowledgments: We would like to acknowledge the contribution of the DPDx and epidemiology teams from the Division of Parasitic Diseases and Malaria at the Centers for Disease Control and Prevention for their assistance in clinical diagnosis of this case and identifying additional published cases. We would also like to thank Dr. Janet Yang for her translation of the medical journals written in the Korean language.

Financial support: There was no funding source for this author-initiated project other than the general support of the authors' time from the University of California Davis Medical Center. The corresponding author had full access to the data included in the case report and had final responsibility for the decision to submit for publication.

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