

8.11.3 Lung flukes (paragonimiasis) 1558

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section 8 Infectious diseases 1558 herbivorous animals that maintain the zoonotic life cycle of *Fasciola* species. This is encouraging given the advances in veterinary vaccine development over recent years. Currently, comprehensive immunization of livestock is under serious consideration by some countries, thereby reducing human infection and economic losses to the parasite. Control of the snail vectors using molluscicides is not considered practical in most situations. In areas where fascioliasis is prevalent, introduction of a health education programme to discourage human consumption of raw, wild watercress and other edible water plants may prove successful. Some Western countries have instigated strict controls on the commercial production of water plants. This would assist in preventing the expansion of endemic areas in developing countries. Increased data from community-based studies assessing seroprevalence, and an increased informed understanding of fascioliasis and its diagnostic difficulties by clinicians, would markedly reduce the magnitude to which fascioliasis affects human health. FURTHER READING Andrews RH, et al. (2008). *Opisthorchis viverrini*: an underestimated parasite in world health. *Trends Parasitol*, 24, 497–501. Hughes T, et al. (2017). Opisthorchiasis and cholangiocarcinoma in Southeast Asia: an unresolved problem. *Intern J Gen Med*, 10, 227–37. Johansen MV, Lier T, Sithithaworn P (2015). Towards improved diagnosis of neglected zoonotic trematodes using a one health approach. *Acta Trop*, 141 (Pt B), 161–9. Khuntikeo N, et al. (2015). Cohort profile: cholangiocarcinoma screening and care program (CASCAP). *BMC Cancer*, 15, 1475–87. Khuntikeo N, et al. (2018). Current Perspectives on Opisthorchiasis Control and Cholangiocarcinoma Detection in Southeast Asia. *Front Med*, 5, 117. doi:10.3389/fmed.2018.00117. Mekky MA, et al. (2015). Human fascioliasis: a re-emerging disease in upper Egypt. *Am J Trop Med Hyg*, 93, 76–9. Petney TN, et al. (2016). Foodborne trematodes: a diverse and challenging group of neglected parasites. *Trans R Soc Trop Med and Hyg*, 110(1), 1–3. Sithithaworn, P, et al. (2008). Food borne Trematodes. In Cook G and Zumla A. eds. *Manson's Tropical Diseases*, p1461–76, Saunders Ltd, Elsevier, Canada. Sayasone S, et al. (2016). Efficacy and safety of tribendimidine against *Opisthorchis viverrini*: two randomised, parallel group, single-blind, dose ranging, phase 2 trials. *Lancet Infect Dis*, 16, 1145–53. Shin SH, et al. (2016). Development of two FhSAP2 recombinant based assays for immunodiagnosis of human chronic fascioliasis. *Am J Trop Med Hyg*, 95, 852–5. 8.11.3 Lung flukes (paragonimiasis) Udomsak

Silachamroon and Sirivan Vanijanonta ESSENTIALS Paragonimiasis is an infection by flukes of the genus *Paragonimus*, with foci of disease in Asia, Africa, and Central and South America. Humans acquire infection by eating metacercariae in improperly cooked freshwater crabs or crayfish. Acute inflammatory and allergic symptoms are rarely serious and usually resolve spontaneously. Chronic manifestations may be (1) pulmonary—most remarkably with a chronic, productive cough with jam-like, brownish-red sputum; and (2) extrapulmonary—most importantly in the central nervous system, often presenting with seizures. Diagnosis is by demonstrating ova in sputum, stool, or pleural fluid. Serology can be used to support the diagnosis, especially in extrapulmonary paragonimiasis. Treatment with praziquantel is almost always effective. Prevention is by health education and the mass treatment of infected people in an endemic area.

Lung fluke infection is caused by *Paragonimus* spp. of which there are more than 40 that cause disease in mammals and about 16 species causing human disease. *Paragonimus westermani* is the most common and widespread. Other species prevalent in some region are *P. heterotremus* in Southeast Asia, *P. africanus* and *P. uterobilateralis* in West Africa, *P. skrjabini* in China, *P. kellicotti* in North America, and *P. mexicanus* and *P. caliensis* in Central and South America.

Aetiology and life cycle Adult flukes are reddish-brown and pea-shaped. They are 0.8–1.6 cm in length, 0.4–0.8 cm in width, and 0.3–0.5 cm thick (Fig. 8.11.3.1). Typically, they are encapsulated in cysts adjacent to the bronchi. Ova (Fig. 8.11.3.2) are expelled through the bronchi and expectorated with sputum or swallowed and passed in the faeces. They hatch in fresh water after a few weeks. The resulting miracidia then infect various species of freshwater snail in which they form sporocysts, rediae, and daughter rediae. Metacercariae develop in susceptible freshwater crabs and crayfish (Fig. 8.11.3.3). Human infection results from ingestion of viable metacercariae in raw or insufficiently cooked crabs and crayfish.

Metacercariae excyst in the intestine, Fig. 8.11.3.1 Adult fluke of *Paragonimus westermani*, approximately 1 cm long. Courtesy of Dr Prayong Radamyos, Faculty of Tropical Medicine, Mahidol University, Bangkok.

8.11.3 Lung flukes (paragonimiasis) 1559 then pass through the peritoneal cavity, diaphragm, and pleural cavity, before finally encysting in the lung. Tunnels may be formed during their migration. Encysted flukes mature over a period of 6–8 weeks and eggs are produced in 10–12 weeks. The circuitous routes of migration allow young flukes to lodge and mature in ectopic locations. The reservoir hosts are wild and domestic mammals. Pigs, wild boars and deer are paratenic hosts in which the flukes remain immature and reside in the muscles. When human consume these meats raw, the young flukes mature into adult worms.

Epidemiology The three major foci of this disease are Asia, Africa, and Central and South America. Human paragonimiasis is not uncommon in North America. Both imported and endemic cases have been reported in recent years. *Paragonimus kellicotti* infection was associated with ingestion of raw crayfish from fresh water river system within the Mississippi River Drainage Basin with the largest number of cases from Missouri.

Pathogenesis and pathology While they migrate, larvae cause irritation, acute inflammatory reactions, traumatic tracts, pressure effects, haemorrhage, and necrosis in affected tissues. Acute, diffuse, fibrinoexudative peritonitis may also occur. Abscess cavities containing young flukes are then formed and become enclosed in a fibrous capsule. Mature cysts adjacent to the bronchi may rupture and their contents then drain into the bronchial system. Single or multiple cysts may occur, usually in the lower lobes of the lungs. Extrapulmonary pathological changes may be caused by aberrant migratory flukes. Cysts, abscesses, and granulomas may be found in the abdominal viscera, subcutaneous tissue, muscles, genital organs, and brain.

Clinical features The clinical manifestations are divided into acute and chronic phases. The acute phase occurs after

consumption of metacercariae. The incubation period varies from a few days to weeks. The severity of symptoms usually correlates with the worm load. Invasion and migration by young flukes cause inflammatory and allergic responses such as fever, rashes, urticaria, migratory swelling, abdominal pain, cough, and chest pain. Acute symptoms are rarely serious and usually resolve spontaneously. A large proportion of cases are asymptomatic. Chronic manifestations may be pulmonary and extrapulmonary. Pulmonary paragonimiasis The most remarkable clinical feature is a chronic, productive cough with jam-like, brownish-red sputum (Fig. 8.11.3.4). Other symptoms include breathlessness and chest pain. Pleural effusion, empyema, or hydropneumothorax can occur. Occasionally, patients

Fig. 8.11.3.2 Ovum of *Paragonimus westermani*, approximately 100 μm long. Courtesy of Dr Prayong Radamyos, Faculty of Tropical Medicine, Mahidol University, Bangkok.

Fig. 8.11.3.3 Metacercaria of *Paragonimus westermani* in a freshwater crab. Courtesy of Dr Prayong Radamyos, Faculty of Tropical Medicine, Mahidol University, Bangkok.

Fig. 8.11.3.4 Typical appearance of sputum coughed up by a patient with pulmonary paragonimiasis. Courtesy of the late Professor Sornchai Looareesuwan.

section 8 Infectious diseases 1560 experience haemoptysis following heavy work or exertion. Physical examination usually shows few abnormalities. Extrapulmonary paragonimiasis Aberrant migration of young flukes to other organs causes extrapulmonary paragonimiasis. The most common and important site is the central nervous system. Presentation of cerebral paragonimiasis depends on the site of the lesion. Seizures are common. Increased intracranial pressure induces persistent intense headache, nausea, vomiting, papilloedema, diplopia, and loss of visual acuity. Mental disturbances of the schizoid and paranoid type may develop. Involvement of the basal meninges results in increased intracranial pressure, hydrocephalus, arterial thrombosis, and stroke. Involvement of intrabdominal organs such as spleen, liver, and small and large intestine causes nonspecific symptoms and signs. Migratory subcutaneous nodules might occur. Spinal involvement presents with back pain, paralysis, and sensory impairment of the lower extremities. Differential diagnosis Pulmonary paragonimiasis should be differentiated from other conditions presenting with chronic cough productive of bloody or rusty sputum, notably pulmonary tuberculosis, bronchiectasis, lung abscess, and tumour. Paragonimiasis is frequently misdiagnosed as tuberculosis but does not respond to antituberculosis treatment. Patients usually look relatively healthy. A careful history of residence or travel to endemic areas and eating habits aids diagnosis. Cerebral paragonimiasis should be differentiated from cerebral cysticercosis, hydatid disease, meningoencephalitis, brain abscesses, and tumours. Subcutaneous paragonimiasis may resemble gnathostomiasis, sparganosis, loiasis, or onchocerciasis. Clinical investigation Blood counts typically show leucocytosis with eosinophilia. Sputum is thick, gelatinous, rust-coloured, or bloody. Microscopic examination shows necrotic tissue, blood, leucocytes, Charcot-Leyden crystals, and ova. In pleuropulmonary paragonimiasis, examination of the pleural fluid may be pathognomonic. This shows an exudate with eosinophils in variable proportions (12–75%). Typically, it has an elevated protein (6–7 g/dl), low glucose level (<10 mg/dl), low pH (<7.10), and elevated lactic dehydrogenase (>1 000 U/litre). Parasite ova may be found in the pleural fluid. A minority of symptomatic patients have normal chest radiographs. Abnormal findings include linear infiltrations, exudative pneumonia, localized pleural effusions, and nodular or cystic lesions. These lesions are found predominantly in the basilar and peripheral regions of both lower lung fields. Cysts may be single or multiple. The most characteristic radiographic feature is a ring shadow with a crescent-shaped opacity along one side of the heart border (Fig. 8.11.3.5). Multiple cysts may aggregate, producing a soap-bubble appearance. Other findings are pleural thickening and

calcification. Fibroatelectasis resembling tubercu- losis may occur. CT is more sensitive for detecting these abnormalities. Cystic nodules are clearly seen even when they are invisible in plain radiographs (Fig. 8.11.3.6). Focal bronchiectasis is commonly (b) (a) Fig. 8.11.3.5 (a) Posteroanterior radiograph of a patient with pulmonary paragonimiasis showing thick-walled cystic lesions in the right perihilar area and left upper lobe. Patchy infiltration and pleural thickening are also seen in the right lower lobe. (b) Enlargement of the left upper lobe cystic lesion. Copyright Dr Udomsak Silachamroon. Fig. 8.11.3.6 CT scan of a patient with paragonimiasis, showing multiple cystic lesions in the subpleural region. Copyright Professor Sirivan Vanijanonta.

8.11.3 Lung flukes (paragonimiasis) 1561 found. Worm migration tracts may be identified. Paragonimiasis is one of the benign lesions that may give an increased uptake in a fluorodeoxyglucose positron emission tomography (FDG-PET) scan and can mimic malignant lung tumour. Characteristic CT findings in cerebral paragonimiasis are conglomerate, multiple ring-shaped enhancing lesions with surrounding oedema (Fig. 8.11.3.7). Demonstration of Paragonimus infection Detection of characteristic eggs in sputum, stool, or pleural fluid confirms the diagnosis. Paragonimus eggs are golden brown in colour and ovoid in shape with an operculum at one end (size 80–120 × 50–60 µm) (see Fig. 8.11.3.2). Egg detection rate is low (12–62%) but repeating the examination results in a higher yield. Paragonimus eggs can be detected by Ziehl-Neelsen staining of sputum sample and this appears superior to the standard wet smear technique. Expectoration of the intact fluke is rare. Various serological tests have been developed to aid the diagnosis. The complement fixation test is sensitive and can be used for evaluation of treatment response, but it is now rarely available. Currently enzyme-linked immunosorbent assay (ELISA) and immunoblot are commonly applied for various kinds of parasitic disease. These tests are highly sensitive (90–100%) and specific (>90%). Species differentiation could be achieved by these tests. They are essential for diagnosis of extrapulmonary paragonimiasis. Positive results persist for some time after successful treatment (4–24 months) so the response to treatment cannot be evaluated. Definitive diagnosis can be made by demonstrating ova in sputum, stool, pleural fluid, or tissue biopsy. In cases where eggs are not detected or paragonimiasis is extrapulmonary, compatible clinical findings with positive serology are accepted as diagnostic. Treatment The drug of choice is praziquantel in a dose of 75 mg/kg per day in three divided doses for 2 to 3 days with a cure rate of nearly 100%. Symptoms improve within a few days. Eggs disappear from the sputum in a few weeks. Radiological improvement takes months, depending on the extent and chronicity of the disease. However, some patients with long duration of respiratory symptoms, high ELISA titre, and multiple pulmonary lesions might relapse after treatment. The cure rate can be improved by giving a second course of praziquantel. Urticaria or a transient increase in eosinophilia is occasionally seen, indicating a reaction to dead parasites. Allergy to praziquantel is rare but when it occurs without an available alternative, desensitization to praziquantel should be considered. Convulsions, coma, and behavioural changes may develop during treatment of cerebral paragonimiasis as a result of brain oedema and increased intracranial pressure. Dexamethasone is suggested for this reaction. Repeated thoracentesis in combination with chemotherapy is required for patients with large pleural effusions. Chronic pleural effusion or empyema may resist chemotherapy because penetration of the drug is limited by pleural thickening. Surgical decortication may be indicated in such cases. Triclabendazole (dose of 10 mg/kg twice a day for 1–2 days), a drug for treatment of fascioliasis, was reported to be as effective as praziquantel for pulmonary paragonimiasis and better tolerated by the patients. When available, it might be considered as an alternative to praziquantel. Bithionol and niclofalan are also effective. Prognosis Pulmonary paragonimiasis is rarely fatal. The lesions

may calcify or resolve completely in a few years. Cerebral paragonimiasis may cause chronic morbidity such as epilepsy, mental changes, and neurological sequelae. Prevention and control Effective control measures are directed towards interruption of the life cycle. However, control and eradication of intermediate hosts is impracticable; health education, changes in social and dietary customs, and the mass treatment of infected people in an endemic area are therefore more effective for prevention and control. FURTHER READING Chai JY (2013). Praziquantel treatment in trematode and cestode infections: an update. *Infect Chemother*, 45, 32–43. Diaz JH (2013). Paragonimiasis acquired in the United States: native and nonnative species. *Clin Microbiol Rev*, 26, 493–504. Fig. 8.11.3.7 Cerebral CT scan of a patient with paragonimiasis, showing multiple ring-shaped enhancing lesions with surrounding oedema. Courtesy of Professor Seung-Yull Cho, Suwon, Korea.

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