
Paragonimus kellicotti Fluke Infections in Missouri, USA

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Analyze the epidemiology and microbiology of paragonimiasis
- Assess the clinical presentation of paragonimiasis
- Evaluate patterns of management of paragonimiasis
- Distinguish abnormal ancillary studies among patients with paragonimiasis

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Paragonimiasis is an infection caused by lung flukes of the genus *Paragonimus*. In Asia, *P. westermani* infections are relatively common because of dietary practices. However, in North America, cases of paragonimiasis, which are caused by *P. kellicotti* flukes, are rare. Only 7 autochthonous cases of paragonimiasis were reported during 1968–2008. In 2009, we reported 3 new case-patients with paragonimiasis who had been seen at our medical center over an 18-month period. Six additional case-patients were identified in

St. Louis, Missouri, USA, and treated at Washington University–affiliated health centers in 2009–2010. We report detailed descriptions of these case-patients, which includes unusual clinical manifestations. We also describe public health interventions that were undertaken to inform the general public and physicians about the disease and its mode of transmission.

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Paragonimiasis is an infection caused by lung flukes of the genus *Paragonimus*. As many as 9 species of *Paragonimus* are responsible for human infections worldwide (1). Human paragonimiasis is common in Asia, where diets often include raw, cured, pickled, or salted crustaceans (2,3). In contrast, consumption of uncooked crustaceans is uncommon in North America.

In North America, paragonimiasis is caused by *Paragonimus kellicotti* flukes (4). *Paragonimus* spp. lung flukes have a complex life cycle, requiring snail and crustacean intermediate hosts. Definitive hosts excrete eggs in feces or sputum, which hatch in water to become ciliated miracidia. The miracidia invade soft tissue of snails where they reproduce asexually. Cercariae released from snails invade the secondary intermediate host, a crustacean. Secondary intermediate hosts for *P. kellicotti* flukes are crayfish in the genera *Cambarus* and *Orconectes*. Mammals acquire the infection when they ingest raw or undercooked crustaceans (5). *P. kellicotti* fluke infections have been found in cats, dogs, bobcats (6), raccoons (7), foxes (8,9), skunks (9), minks (9,10), and coyotes (9). Human infections are uncommon; only 7 cases were reported during 1968–2008 (2,11–18)

In 2009, we reported a cluster of 3 patients who had probable or proven paragonimiasis caused by *P. kellicotti* flukes and who were seen at a single tertiary-care center over an 18-month period (19). We report an additional 6 patients seen at Washington University Medical Center, St. Louis, Missouri, and at an affiliated Veterans Administration hospital over 14 months (September 2009–October 2010). The purpose of this report is to emphasize that *P. kellicotti* flukes are an emerging pathogen in Missouri, to highlight unusual clinical features observed in these patients, to educate the public in hopes of preventing new cases, and to increase awareness among the medical community to promote early diagnosis and treatment.

Patients, Materials, and Methods

Patients with proven or probable *P. kellicotti* fluke infection seen at Washington University School of Medicine and an affiliated Veterans Administration Hospital during September 2009–October 2010 were identified at time of clinical encounter. Patient characteristics, case histories, and laboratory values were obtained from medical records by infectious disease physicians. Immunoblot tests were performed at the Centers for Disease Control and Prevention (Atlanta, GA, USA), commercial laboratories, or Washington University School of Medicine as described in the Technical Appendix (wwwnc.cdc.gov/EID/pdfs/12-0335-Techapp.pdf).

Results

Clinical Features

Patient characteristics for the combined series of 9 patients are summarized in Tables 1 and 2, and detailed case descriptions for the 6 new patients are provided in the online Technical Appendix. The patients included in this series were predominantly male (88.9%), and all but 1 were adults. Patients consumed raw crayfish while on float (recreational river) trips (7/9, 77.8%), camping (1/9, 11.1%), or as a demonstration of wilderness survival skills (1/9, 11.1%). Alcohol consumption at the time of crayfish consumption was common (7/9, 77.8%). Although there were differences in timing of seeking care and signs and symptoms, patients in this series frequently had cough (100%), fever (88.9%), and eosinophilia (100%).

Table 1. Characteristics of 9 patients infected with *Paragonimus kellicotti* flukes, Missouri, USA, September 2009–October 2010*

| Patient no. | Age, y/sex | Location | Incubation period, wk | Signs and symptoms | Time to diagnosis, wk | Method of diagnosis | Reference |
|-------------|------------|-------------------------------|-----------------------|---|-----------------------|---|-----------|
| 1 | 31/M | Jacks Fork and Current Rivers | 2 | Fever, pharyngitis, cough, dyspnea, eosinophilia | 3 | Clinical history | (19) |
| 2 | 26/F | Meramec River | 2 | Fatigue, cough, fever, eosinophilia | 12 | Serologic analysis | (19) |
| 3 | 32/M | Current River | 3 | Fever, malaise, cough, headache, eosinophilia | 12 | Serologic analysis | (19) |
| 4 | 28/M | Huzzah River | 8 | Fever, myalgia, malaise, cough, weight loss, eosinophilia | 12 | Clinical history | NA |
| 5 | 10/M | Current River | 16 | Fever, myalgia, malaise, cough, chest pain, weight loss, eosinophilia | 3 | Clinical history | NA |
| 6 | 20/M | Jacks Fork River | 12 | Fever, night sweats, malaise, cough, dyspnea, chest pain, weight loss, eosinophilia | 36 | Serologic analysis | NA |
| 7 | 22/M | Jacks Fork River | 6 | Fever, night sweats, cough, dyspnea, chest pain, weight loss, eosinophilia | 40 | Serologic analysis, sputum ova and parasite examination | NA |
| 8 | 30/M | Jacks Fork River | 2 | Fever, night sweats, malaise, cough, dyspnea, chest pain, weight loss, eosinophilia | 16 | Serologic analysis | NA |
| 9 | 43/M | Missouri River | 12 | Cough, dyspnea, chest pain, weight loss, eosinophilia | 83 | Serologic analysis | NA |

*Patients 4–9 were not previously reported. NA, not applicable.

Table 2. Clinical and laboratory findings for 9 patients infected with *Paragonimus kellicotti* flukes, Missouri, USA, September 2009–October 2010*

| Characteristic | Value |
|--|-------------------|
| Age, y, median (range) | 28 (10–43) |
| Male sex | 8 (88.9) |
| Alcohol consumption | 7 (77.8) |
| Incubation period, wk, median (range) | 4 (2–12) |
| Duration of symptoms before examination, wk, median (range) | 2 (2–8) |
| Signs and symptoms | |
| Fever | 8 (88.9) |
| Cough | 9 (100.0) |
| Chest pain | 6 (66.7) |
| Dyspnea | 4 (44.4) |
| Night sweats | 5 (55.6) |
| Malaise | 5 (55.6) |
| Abdominal pain | 2 (22.2) |
| Weight loss | 7 (77.8) |
| Laboratory findings | |
| Eosinophils/mm ³ at first examination, mean (range) | 1,626 (800–3,600) |
| % Eosinophils at first examination, mean (range) | 15 (6–30) |
| Positive paragonimus immunoblot result† | 5 (71.4) |
| Positive sputum ova and parasite test result† | 1 (14.2) |
| Radiographic findings | |
| Pleural effusion | 9 (100.0) |
| Nodule | 4 (44.4) |
| Pericardial effusion | 4 (44.4) |

*Values are no. (%) unless otherwise indicated.
†n = 7.

Paragonimiasis can be difficult to diagnose in its early stages because of the nonspecific nature of initial symptoms. In some regions, paragonimiasis may be mistakenly diagnosed as tuberculosis. In this series of patients, initial diagnoses included pneumonia, bronchitis, influenza, gastroenteritis, acute cholecystitis, and pulmonary embolism. The median time between crayfish ingestion and the onset of clinical signs and symptoms was 4 weeks (range 2–12 weeks). The median interval between the onset of symptoms and the initial visit to health care facilities was 2 weeks (range 2–8 weeks). However, the median time from symptom onset to the correct diagnosis was 12 weeks (range 3–83 weeks). Before diagnosis of paragonimiasis, patients received multiple unnecessary medications and treatments, and these were sometimes associated with serious illness. All patients were treated with antimicrobial drugs.

Clostridium difficile infection developed in 1 patient after multiple courses of antimicrobial drug therapy. Six (67%) patients were treated with ≥ 1 course of corticosteroids. One patient also underwent multiple thoracentesis procedures, and 1 of these procedures resulted in pneumothorax that required chest tube replacement. This patient also underwent decortication because of recurrent pleural effusions. One patient underwent laparoscopic cholecystectomy after having right upper quadrant pain. This finding may have been related to parasite migration

across the diaphragm because the gallbladder did not show any pathologic changes.

Laboratory Test Results

Patients with paragonimiasis often have abnormal laboratory test results that are useful for making a diagnosis. Eosinophilia has been reported in 62%–66% of patients with infection caused by *P. westermani* flukes (20,21) and in 75% of patients with paragonimiasis in North America (19). All patients in this series had eosinophilia at initial examination (absolute eosinophil count range 600 cells/mm³–2,300 cells/mm³, % range 5.6%–21%). Pleural fluid analysis showed eosinophilia in 3 patients. Chest radiographic findings were abnormal for all patients with paragonimiasis in North America (19). Pleural effusions were present in 37% of paragonimiasis patients in Asia and in 60% of previously described patients in North America (19,22). All patients in this series had pleural effusions. Other chest radiographic findings included nodules, opacities, and infiltrates. Chest computed tomography scans showed pleural thickening, pericardial thickening, pericardial effusions, and worm nodules (23).

Four of 6 patients in the current series had pericardial effusions documented by either computed tomography or echocardiography. Although most pericardial effusions were small and did not cause hemodynamic compromise, 1 patient had cardiac tamponade that required emergency pericardiocentesis and drain placement. Analysis of pericardial fluid showed marked eosinophilia. Eosinophilic pericardial effusions were documented in 3 children with paragonimiasis caused by *P. mexicanus* flukes in Costa Rica (24,25). Pericardial effusion has also been reported for 1 patient with paragonimiasis in Asia (26). Pericardial effusions have not been reported for patients with *P. kellicotti* flukes infection, although various *Paragonimus* spp. flukes have been reported to invade soft tissue (19,20,27,28) and the central nervous system (19,29).

Serologic analysis can be useful for confirming a diagnosis of paragonimiasis. However, available serologic tests have limitations. An immunoblot for *P. westermani* flukes performed at the Centers for Disease Control and Prevention (Atlanta, GA, USA) has been reported to be highly sensitive (96%) and specific (99%) (30). However, this assay has not been validated for *P. kellicotti* flukes. In our series, 2 patients had negative immunoblot results at the Centers for Disease Control and Prevention for samples that had been positive by Western blot with *P. kellicotti* fluke antigen at Washington University (G.J. Weil, et al., unpub. data). These patients had symptoms and abnormal laboratory test results suggestive of paragonimiasis after ingestion of raw crayfish, and their symptoms resolved after therapy with praziquantel. Diagnosis by identification of ova in sputum specimens is specific, but has low sensitivity

(30%–40%) (1). Ova were present in sputum from only 1 patient in our series (5). Examination of stool for ova has low sensitivity (11%–15%) (31,32).

Response to Therapy

Praziquantel (75 mg/kg in 3 divided doses for 2 days) is the treatment of choice for paragonimiasis in the United States (33). Cure rates of 71%–75%, 86%–100%, and 100% have been reported with 1-, 2-, and 3-day courses, respectively (1,34). All patients in this series were treated with praziquantel for 2–3 days, and 7 (77.8%) experienced rapid clinical improvement or cure after treatment. One patient had some residual dyspnea and chest tightness 4 weeks after treatment. These findings may have been related to the protracted time between onset of his symptoms and initiation of appropriate therapy. He was asymptomatic at the 6-month follow-up visit. One atypical patient with chronic paragonimiasis who also had preexisting chronic obstructive pulmonary disease did not notice much improvement in his chronic dyspnea after praziquantel treatment, but defervescence and a weight gain of 30 pounds represented a clear clinical response to therapy.

Public Health Interventions

Control of this organism in the wild is not feasible because of the wide geographic distribution of crayfish and mammalian intermediate hosts that eat crayfish and serve as definitive hosts for the parasite. *P. kellicotti* flukes are highly prevalent among crayfish in rivers that are used for recreation in Missouri (5). Effective prevention strategies should focus on physician education to improve awareness of this disease and education targeted at the general population. We worked with public health officials to help improve awareness of this disease in physicians and in the general public. For example, we assisted the Missouri Department of Health and Senior Services in creating a health advisory (www.health.mo.gov/emergencies/ert/alertsadvisories/pdf/HAd4-30-10.pdf) for physicians in Missouri with the goal of educating physicians on the risk factors, clinical signs and symptoms, and treatment for this infection. In September 2009, we collaborated with the Missouri Department of Health and Senior Services and the Missouri Department of Natural Resources to create a warning poster (www.health.mo.gov/living/environment/fishadvisory/pdf/crayfish.pdf) that was posted at canoe rental facilities and campgrounds along rivers in Missouri. This poster warned the general public about the risk for consuming raw crayfish.

In addition, during the spring of 2010, four of the authors (M.A.L., L.M.D., T.C.B., G.J.W.) provided information to local and national print, radio, and television media to increase awareness of this infection. Three cases were identified after this media campaign. One patient

sought care at our medical facility after his mother, a nurse, saw an article about paragonimiasis in her local newspaper. One patient was referred to our clinic by a friend who had seen a report on paragonimiasis on a local television station. Another patient had atypical features, but increased physician awareness helped to establish the diagnosis in this patient.

Discussion

Although only a small number of cases of human paragonimiasis have been described in the medical literature since 1984, we have seen 9 patients with this disease in St. Louis since 2006. Five other patients with this disease in Missouri have been reported to the Missouri Department of Health and Senior Services since 2009 (P. Lo, pers. comm.). *P. kellicotti* flukes are believed to be widely distributed throughout the North America. In addition, outdoor activities such as camping and float trips when combined with alcohol consumption are not uniquely confined to Missouri. It is likely that there are case-patients in other regions who have not been given a diagnosis or treated. Although most patients reported to date have been adults, this series shows that children are also at risk for infection if they ingest uncooked crayfish.

As this patient series demonstrates, delayed diagnosis can lead to unnecessary medical treatments and procedures that can cause serious illness. Clinicians should consider the diagnosis of paragonimiasis in all patients with cough, fever, and pleural effusion with peripheral eosinophilia. We are developing a new antibody assay that may help clinicians identify and treat patients with this infection. Additional efforts to raise awareness of this parasite among physicians will potentially help appropriately identify and treat currently infected persons. These efforts should also target the general public to warn them of the dangers of consuming raw crayfish.

Dr Lane is an assistant professor of medicine at Washington University School of Medicine in St. Louis. His research interests are clinical outcomes, patient safety, and quality improvement.

References

1. Procop GW. North American paragonimiasis (caused by *Paragonimus kellicotti*) in the context of global paragonimiasis. *Clin Microbiol Rev.* 2009;22:415–46. <http://dx.doi.org/10.1128/CMR.00005-08>
2. Liu Q, Wei F, Liu W, Yang S, Zhang X. Paragonimiasis: an important food-borne zoonosis in China. *Trends Parasitol.* 2008;24:318–23. <http://dx.doi.org/10.1016/j.pt.2008.03.014>
3. Sharma OP. The man who loved drunken crabs. A case of pulmonary paragonimiasis. *Chest.* 1989;95:670–2. <http://dx.doi.org/10.1378/chest.95.3.670>
4. Ward HB. On the presence of *Distoma westermanni* in the United States. *Vet Med.* 1894;1:355–7.

5. Fischer PU, Curtis KC, Marcos LA, Weil GJ. Molecular characterization of the North American lung fluke *Paragonimus kellicotti* in Missouri and its development in Mongolian gerbils. *Am J Trop Med Hyg.* 2011;84:1005–11. <http://dx.doi.org/10.4269/ajtmh.2011.11-0027>
6. Watson TG, Nettles VF, Davidson WR. Endoparasites and selected infectious agents in bobcats (*Felis rufus*) from West Virginia and Georgia. *J Wildl Dis.* 1981;17:547–54.
7. Cole RA, Shoop WL. Helminths of the raccoon (*Procyon lotor*) in western Kentucky. *J Parasitol.* 1987;73:762–8. <http://dx.doi.org/10.2307/3282410>
8. Davidson WR, Nettles VF, Hayes LE, Howerth EW, Couvillion CE. Diseases diagnosed in gray foxes (*Urocyon cinereoargenteus*) from the southeastern United States. *J Wildl Dis.* 1992;28:28–33.
9. Ramsden RO, Presidente PJ. *Paragonimus kellicotti* infection in wild carnivores in southwestern Ontario: I. Prevalence and gross pathologic features. *J Wildl Dis.* 1975;11:136–41.
10. Ameel DJ. More data on the lung fluke, *Paragonimus*, in North America. *Science.* 1931;74:493–4. <http://dx.doi.org/10.1126/science.74.1924.493>
11. Béland JE, Boone J, Donevan RE, Mankiewicz E. Paragonimiasis (the lung fluke). Report of four cases. *Am Rev Respir Dis.* 1969;99:261–71.
12. Boé DM, Schwarz MI. A 31-year-old man with chronic cough and hemoptysis. *Chest.* 2007;132:721–6. <http://dx.doi.org/10.1378/chest.07-0712>
13. Castilla EA, Jessen R, Sheck DN, Procop GW. Cavitary mass lesion and recurrent pneumothoraces due to *Paragonimus kellicotti* infection: North American paragonimiasis. *Am J Surg Pathol.* 2003;27:1157–60. <http://dx.doi.org/10.1097/0000478-200308000-00015>
14. DeFrain M, Hooker R. North American paragonimiasis: case report of a severe clinical infection. *Chest.* 2002;121:1368–72. <http://dx.doi.org/10.1378/chest.121.4.1368>
15. Madariaga MG, Ruma T, Theis JH. Autochthonous human paragonimiasis in North America. *Wilderness Environ Med.* 2007;18:203–5. <http://dx.doi.org/10.1580/06-WEME-CR-063R2.1>
16. Mariano EG, Borja SR, Vruno MJ. A human infection with *Paragonimus kellicotti* (lung fluke) in the United States. *Am J Clin Pathol.* 1986;86:685–7.
17. Pachucki CT, Levandowski RA, Brown VA, Sonnenkalb BH, Vruno MJ. American paragonimiasis treated with praziquantel. *N Engl J Med.* 1984;311:582–3. <http://dx.doi.org/10.1056/NEJM198408303110906>
18. Procop GW, Marty AM, Scheck DN, Mease DR, Maw GM. North American paragonimiasis. A case report. *Acta Cytol.* 2000;44:75–80. <http://dx.doi.org/10.1159/000326230>
19. Lane MA, Barsanti MC, Santos CA, Yeung M, Lubner SJ, Weil GJ. Human paragonimiasis in North America following ingestion of raw crayfish. *Clin Infect Dis.* 2009;49:e55–61. <http://dx.doi.org/10.1086/605534>
20. Shim YS, Cho SY, Han YC. Pulmonary paragonimiasis: a Korean perspective. *Semin Respir Med.* 1991;12:35–45. <http://dx.doi.org/10.1055/s-2007-1006223>
21. Singh TS, Mutum SS, Razaque MA. Pulmonary paragonimiasis: clinical features, diagnosis and treatment of 39 cases in Manipur. *Trans R Soc Trop Med Hyg.* 1986;80:967–71. [http://dx.doi.org/10.1016/0035-9203\(86\)90275-0](http://dx.doi.org/10.1016/0035-9203(86)90275-0)
22. Im JG, Whang HY, Kim WS, Han MC, Shim YS, Cho SY. Pleuropulmonary paragonimiasis: radiologic findings in 71 patients. *AJR Am J Roentgenol.* 1992;159:39–43.
23. Henry TS, Lane MA, Weil GJ, Bailey TC, Bhalla S, Chest CT. Features of North American paragonimiasis. *AJR Am J Roentgenol.* 2012;198. In press. <http://dx.doi.org/10.2214/AJR.11.7530>
24. Brenes Madrigal R, Rodriguez-Ortiz B, Vargas Solano G, Monge Ocampo Obando E, Ruiz Sotela PJ. Cerebral hemorrhagic lesions produced by *Paragonimus mexicanus*: report of three cases in Costa Rica. *Am J Trop Med Hyg.* 1982;31:522–6.
25. Saborio P, Lanzas R, Arrieta G, Arguedas A. *Paragonimus mexicanus* pericarditis: report of two cases and review of the literature. *J Trop Med Hyg.* 1995;98:316–8.
26. Yang SP, Huang CT, Cheng CS, Chiang LC. The clinical and roentgenological courses of pulmonary paragonimiasis. *Dis Chest.* 1959;36:494–508.
27. Chang HT, Wang CW, Yu CF, Hsu CF, Fang JC. Paragonimiasis; a clinical study of 200 adult cases. *Chin Med J.* 1958;77:3–9.
28. Kagawa FT. Pulmonary paragonimiasis. *Semin Respir Infect.* 1997;12:149–58.
29. Shih YC, Ch'En Chang YC. Paragonimiasis of central nervous system; observations on 76 cases. *Chin Med J.* 1958;77:10–9.
30. Slemenda SB, Maddison SE, Jong EC, Moore DD. Diagnosis of paragonimiasis by immunoblot. *Am J Trop Med Hyg.* 1988;39:469–71.
31. Kim JS. A comparison of sensitivity on stool and sputum examination for diagnosis of paragonimiasis. *Kiseangchunghak Chapchi.* 1970;8:22–4.
32. Shin DH, Joo CY. Prevalence of *Paragonimus westermani* in some Ulchin school children. *Acta Paediatr Jpn.* 1990;32:269–74. <http://dx.doi.org/10.1111/j.1442-200X.1990.tb00824.x>
33. Drugs for parasitic infections. *Med Lett.* 2010;8(suppl):e1–20.
34. Rim HJ, Chang YS, Lee JS, Joo KH, Suh WH, Tsuji M. Clinical evaluation of praziquantel (Embay 8440; BiltricideO) in the treatment of *Paragonimus westermani*. *Kiseangchunghak Chapchi.* 1981;19:27–37.

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Paragonimus kellicotti Flukes in Missouri, USA

Technical Appendix

Patients

We report the characteristics of patients 4–9. Characteristics of patients 1–3 may be found in the report by Lane et al. (1).

Patient 4

Patient 1 was a 28-year-old man who sustained a traumatic eye injury during a float (recreational river) trip on the Huzzah River on August 1, 2009. He underwent surgical repair of lacerations of the upper and lower eyelids and lacrimal duct. He was treated with oral prednisone for 6 weeks. Approximately 3 weeks later, he came to a local hospital with acute right upper quadrant and right shoulder pain. This pain initially began in late June 2009. At his hospital visit, he had leukocytosis and eosinophilia. The patient had an abnormal hepatobiliary iminodiacetic acid scan result and underwent laparoscopic cholecystectomy for presumed acalculous cholecystitis. However, histopathologic analysis of the gall bladder showed normal results.

Several days after completing the course of prednisone, myalgias, nonproductive cough, and fever $\leq 39^{\circ}\text{C}$ developed. He was treated by his primary care provider for influenza and community-acquired pneumonia with sequential courses of oseltamavir, azithromycin, amoxicillin/clavulanate, and linezolid without resolution of symptoms.

In October 2009, after several weeks with persistent symptoms of cough and fever, the patient came to a local emergency department. A computed tomography (CT) scan showed a moderate right-sided pleural effusion with right upper lobe consolidation and a large pericardial effusion. Laboratory studies showed a leukocyte count of 12,800 cells/mm³ with 640 eosinophils/mm³ (5.0%). He was transferred to our tertiary care hospital for further evaluation. At that time, he had a temperature of 38.0°C, an oxygen saturation on room air of 93%, and decreased breath sounds at the right base with dullness to percussion. Remaining physical

examination results were normal. Laboratory studies indicated a leukocyte count of 8,900 cells/mm³ with 1,400 eosinophils/mm³ (16%) and an erythrocyte sedimentation rate of 81 mm/h. A chest radiograph showed right upper lobe consolidation with a moderate pleural effusion.

Thoracentesis was performed and pleural fluid analysis showed orange fluid with 16,900 total cells, and 10,900 leukocytes with 66% eosinophils. The pleural fluid lactate dehydrogenase level was 2,153 IU/L and the albumin level was 3.3 mg/dL. The serum lactate dehydrogenase level was 148 IU/L and the serum protein level was 7.7 g/dL. A transthoracic echocardiogram confirmed the pericardial effusion. The patient was treated with intravenous vancomycin and cefepime. A purified protein derivative (PPD) skin test result was negative. Additional history showed that he had consumed 2 raw crayfish on a dare during a float trip on the Huzzah River in Missouri in early June 2009. His symptom onset with abdominal and shoulder pain began 3 weeks after crayfish ingestion.

A clinical diagnosis of paragonimiasis was made and antimicrobial drug therapy was discontinued. The patient was treated with oral praziquantel (25 mg/kg, 3×/d 2 days). Within 24 h, he showed had defervescence and his other symptoms improved. Sputum, fecal, and pleural fluid samples were negative for ova and parasites. Results of a *P. westermani* immunoblot performed at the Centers for Disease Control and Prevention (CDC) were negative. At follow-up 8 weeks after treatment, complete and differential blood counts were within reference ranges. A paragonimus enzyme immunoassay (Parasitic Disease Consultants, Tucker, GA, USA) showed a titer of 8, which was less than the threshold of 32 for positivity. A Western blot result with *P. kellicotti* fluke antigen performed at Washington University was positive (2). A repeat chest radiograph 8 weeks after treatment showed a residual, small, right-sided pleural effusion.

Patient 5

Patient 5 was a 10-year-old boy who came to his primary care physician with a 3-week history of fever, cough, and chest pain. He was treated with oseltamivir and amoxicillin for presumed influenza and bacterial superinfection. His symptoms improved, and he returned to his regular activities. However, during football practice, he sustained blunt chest trauma after which chest pain and fever returned. He was treated again with amoxicillin with no improvement, and he was referred to a local hospital for imaging.

Chest radiography showed a large, left-sided, pleural effusion and an enlarged cardiac silhouette. A chest CT scan showed large left pleural and pericardial effusions, prompting his transfer to St. Louis Children's Hospital. An echocardiogram confirmed a pericardial effusion without evidence of tamponade. Laboratory studies showed a peripheral blood eosinophil count of 1,560 cells/mm³ (8%). Thoracentesis was performed, and examination of pleural fluid showed 3,805 cells, with 3,320 nucleated cells, 44% of which were eosinophils. No malignant cells were identified by cytologic analysis. The pleural fluid was tested by routine, fungal and mycobacterial culture, and no organisms were visualized by direct staining or on culture. He was treated empirically with cefotaxime and vancomycin but continued to have high fever despite antimicrobial drug therapy. Blood cultures and serologic testing for *Toxocara canis*, *Strongyloides* spp., histoplasmosis, and *Mycoplasma* spp. showed negative results. A tuberculin skin test result was negative. A repeat chest radiograph on hospital day 2 confirmed reaccumulation of his pleural effusion.

On further questioning, it was learned that the patient's uncle, an outdoor survivalist, had taught the patient to eat raw crayfish 1 year before the onset of his symptoms. Approximately 3 months before onset of his illness, the boy demonstrated his survival skills to his cousins during a family outing on the Current River in southeastern Missouri by ingesting a raw crayfish. On the basis of this history and his clinical manifestations, he was treated with praziquantel (25 mg/kg, 3×/d for 2 days) for a presumptive diagnosis of paragonimiasis. His chest pain and other symptoms promptly improved and he was discharged. At a follow-up clinic visit 1 month after treatment, his symptoms, eosinophilia, and effusions had resolved. A paragonimus immunoblot on acute-phase and convalescent-phase serum samples was performed at CDC and results were negative. However, results of a Western blot with *P. kellicotti* fluke antigen at Washington University were positive (2).

Patient 6

Patient 6 was a 20-year-old man with no medical history who came for medical care with a 2-week history of fever, diarrhea, and night sweats in September 2009. He was evaluated by his primary care physician who prescribed azithromycin for acute gastroenteritis. Routine stool cultures at that time were negative. Dyspnea and anorexia developed, and a 10-lb weight loss prompted return to his primary care physician in early November 2009. A chest radiograph at that time showed moderate bilateral pleural effusions.

The patient was admitted to a hospital. His absolute eosinophil count was 1,300 cells/mm³, and a CT scan of the chest showed moderate bilateral pleural effusions and a small pericardial effusion. Transthoracic echocardiography showed a pericardial effusion with cardiac tamponade. Pericardiocentesis were performed with placement of pericardial drain Pericardial fluid had a leukocyte count of 60,800 cells/mm³ with 50% eosinophils. Thoracentesis of a left pleural effusion yielded 1,200 mL of yellow–green fluid with a leukocyte count of 1,952 cells/mm³ (55% eosinophils), a protein level of 6.6 g/dL (serum protein 8.0 g/dL), a lactate dehydrogenase level of 2,295 IU/L, a glucose level <5 mg/dL, and negative cytologic and routine microbiological result. After these procedures, the patient’s dyspnea improved, and the pericardial drain was removed after several days. Prednisone (60 mg/day) was given empirically, and the patient was discharged shortly thereafter.

Over the next 3 months, peripheral eosinophilia and pleural effusions recurred coincident with tapering of corticosteroids, prompting 2 thoracenteses, both of which showed lymphocytic exudates. Corticosteroids had been discontinued in January 2009, one month before the patient’s first visit to the pulmonary clinic at our institution. He reported persistent, low-grade exertional dyspnea and cough with sputum. Upon detailed questioning regarding travel history and exposures, the patient reported eating raw bratwurst during a camping trip 9 months earlier. Vital signs were normal, and physical examination showed decreased breath sounds and tactile fremitus with dullness to percussion at both lung bases. The absolute eosinophil count was 2,200 cells/mm³, the IgE level was 259 IU/mL, stool ova and parasite examination results were negative, and a PPD skin test result was negative. Serum was sent to CDC for serologic analysis, and a chest radiograph showed a small left pleural effusion. The patient was unable to provide a sputum sample.

Several weeks later, results for a *Strongyloides* indirect hemagglutination assay performed at CDC were positive (7.29 U/mL, reference value <1.7 U/mL). Ivermectin was prescribed; 2 doses of 0.2 mg/kg were to be taken 2 weeks apart. Subsequently, a paragonimiasis immunoblot performed at the CDC showed positive results. A Western blot with *P. kellicotti* fluke antigen performed at Washington University showed positive results (2). Praziquantel (25 mg/kg, 3×/d 2 days) was prescribed. After discussing the test results with the patient, he disclosed that acting on a dare from the younger members of his party, he and several other

friends had eaten raw crayfish while intoxicated during the float trip on the Jacks Fork River in June 2009, nine months before the time of diagnosis and 12 weeks before the onset of symptoms.

At a follow-up visit 1 month after treatment with praziquantel, the patient was asymptomatic. The absolute eosinophil count was 900 cells/mm³, and a chest radiograph showed a small, residual, left pleural effusion.

Patient 7

Patient 7 was a previously healthy 22-year old man who had with midepigastic pain, fever $\leq 38.3^{\circ}\text{C}$, subjective chills, and night sweats in August 2009. Shortness of breath, cough, and hemoptysis gradually developed, Two weeks after symptom onset, he awoke from sleep with the sudden onset of left-sided pleuritic chest pain.

He was admitted to a hospital where laboratory studies showed a leukocyte count of 8,100 cells/mm³. The differential cell count was 66% neutrophils, 15% lymphocytes, 7% monocytes, and 10.5% eosinophils (absolute count 850 cells/mm³). A CT of the chest showed a filling defect in the posterior basal segment of the right lower lung lobe, peribronchovascular opacities at both lung bases, a density in the right lower lobe, and a 3-mm nodule in the right upper lobe. A D-dimer test result was increased. Levels of thyroid-stimulating hormone, factor V Leiden, lupus anticoagulant, antinuclear antibody, antithrombin III, protein S, and protein C were within reference ranges. A transthoracic echocardiogram result was normal. Bilateral lower extremity venous duplex ultrasound did not show evidence of thrombi. The patient was treated with heparin and then warfarin for possible pulmonary embolism.

The patient continued to have cough, hemoptysis, night sweats and noted a 10–15-lb weight loss. In November 2009, a repeat chest radiograph showed a small pleural effusion and a pulmonary infiltrate. He was treated with azithromycin for 5 days, followed by cefuroxime for 7 days, and showed no improvement in symptoms. Repeat chest radiographs showed increasing pleural effusions. He was again admitted to the hospital and treated with moxifloxacin. A thoracentesis was performed, and 2 L of thin yellow-orange fluid was removed. The cell count was 1,112 cells/mm³ with 32% neutrophils, 61% lymphocytes, and 3% eosinophils. Routine bacterial, acid-fast bacilli, and fungal cultures were negative. Pleural fluid cytologic analysis showed peripheral blood cells and mesothelial cells. Results for hepatitis were negative, and levels of antinuclear antibody, cyclic citrulline peptide, cardiolipin, β -2 glycoprotein, and

rheumatoid factor were within reference limits. A PPD skin test result was negative. The patient's course was complicated by *Clostridium difficile* infection requiring treatment with metronidazole.

In January 2010, he was hospitalized because of increasing shortness of breath and continued hemoptysis, cough, and night sweats. Imaging showed a recurrence of the right pleural effusion and opacities in the left mid and lower lungs. He underwent a video-assisted thorascopic decortication of the right lung, and 1.5 L of murky fluid was drained. Cultures were not performed and cell counts were not performed for the fluid.

The patient continued to have night sweats, productive cough with rusty-colored sputum, and progressive weight loss (20 lbs). His fever and chills had resolved. Over the course of the next 4 months, progressive shortness of breath and chest pain developed. Laboratory studies showed a leukocyte count of 11,400 cells/mm³ with an absolute eosinophil count of 800 cells/mm³ (7.4%). Test results for double-stranded DNA and Sjögrens syndrome antinuclear SSA and SSB antibodies were within reference limits. Repeat chest radiograph showed bilateral pleural effusions. A chest CT scan showed a 10 mm–thick pericardial effusion but no other evidence of pulmonary embolism; enlarged mediastinal and epicardial lymph nodes and a moderate pleural effusion were noted. Corticosteroid therapy was initiated for treatment of a possible connective tissue disorder.

In June 2010, the patient's mother read a newspaper article about recent cases of paragonimiasis and brought her son to our clinic for further evaluation. At that time, the patient reported that he had eaten a raw crayfish on a float trip on the Jack's Fork River in southern Missouri in July 2009, ≈4–6 weeks before onset of his illness. His physical examination was notable for dullness to percussion at the right base. Paragonimus ova were seen on examination of sputum. Results of a paragonimus immunoblot performed at CDC were positive. A Western blot result with *P. kellicotti* fluke antigen at Washington University was positive (2). The patient was treated with praziquantel, 25 mg/kg, 3×/d for 3 days. At a follow-up visit ≈4 weeks after completing therapy, the patient's cough, hemoptysis, and night sweats had resolved. Dyspnea had improved, but had not resolved. Eosinophilia had resolved (absolute eosinophil count 200 cells/mm³). The chest radiograph showed bilateral, small-to-moderate pleural effusions. He had no residual symptoms 6 months after treatment.

Patient 8

Patient 8 was a healthy 30-year-old man who in July 2010 had a 2-week history of fever $\leq 38.9^{\circ}\text{C}$, night sweats, right-sided chest pain, productive cough with brown sputum and watery diarrhea. He was seen by his primary care physician and given a diagnosis of community-acquired pneumonia after a chest radiograph showed a right lung infiltrate and right-sided pleural effusion. He was treated with levofloxacin and corticosteroids for 10 days. The cough and dyspnea improved after treatment with prednisone. However, when the prednisone was discontinued, dyspnea returned and the patient noted a 10-lb weight loss.

He returned to his primary care physician 1 month later. A repeat chest radiograph showed persistent, right-sided pleural effusion. He received a second course of levofloxacin and corticosteroids, which improved his symptoms. However, symptoms again returned after stopping corticosteroids. A chest radiograph showed bilateral pleural effusions. A chest CT scan showed a left, upper-lobe infiltrate and bilateral pleural effusions. A CBC showed a leukocyte count of $15,000\text{ cells/mm}^3$ with $3,100\text{ eosinophils/mm}^3$ (21%).

In October 2010, the patient came to Washington University Medical Center for an outpatient evaluation. At that time, he was afebrile. Results of a physical examination were remarkable only for decreased breath sounds at the left base and some scant crackles. Laboratory studies showed a leukocyte count of $7,400\text{ cells/mm}^3$ with 0.6% eosinophils. A chest radiograph showed bilateral pleural effusions. Medical history showed that the patient had consumed 2 raw crayfish from the Jack's Fork River while intoxicated 2 weeks before symptom onset. Fecal and sputum examination results for ova and parasites were negative. However, a paragonimus immunoblot performed at CDC showed a positive result. A Western blot with *P. kellicotti* fluke antigen performed at Washington University showed a positive result (2). The patient was treated with praziquantel (25 mg/kg, 3 \times /d for 2 days). At follow-up 3 weeks after treatment, the patient's symptoms had resolved.

Patient 9

Patient 9 was a 43-year-old man with hypertension and tobacco dependence who in November 2008 came to a primary care outpatient clinic in southern Missouri with a 2-month history of progressive dyspnea on exertion, chest pain, and nonproductive cough. A physical examination showed that he was afebrile, and he had decreased breath sounds bilaterally with

wheezing. Laboratory studies showed a leukocyte count of 8,900 cells/mm³ and an absolute eosinophil count of 800 cells/mm³ (9%). Pulmonary function tests showed obstructive disease. A chest CT showed bilateral pleural effusions. An echocardiogram showed a negative result. He was given a diagnosis of acute bronchitis and treated with moxifloxacin.

He returned for treatment September 2009 at which time he reported continued shortness of breath. A chest radiograph and chest CT scan showed a right pleural effusion. He was treated with a short course of amoxicillin, but his symptoms did not improve. In December 2009, he was referred to the John Cochran Veteran's Administration Medical Center in St. Louis for further evaluation. At this time, his leukocyte count was 7,000 cells/mm³ with an absolute eosinophil count of 360 cells/mm³ (5%). He underwent thoracentesis, and 1,600 mL of straw-colored fluid was drained. The fluid cell count was 952 leukocytes/mm³ (29% neutrophils, 14% lymphocytes and 57% mesothelial cells). The patient was again treated with antimicrobial drugs but did not show clinical improvement. A CT scan 6 weeks after thoracentesis follow-up showed a persistent right lower-lobe infiltrate with reaccumulation of the right-sided pleural effusion.

In April 2010, the patient had an absolute eosinophil count of 710 cells/mm³ (8%). In May 2010, he underwent a video-assisted thoracoscopic surgery procedure to obtain lung and pleural biopsy specimens for further evaluation of the recurrent pleural effusion. Pathologic examination of pleural tissue showed thickening of the alveolar septae and patchy chronic inflammation. No evidence of malignancy, fungal elements, or acid-fast bacilli were seen in the pleural tissue. Lung tissue did not show evidence of malignancy. Four nodular structures (diameter 2–4 mm) were observed. The lesions contained fibrous tissue with central calcification and mild chronic inflammation. Pathologic analysis of these nodules did not show evidence of malignancy or vasculitis.

Staining with Grocott methanamine silver and periodic acid–Schiff showed rare 3-mm and 8-mm yeast-like organisms without budding. Mucicarmine staining suggested the presence of capsules. Cryptococcus serum antigen, histoplasma complement fixation, and urine Histoplasma spp. antigen, blastomyces antibody and complement fixation, coccidioidomycosis complement fixation and antibody, PPD, fungal blood cultures and HIV test were all negative. Pleural and lung tissue cultures for fungi also showed negative results. The patient was treated with fluconazole in May 2010.

The patient showed no improvement in symptoms after 8 weeks of therapy with fluconazole. In addition, he had lost >20 lbs. Biopsy specimen slides were reviewed at the Armed Forces Institute of Pathology (Washington, DC, USA). Analysis did not confirm the presence of fungal elements. Additional information regarding exposures was obtained from the patient. The patient indicated that he had eaten crayfish while camping at least once a year for the past 20 years. However, he recalled consuming poorly cooked or raw crayfish while intoxicated on a camping trip ≈3 months before he initially sought care for dyspnea in 2008. A Western blot with *P. kellicotti* fluke antigen at Washington University showed a positive result (2). A paragonimus immunoblot performed at CDC also showed a positive result.

The patient was treated with praziquantel (25 mg/kg, 3×/d for 2 days). At the 6-month follow-up, chest radiograph showed resolution of pleural effusions. The patient had gained 25 lbs, but still had some residual shortness of breath. An immunoblot performed at CDC at the 60month follow-up showed positive results. A complete blood count was within reference limits and showed no eosinophilia. At the 1-year follow-up, repeat imaging showed no recurrence of pleural effusion. The eosinophil count remained within reference limits. The patient continued to have dyspnea attributed to underlying chronic obstructive pulmonary disease.

References

1. Lane MA, Barsanti MC, Santos CA, Yeung M, Lubner SJ, Weil GJ. Human paragonimiasis in North America following ingestion of raw crayfish. *Clin Infect Dis*. 2009;49:e55–61. [PubMed](https://pubmed.ncbi.nlm.nih.gov/19111111/) <http://dx.doi.org/10.1086/605534>
2. Fischer PU, Curtis KC, Marcos LA, Weil GJ. Molecular characterization of the North American lung fluke *Paragonimus kellicotti* in Missouri and its development in Mongolian gerbils. *Am J Trop Med Hyg*. 2011;84:1005–11. [PubMed](https://pubmed.ncbi.nlm.nih.gov/21111111/) <http://dx.doi.org/10.4269/ajtmh.2011.11-0027>