The Trematodes

6

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6.1 Introduction

The trematodes belong to the phylum Platyhelminthes or flatworms. Their characteristics include a flattened body with an outer tegument and two suckers, which is a characteristic feature of this group. Most trematodes are hermaphroditic, with well-developed reproductive organs and digestive system. Trematodes inhabit the alimentary canal of vertebrates and may involve other organs such as liver, biliary tract, lung, and urinary tract. Trematode infections are prevalent worldwide [1–3].

There are three groups of trematodes: Monogenea, Aspidogastrea, and Digenea.

Monogenea are external parasites of fish, with direct life cycles.

Aspidogastrea are endoparasites with their entire ventral surface as the adhesive organ.

Digenea are also endoparasites with simple adhesive organs and require one or more intermediate hosts.

This chapter is focused on the Digenean trematodes. Most Digenean trematodes, including *Fasciola* species, *Clonorchis sinensis*, and *Schistosomes*, primarily parasitize the liver and intestines in the human host, with the exception of *Paragonimus westermani*, which infect the lungs. These parasites have a complex life cycle, involve a mollusk host, and may have up to six larval stages. The trematode eggs have a smooth hard shell, and majority of them are operculate.

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6.2 Specific Pathogenic Parasites

6.2.1 *Paragonimus westermani*

Paragonimus westermani is the commonest species of the genus *Paragonimus*, parasitizing both humans and animals, causing pulmonary paragonimiasis. There are 16 species of *Paragonimus* that are pathogenic to humans. The infection is seen in the Far East including China, Japan, Korea, Taiwan, Philippines, Indonesia, and parts of Southeast Asia including India and Nepal [4]. *Paragonimus* sp. infection has been also reported from Canada, North and Central America [5], and parts of South America. *Paragonimus africanus* has been reported from Nigeria, Libya, Liberia, and Zaire [1–3].

The adult fluke is egg-shaped, thick, fleshy, and red brown in color, measuring 7.5–20 mm long and 2.5–5 mm thick. The body wall has a thick tegument up to 40 um, two or more layers of smooth muscle, and a row of tegumental cells. There is a ventral and oral sucker and well-developed ovary, testes, uterus, vitellaria, and excretory bladder within the parenchyma. The eggs are golden brown, oval with thick birefringent shell, and 80–120 um by 45–65 um, with a flat operculum at one end (Figs. 6.1, 6.2, and 6.3).

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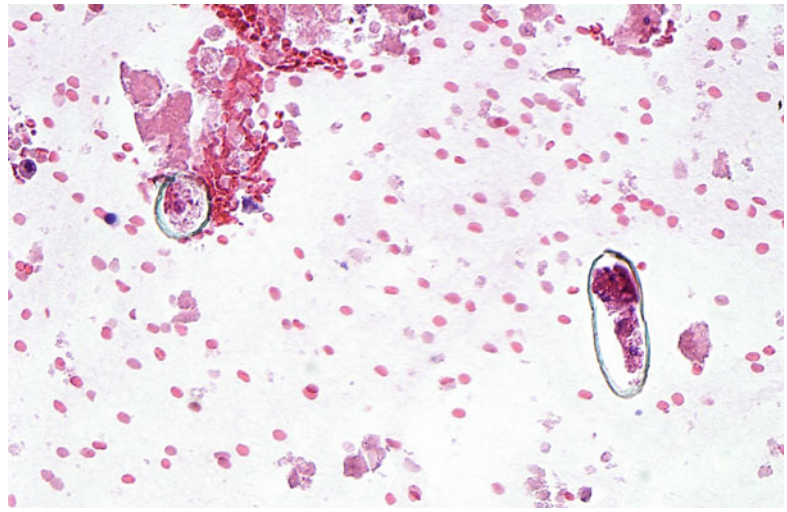

Fig. 6.1 Low magnification photomicrograph of eggs of *P. westermani* diagnosed in a fine needle aspiration biopsy, using cell block preparation. The eggs are surrounded by inflammatory cells and have thick shells (Photograph courtesy of Dr. Rodolfo Laucirica, Department of Pathology, Baylor College of Medicine, Houston, Texas)

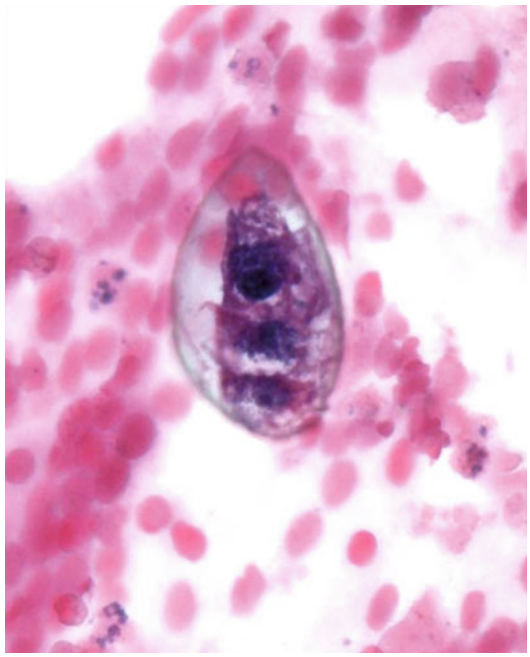

Fig. 6.2 Higher magnification of a *P. westermani* egg showing thick birefringent shell wall and a flattened operculum at one end (Photograph courtesy of Dr. Rodolfo Laucirica, Department of Pathology, Baylor College of Medicine, Houston, Texas)

The adult worms live in pairs or triplets in the respiratory tract of humans, encapsulated within a cyst. Eggs laid by the worms are either coughed up or swallowed and excreted in the feces. In the external environment, the eggs become embryonated, hatch in 2–3 weeks, releasing a ciliated miracidia, and seek the intermediate host, the snail. Within the snail, the miracidia develop into the cercariae, which invade the second intermediate host, a crustacean such as a crab or crayfish evolving into the metacercariae, the infective stage for mammalian host. Human infection occurs by eating inadequately cooked crab or crayfish. Human infection can also occur from ingesting raw or partially cooked meat of infected pigs and dogs. Once ingested, the metacercariae excyst in the duodenum, penetrate through the intestinal wall into the peritoneal cavity, and migrate through the diaphragm into the thoracic cavity and lungs, where they become encapsulated and develop into adults. Most adult worms die in 5–6 years, but some may live for up to 20 years. *P. westermani* requires encapsulation of two or three worms for insemination; therefore, when they are single, these worms migrate extensively in the thoracic cavity to find a mate, producing much inflammation. *P. pulmonalis* prevalent in Japan, Korea, and Taiwan is parthenogenetic and does not require another worm for insemination [1].

6.2.1.1 Clinical Manifestations

The clinical manifestations of paragonimiasis are nonspecific, and some patients may be asymptomatic. With heavy infection, patients develop cough, dyspnea, chest pain, fever and night

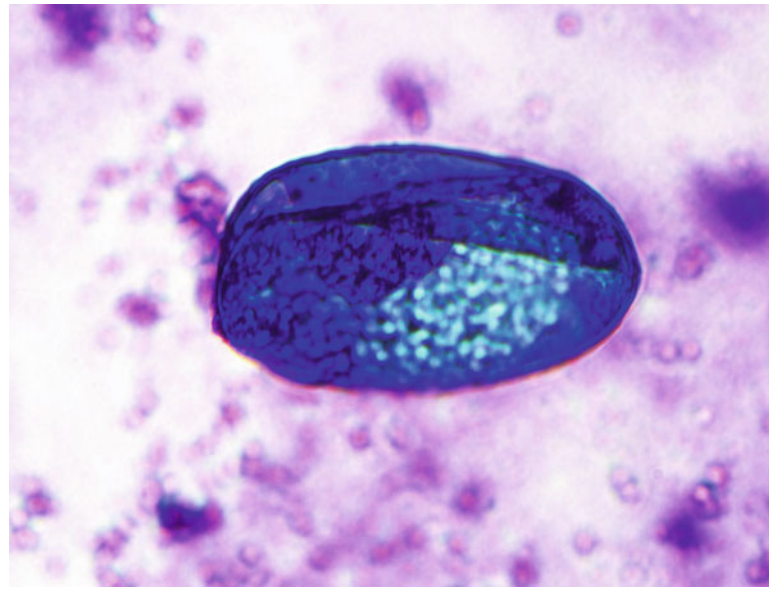

Fig. 6.3 *P. westermani* egg seen with Giemsa-stained cell block preparation of the fine needle aspirate of lung (Photograph courtesy of Dr. Rodolfo Laucirica, Department of Pathology, Baylor College of Medicine, Houston, Texas)

sweats, and hemoptysis. Bronchitis and bronchiectasis may develop over time. Peripheral eosinophilia of up to 25 % may be seen. Chest X-rays may show diffuse infiltrates, consolidation, nodules, pleural effusion, or empyema. The disease clinically resembles pulmonary tuberculosis. The active infection with nodules can be mistaken for malignancy on positron emission tomography with computed tomography scans (PET-CT) [6, 7]. There may be dissemination of infection to the brain, heart, abdominal cavity, and subcutaneous tissue, with patients presenting with unusual clinical manifestations [8].

6.2.1.2 Pathology

The pathologic changes depend on the degree of infestation, host immunity, and duration of infection. In the lungs, there is local suppurative inflammation surrounding the adult worm and eggs, with abundant plasma cells, neutrophils, eosinophils, macrophages, and foreign body giant cells. Older lesions may not show the parasites, but have a thick fibrous wall and chronic inflammatory infiltrate, and calcifications [1]. Since many worms lodge near the large bronchioles or bronchi, the inflammatory reaction is mostly around the airways, and the cysts may rupture and discharge eggs into the airways; there is often pleural inflammation, thickening, and fibrosis, associated with the invasion of the worms during migration. Fine needle aspiration (FNA) of lung lesions and pleural fluid or pleural biopsy may yield the characteristic eggs of *P. westermani*, surrounded by inflammatory cells. Figures 6.1, 6.2, and 6.3 show a cell block prepared from a lung FNA. The eggs of *P. westermani* have a flattened operculum at one end, a birefringent cell wall, and appeared to be embryonated.

6.2.1.3 Diagnosis

The suppurative inflammation and hemoptysis may be mistaken for bacterial pneumonia, pulmonary tuberculosis, and other parasitic infections, such as strongyloidiasis and dirofilariasis. Diagnosis depends on finding the characteristic ovoid, brownish, thick-shelled, and operculated eggs in the sputum, pleural fluid, and/or feces. Fine needle aspirate of the nodule may yield the eggs or parasite for a definitive diagnosis [9]. Serologic tests, particularly ELISA, are useful for diagnosis [10]. Recently, loop-mediated isothermal amplification (LAMP) assay has been used to provide a rapid and sensitive tool for detection of *P. westermani* DNA in sputum and pleural fluid [11].

6.2.2 Schistosomiasis

Schistosomiasis is infection of humans by trematodes belonging to the Schistosoma superfamily of trematodes. There are three main species pathogenic to humans, *S. mansoni*, *S. japonicum*, and *S. haematobium*, and three additional species that are less common with restricted geographic ranges. An estimated 200 million people in Africa, the Americas, and the Far East are infected with Schistosomes. Humans in these areas have been affected for many millennia; calcified ova have been found in the remains of Egyptian mummies. *S. mansoni* is the only species found in the Western Hemisphere, in Brazil, West Indies, and Puerto Rico. *S. japonicum* is found in Asia, including the Philippines and China. *S. haematobium* is found throughout most of Africa, southern Europe, and western Asia. In the USA, approximately 400,000 people are infected, primarily immigrants from other endemic countries [1, 12].

The Schistosomes are the only trematodes that live in the bloodstream of warm-blooded hosts. They differ from other trematodes in having separate sexes. The male worm resembles a rolled leaf and harbors the female in the ventral canal (the gynaecophoric canal). They require definitive and intermediate hosts to complete their life cycle [1]. Lung involvement is seen in infections with *S. mansoni*, *S. japonicum*, and *S. mekongi*.

6.2.2.1 Life Cycle

Adult worms of *S. mansoni* and *S. japonicum* live in the venous plexuses draining the rectum and colon, anterior mesenteric vessels, and portal vein, while those of *S. haematobium* live in the vesical plexus draining the urinary bladder. Since *S. haematobium* infection of the lung is not reported, we will focus on the other two *Schistosome* species in this chapter.

The eggs laid by the female worm enter the intestinal lumen from the vessels by a process of extrusion through the venule wall and pass in the feces. Once the eggs reach freshwater, they hatch, releasing a miracidium which enters a snail, and start asexual multiplication, with release of cercariae in the water. Humans are infected when the cercariae penetrate the skin, enter circulation to reach the portal vein in the liver, and mature into adult worms. The majority of adult worms live 2–4 years, but some may live longer. The adult males of the *S. mansoni* and *S. japonicum* are up to 15 mm, and females are up to 10 mm in length, and both have oral and ventral suckers. The adults of *S. japonicum* are longer and narrower. The eggs of *S. mansoni* are 114–175 um long and 45–68 um wide, yellowish brown, and have a lateral spine, with an acid-fast shell when stained with Ziehl-Neelsen stain. The eggs of *S. japonicum* are smaller measuring 55–85 um by 40–60 um and oval with a lateral spine.

6.2.2.2 Clinical Manifestations

Clinical manifestations of both *S. mansoni* and *S. japonicum* are related to the host reaction to the eggs, with formation of granulomas in the infected tissues. Heavy primary infection can cause high fever, hepatosplenomegaly, lymphadenopathy, eosinophilia, and dysentery (Katayama syndrome) and correlates with tissue migration of the worms. Chronic infection may be associated with diarrhea, weight loss, anemia, hepatosplenomegaly, portal hypertension, and ascites. Asymptomatic infections are common in most endemic areas [1, 12]. Pulmonary infection results from embolization of large number of eggs into the pulmonary vasculature with development of pulmonary hypertension, hemoptysis, cyanosis, and congestive heart failure. These complications occur in approximately 5 %, a small minority of schistosomiasis cases, and reportedly more common with *S. mansoni* infection [12]. The presence of hepatic infection and portal hypertension with portocaval collaterals is necessary for the development of pulmonary symptoms. Heavy infection of the lung may be associated with granulomatous pulmonary arteritis [13, 14].

6.2.2.3 Pathology

During active infection, granulomas at different stages of evolution may be seen in the colon, liver, and in the lungs. Early granulomas, both in the lung and in pulmonary arterioles, have many eosinophils, macrophages, and epithelioid cells,

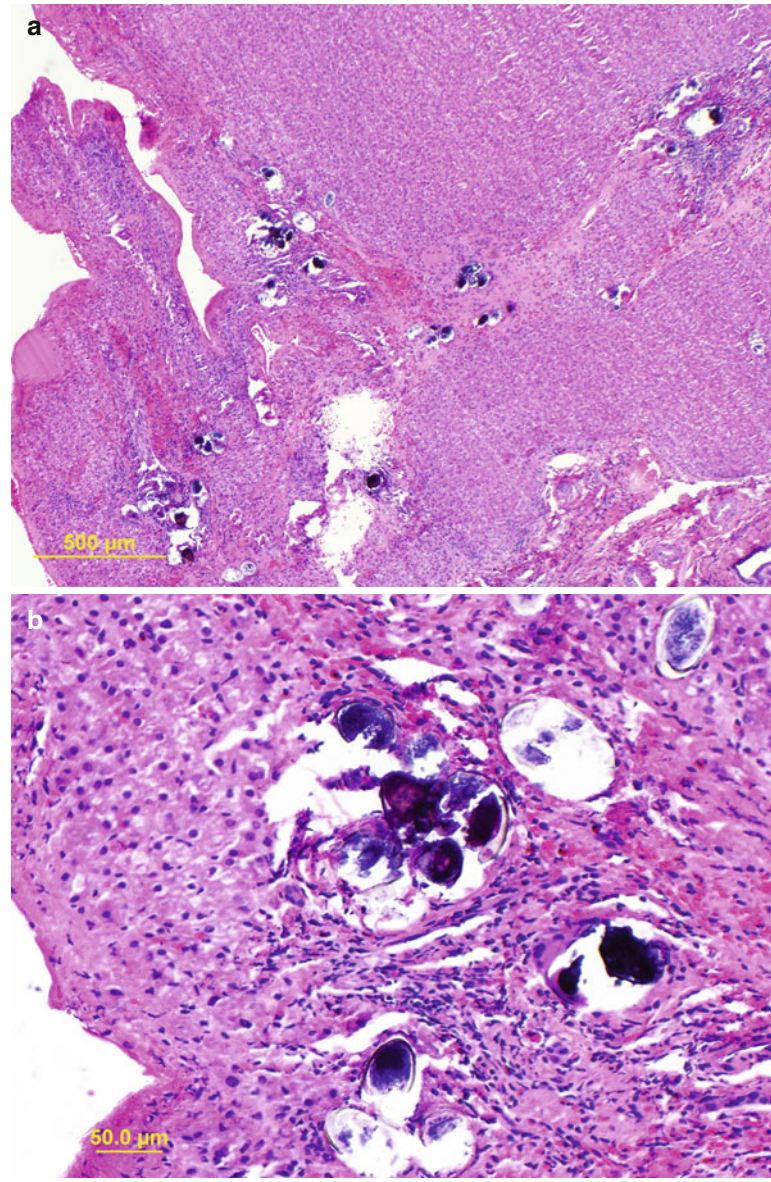

Fig. 6.4 Photomicrographs (**a**) (low magnification) and (**b**) (high magnification) of composite granulomas seen in the hepatic portal tract. The calcified eggs are surrounded by chronic inflammatory cells and fibrosis. Lung infections show similar histologic features (Photographs courtesy of Dr. Juan Olano, Department of Pathology, University of Texas Medical Branch, Galveston, Texas)

with the mature miracidium or the egg present in the center. On an average, the granulomas are 250–375 um in diameter. Pulmonary arterioles may show microthrombi, necrotizing arteriolitis, medial hypertrophy and hyalinization, and intimal thickening. Severe pulmonary hypertensive changes including plexiform lesions may develop [1]. *S. mansoni* granulomas are scattered and discrete, up to 550 um in diameter, and contain a single egg, while the *S. japonicum* granulomas form composite granulomas containing more than one or clusters of eggs in the center [1, 14–18].

Figure 6.4 shows multiple composite granulomas surrounding clusters of calcified eggs within liver portal tracts. There is fibrosis of adjacent hepatic tissue. Similar granulomas are seen in lung infections. The composite granulomas are seen in *S. haematobium* and *S. japonicum* infections.

6.2.2.4 Diagnosis

Diagnosis is based on the history of exposure and travel to endemic areas. Definitive diagnosis of schistosomiasis can be made by finding the characteristic eggs in the feces or urine, using concentration method if necessary. The eggs need to be measured to determine the species. When eggs cannot be found with the concentration method, a rectal biopsy may be required. Tissue diagnosis depends on finding the typical eggs or parasite. The eggs of *S. mansoni* and *S. japonicum* are acid-fast positive and those of *S. haematobium* are negative with modified Ziehl-Neelsen technique [1]. Serologic tests using ELISA can be diagnostic. A loop-mediated isothermal amplification (LAMP) assay may be used for detection of *S. japonicum* DNA in serum [19].

References

1. Gutierrez Y. The trematodes. In: Diagnostic pathology of parasitic infections with clinical correlations. 2nd ed. New York: Oxford University Press; 2000. p. 535–617.
2. Sinniah B. Paragonimiasis. In: Connor DH, Chandler FW, editors. Pathology of infectious diseases, vol. 2. Stamford: Appleton & Lange; 1997. p. 1527–30.
3. Meyers WM, Neafie RC. Paragonimiasis. In: Binford CH, Connors DH, editors. Pathology of tropical and extraordinary diseases. Washington, DC: Armed Forces Institute of Pathology; 1976. p. 517–23.
4. Sohn BS, Bae YJ, Cho YS, Moon HB, Kim TB. Three cases of paragonimiasis in a family. Korean J Parasitol. 2009;47:281–5.
5. 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.
6. Yoole R, Park HJ, Hyun J, Chung YA, Sohn HS, Chung SK, et al. Two cases of pulmonary paragonimiasis on FDG-PET CT imaging. Ann Nucl Med. 2006;20:311–5.
7. Osaki T, Takama T, Nakagawa M, Omaya T. Pulmonary Paragonimus westermani with false – positive fluorodeoxyglucose positron emission tomography mimicking primary lung cancer. Gen Thorac Cardiovasc Surg. 2007;55:470–2.
8. 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.
9. Zarrin-Khameh N, Citron DR, Stager CE, Laucirica R. Pulmonary paragonimiasis diagnosed by fine-needle aspiration biopsy. J Clin Microbiol. 2008;46:2137–40.
10. Zhang Z, Zhang Y, Shi Z, et al. Diagnosis of active Paragonimus westermani infections with monoclonal antibody-based antigen detection assay. Am J Trop Med Hyg. 1993;49:329–34.
11. Chen MX, Ai L, Zhang RL, Xia JJ, Wang K, Chen SH, et al. Sensitive and rapid detection of Paragonimus westermani infection in humans and animals by loop-mediated isothermal amplification (LAMP). Parasitol Res. 2011;108:1193–8.
12. von Lichtenberg F. Schistosomiasis. In: Connor DH, Chandler FW, editors. Pathology of infectious diseases. 2nd ed. Stamford: Appleton & Lange; 1997. p. 1537–51.
13. Morris W, Knauer CM. Cardiopulmonary manifestations of schistosomiasis. Semin Respir Infect. 1997;12:159–70.
14. Andrade ZA, Andrade SG. Pathogenesis of schistosomal pulmonary arteritis. Am J Trop Med Hyg. 1970;19:305–10.
15. Smith JH, Christie JD. The pathobiology of Schistosoma haematobium infection of humans. Hum Pathol. 1986;17:333–45.
16. Cheever AW, Kamel LA, Elwi AM, Mossimann JE, Danner R. Schistosoma mansoni and S. haematobium infections in Egypt II. Quantitative parasitological findings at necropsy. Am J Trop Med Hyg. 1977;26:702–16.
17. Cheever AM. A quantitative post-mortem study of schistosomiasis mansoni in man. Am J Trop Med Hyg. 1968;17:38–64.
18. Von Lichtenberg F. Consequences of infections with schistosomes. In: Rollinson D, Simpson AJG, editors. The biology of Schistosomes, from genes to latrines. London: Academic; 1987. p. 185–232.
19. Xu J, Rong R, Zhang HQ, Shi CJ, Zhu XQ, Xia CM. Sensitive and rapid detection of Schistosoma japonicum DNA by loop-mediated isothermal amplification (LAMP). Int J Parasitol. 2010;40:327–31.