The Current Status of Parasitic Diseases in Japan

Fukumi NAKAMURA-UCHIYAMA, Kenji HIROMATSU, Kenji ISHIWATA,
Yukiko SAKAMOTO and Yukifumi NAWA

Abstract

In Japan parasitic diseases have been considered to be successfully controlled in the last 30 years. However, some parasitic diseases, such as food-borne zoonoses and/or larva migrans, are emerging and/or re-emerging in Japan. Furthermore, imported parasitic diseases like malaria are also gradually increasing. Unfortunately accurate numbers of parasitic diseases other than echinococcosis, malaria, amebiasis, giardiasis, or cryptosporidiosis are obscure in Japan because of the lack of a legal registration system. Since symptoms and diagnostic imaging patterns of parasitic diseases are non-specific and have similarities with other infectious diseases or cancer, parasitic diseases are sometimes overlooked or left misdiagnosed. In this review, the current status of parasitic diseases in Japan is briefly summarized based on the analysis of the accumulated cases seen in our department. We also outline the clinical features, differential diagnosis and treatment of representative parasitic diseases for the better understanding and management of the parasitic diseases in Japan.

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Key words: food-borne zoonoses, emerging/re-emerging diseases, larva migrans, imported parasitoses, differential diagnosis, orphan drugs

Have Parasitic Diseases Really Been Eradicated in Japan?

In the immediate post-World War II period, Japan was regarded as “Paradise of Parasites” because of spreading of soil-transmitted parasitoses such as ascariasis, trichuriasis and hookworm disease. After a nationwide campaign, mass screening, treatment and prevention of parasitic diseases under the Parasite Control Law, the egg detection rates of *Ascaris* and hookworm in stool examination decreased from 59.6% and 4.5% in 1950 to <0.1% and 0% in 1980s, respec-

tively. Some other helminthes that cause serious diseases such as schistosomiasis, domestic malaria and lymphatic filaria were also successfully eradicated by the middle of 1980s (1). Such successful eradication/control of parasitic diseases resulted in the termination of the Parasite Control Law in 1994 (1). Although the new Infectious Diseases Control Law was applied in 1999, only five parasitic diseases, four protozoan diseases (amebiasis, cryptosporidiosis, giardiasis and malaria) and one helminthiasis, echinococcosis are assigned as the notifiable parasitoses. Now not only the public but also medical professionals tend to consider parasitoses as a disease of the past. However, the number of patients having parasitic diseases referred to and diagnosed in our laboratory has been increasing every year (Fig. 1A) (2, 3). In agreement with our experience, Arizono has recently reported that more than 1,000 case reports of parasitic diseases were found in the database, Igaku-Chuo-Zasshi (Japan Centra Revuo Medicina) between 1995 and 1999 (4). In this review, we summarize the current status of parasitic diseases in Japan together with clinical features, diagnosis and treatment of clinically important and frequently experienced parasitoses.

Current Status of Parasitic Diseases in Japan

It is difficult to grasp the concrete number of parasitic diseases, especially those of helminthiasis in Japan due to the changeover of legislation for infectious diseases. We implemented the immuno-serological tests for diagnosis of parasitic diseases in 1986. Multiple-dot ELISA method (Fig. 1B), which was introduced in 1991 for the primary screening to detect parasite-specific antibodies, has enabled us to respond faster than before to the attending physicians. The number of samples referred to our laboratory has drastically increased since 1995, and reached over 400 new samples and 200 samples for follow-up per year in 2000 and 2001. Among those consultations, about 40% of patients were diagnosed as having parasitoses (Fig. 1A). The incidence of each parasitic disease referred to and diagnosed in our laboratory is summarized in Table 1.

The majority of cases diagnosed in our laboratory are

Multiple-dot ELISA Test for Parasitic Diseases

Figure 1. Number of cases referred to our laboratory (A) and multiple-dot ELISA for parasitic diseases (B). Recently about 40% of the cases were diagnosed as having parasitoses (A). The patient's serum and pleural effusion showed a high titer of IgG against *Paragonimus westermani* with some cross-reactions to other trematode antigens (B). Pw: *P. westermani*, Pm: *P. miyazakii*, Fh: *Fasciola hepatica*, Cs: *Clonorchis sinensis*, Se: *Spirometra erinaceieuropaei*, Cc: *Cysticercus cellulosae*, Di: *Dirofilaria immitis*, Tc: *Toxocara canis*, As: *Ascaris suum*, Asx: *Anisakis simplex*, Gd: *Gnathostoma doloresi*, Sr: *Strongyloides ratti*. (b: Reprinted from Clinics in Chest Medicine, 23, Nakamura-Uchiyama F et al, "Paragonimiasis: A Japanese perspective", 409-420, Copyright 2002, with permission from Elsevier Science).

Table 1. Incidence of Various Parasitic Diseases Diagnosed in Our Laboratory during 1999-2001

Protozoa	Giardiasis	1
	Entoamebiasis	3
	Malaria	5
	Paragonimiasis	99
	Fascioliasis	10
Trematoda	Schistosomiasis	4
	Clonorchiasis	1
	Metagonimiasis	1
	Diphyllobothriasis	3
Cestoda	Diplogonoporiasis	2
	Taeniasis saginata	2
	Sparganosis	7
	Cysticercosis	5
	Echinococcosis	2
Nematoda	Ascariasis lumbricoides	8
	Strongyloidiasis	16
	Hookworm disease (human origin)	3
	Trichuriasis	3
	Enterobiasis	2
	Thelaziasis	1
	Lymphatic filariasis	2
	Angiostrongyliasis	7
	A. suum-/ T. canis-VLM	170
	Anisakiasis	19
Others	Gnathostomiasis	42
	Spiruroid larva migrans	3
	Hookworm disease (animal origin)	9
	Dirofilariasis	10
	Tick bite	5
	Myiasis	3
	Scabies	1

Bold-face: Food-borne zoonoses, : Larva migrans.

area of this disease (5). Meanwhile *A. suum*-VLM is an emerging disease in this area probably due to recent concentration of cattle, pig and poultry farms in southern Kyushu (6). Although imported parasitic diseases are rather rare in our data, we encountered some patients assumed to be infected during traveling overseas, such as giardiasis, malaria, cysticercosis and creeping eruption due to percutaneous infection with larval dog hookworm. It should also be pointed out that classical soil-transmitted parasites are still present to cause diseases in Japan.

In contrast to our data, protozoan diseases accounted for about 45% of total case reports of parasitoses from an analysis of the Japanese database, Igaku-Chuo-Zasshi, during 1995 and 1999 (Table 2) (4). All patients with malaria were infected during travel in tropical and subtropical countries. However, patients with other protozoan diseases seemed to be infected in Japan. In fact, amebiasis is currently epidemic in male homosexuals and institutionalized people; few cases are imported (7). Two water-borne outbreaks of cryptospori-

food-borne helminthiasis, especially of zoonotic nature and/or larva migrans as indicated in Table 1. Among them, *Ascaris suum*-VLM (visceral larva migrans) and paragonimiasis are the two foremost parasitic diseases. The majority of these cases were from Kyushu (2). Paragonimiasis is a re-emerging disease in Kyushu a previously heavily endemic

Table 2. Numbers of Parasitic Diseases Case Reports in Japan Found in Japana Centra Revuo Medicina Database (1995–1999) (4)

Protozoa		Trematoda		Cestoidea		Nematoda	
<i>Entamoeba</i>	167	<i>Schistosoma</i>	90	<i>Diphyllobothrium</i>	62	<i>Anisakis</i>	99
<i>Pneumocystis</i>	154	<i>Paragonimus</i>	49	<i>Sparganum</i>	31	<i>Dirofilaria</i>	54
<i>Toxoplasma</i>	102	<i>Clonorchis</i>	16	<i>Taenia solium</i>	27	<i>Ascaris</i>	52
<i>Plasmodium</i>	94	<i>Fasciola</i>	13	<i>Echinococcus</i>	21	<i>Strongyloides</i>	48
<i>Acanthamoeba</i>	35			<i>Taenia saginata</i>	6	<i>Toxocara</i>	27
<i>Giardia</i>	14			<i>Diplogonoporus</i>	5	<i>Gnathostoma</i>	23
<i>Leishmania</i>	13					<i>Spirurina</i>	19
<i>Amebic encephalitis</i>	10					<i>Ascaris suum</i>	16
<i>Isospora</i>	6					<i>Hookworms</i>	11
<i>Trichomonas</i>	6					<i>Enterobius</i>	10
<i>Cryptosporidium</i>	5					<i>Angiostrongylus</i>	8
						<i>Trichuris</i>	8
						<i>Trichinella</i>	5
Total	606		155		152		393

diosis are still fresh in our mind (8, 9). *Cryptosporidium* oocysts and *Giardia* cysts were detected in raw and even in filtrated water in Japan (10). Among the helminthiasis in this database, most are food-borne zoonoses and/or larva migrans, as seen in our data. It should be emphasized again that classical parasites such as *Ascaris* and hookworm continue to exist at a low level in Japan.

One of the notable findings from the analyses of our data and the literature survey from the databases is that the majority of helminthiasis is food-borne zoonoses. This trend may be reflecting preferential food-habits of the Japanese consuming raw materials as “Sushi” or “Sashimi” with “Soy sauce”. For example anisakiasis and diphyllbothriasis are highly prevalent in Japan. Creeping eruption and acute abdomen due to *Spirurina* Type X larvae infection after eating small scintillant squids has recently emerged (11). In addition to marine fishes, crustaceans and shellfishes, freshwater fishes and wild animal meat are also served as “Sushi” or “Sashimi”. In this aspect, it is interesting that more than 70% of the recent paragonimiasis cases were coming from eating raw wild boar meat, though freshwater crabs have been considered the important source of *Paragonimus* infection (5). The major source of *Gnathostoma* sp. infection is freshwater fishes such as brook trout, imported loach or snakehead fish (12). In addition, snakes are also important reservoir hosts of *G. doloresi* as well as *Spirometra erinaceieuropaei* (13, 14). Some gnathostomiasis and sparganosis patients were infected by eating snakes as “Sashimi”, since they believed in tonic effects of raw snake meat (15). Chicken/cattle liver is an important source for infection with *A. suum*- and *Toxocara canis*-VLM in middle-aged men (16). Related to this, some Japanese ingest actively raw materials as medicine. For example, freshwater crab juice given for asthma treatment caused paragonimiasis, and ingestion of raw slugs for treatment of lumbago or mineral supplement caused

angiostrongyliasis (17–19).

The increase in number of imported parasitoses such as malaria and giardiasis is directly related to the increasing number of overseas travelers. However foreign foods contaminated by parasites are also imported in Japan. Recently, we encountered paragonimiasis cases among foreigners living in Japan. The sources of their infection were imported Chinese crabs served in a Chinese restaurant or bottled drunken (liquor-soaked) crabs brought out from China as a souvenir (20). Food-borne outbreaks associated with parasites have been reported in the world (21). We may be seeing more patients with food-borne parasitic diseases in Japan with the increment of food trading and the popularization of ethnic dishes.

In summary, parasitic diseases currently seen in Japan are characterized as follows:

- 1) Food-borne diseases and/or larva migrans related to Japanese food-habits: anisakiasis, diphyllbothriasis, gnathostomiasis, sparganosis and other diseases.
- 2) Emerging/Re-emerging diseases: cryptosporidiosis, echinococcosis, spiruroid larva migrans, *A. suum*-VLM, paragonimiasis and other diseases.
- 3) Gradually increasing imported parasitoses: malaria, giardiasis and cysticercosis.
- 4) Persistent occurrence of classical soil-transmitted parasitoses: ascariasis lumbricoides, hookworm and other diseases.

Clinical Features of Parasitoses: Symptoms, Diagnosis and Treatment

In the analysis of the current trends of parasitic diseases in Japan, we have noticed that a few malaria patients are still dying almost every year because of delayed and/or inadequate diagnosis (22). Furthermore, parasitic zoonoses are

Table 3. Clinical Symptoms and Possible Parasitoses, Diagnosis and Treatment

1. Fever

Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Malaria		Travel abroad Anemia Kidney failure/CNS involvement	Blood smear	Vary*

2. Abdominal symptom—Diarrhea

Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Entamoebiasis	Mucous and bloody stool Loose passage/Watery stool	STD, Immunodeficiency (HIV)	Stool examination (trophozoites)	MNZ (1,000 mg/day for 10 days)
Giardiasis		Travel abroad, Water supply Ingestion of imported fruits	Stool examination (cysts)	MNZ (750 mg/day for 7–10 days)
Cryptosporidiosis		Immunodeficiency (HIV)	Stool examination (oocysts)	Symptomatic treatment
Strongyloidiasis		Immunodeficiency (ATL, HIV) Eosinophilia Origin/Habitat (Okinawa)	Stool examination (larvae) Immunodiagnosis	TBZ (30–50 mg/kg/day for 3 days) IVM (A dose of 200 µg/kg at once)
	Loose passage/Watery/Fatty stool			
Metagonimiasis		Ingestion of freshwater fish “Ayu”		PZQ (50 mg/kg/day for 1–2 days)
Ascariasis				PP
Hookworm infection		Ingestion of organic vegetables	Stool examination (eggs) ^b	(A single dose of 5–10 mg/kg)
Tapeworm		Ingestion of marine fish, beef or pork		PZQ ^c (10 mg/kg at one time) +Laxative

3. Abdominal symptom—Acute abdomen

Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Anisakiasis (Stomach)			Endoscopically	Pick out
Anisakiasis (Small intestine)		Ingestion of marine fish and squid		
	X-p; Ileus (Eosinophilia)		Immunodiagnosis	Symptomatic treatment
Spiruroid larva migrans		Ingestion of small scintillated squids		
Ascariasis (ectopic migration)		Ingestion of organic vegetables	Endoscopically	Pick out

4. Liver or biliary tract lesions

Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Amebiasis	US, CT, MR: liver abscess with clear irregular margin	STD Immunodeficiency (HIV) Not always including the intestinal lesion	Immunodiagnosis Detection of trophozoites in abscess drainage	MNZ (1,500 mg/day for 10 days)
Fascioliasis	US, CT, MR: SOL with irregular margin (>3–4 cm) Eosinophilia	Ingestion of herb or cattle liver Cattle farmer	Immunodiagnosis (Detection of eggs)	TCBZ (A dose of 10 mg/kg at once)

(Table 3. continued)

<i>A. suum</i>-/<i>T. canis</i>-VLM	US: Beads sign CT, MR: Small multiple nodule (0.5–1.0 cm) Eosinophilia	Ingestion of chicken/cattle liver or organic vegetables History of dog parenting Lung/Ocular/CNS involvements		ABZ (10–15 mg/kg/day for 4–8 weeks)
Echinococcosis	US, CT, MR: Poly cystic SOL with irregular margin Calcification	Origin/Habitat <i>E. multilocularis</i> : Hokkaido <i>E. granulosus</i> : Manchuria CNS (Lung) involvements	Immunodiagnosis	Surgical resection ABZ (Repeated administration of 10–15 mg/kg/day for 4 weeks)
Paragonimiasis	Hepatic capsulitis, Calcification (Eosinophilia)	Ingestion of freshwater crabs or wild bore Lung/Skin/CNS involvements		PZQ (75 mg/kg/day for 3 days)
5. Respiratory symptoms or lesions				
Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Paragonimiasis	X-p, CT: Vary (Pleurisy or parenchymal lesions) Eosinophilia	Ingestion of freshwater crabs or wild bore Skin/CNS involvements	Immunodiagnosis (Egg detection)	PZQ (75 mg/kg/day for 3 days)
Löffler Syndrome Ascariasis Hookworm disease Strongyloidiasis	X-p, CT: Diffuse mottled infiltration (resemble military tuberculosis or viral pneumonia) Eosinophilia	Ingestion of organic vegetables Origin/Habitat (Okinawa) Immunodeficiency (HIV, ATL)	Detection of larvae in sputum Immunodiagnosis	ABZ (10–15 mg/kg/day for 3 days) TBZ (30–50 mg/kg/day for 3 days) IVM (A single dose of 200 µg/kg)
<i>A. suum</i>-/<i>T. canis</i>-VLM	X-p, CT: Diffuse mottled infiltration Eosinophilia	Ingestion of chicken/cattle liver or organic vegetables History of dog parenting Liver/Ocular/CNS involvements	Immunodiagnosis ^d	ABZ (10–15 mg/kg/day for 4–8 weeks)
Dirofilariasis	X-p, CT: Single nodular lesion (coin lesion) (Eosinophilia)			DEC (6 mg/kg/day for 2–4 weeks)
6. Skin lesions				
Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Dog hookworm infection	Eosinophilia (–) Creeping eruption	Travel abroad (Resort beach)	Biopsy	Surgical resection ABZ (10–15 mg/kg/day for 3 days) IVM (A dose of 200 µg/kg at once)
Spiruroid larva migrans		Ingestion of small scintillated squids		Surgical resection
Gnathostomiasis		Ingestion of freshwater fish or snakes	Immunodiagnosis	Surgical resection ABZ (10–15 mg/kg/day for 3 days)
Sparganosis	Mobile nodular lesion	Ingestion of chicken, snake or frog	Biopsy	Surgical resection ^e PZQ (75 mg/kg/day for 3 days)
Paragonimiasis		Ingestion of freshwater crabs or wild bore		PZQ (75 mg/kg/day for 3 days)

(Table 3. continued)

7. CNS symptoms

Possible parasitoses	Findings	Remarks	Diagnosis	Treatment
Angiostrongyliasis	Eosinophilia (blood, CSF)	Ingestion of snails or slugs Ingestion of vegetables contaminated by infectious molluscan		Symptomatic treatment
	Meningitis			
Paragonimiasis	X-p, CT: Soap bubble sign (chronic) Calcification appeared solitary round cystic, oval cystic Eosinophilia (blood, CSF)	Ingestion of freshwater crabs or wild bore		PZQ (75 mg/kg/day for 3 days)
			Immunodiagnosis	
Cysticercosis	CT, MRI: vary depending on the stage of disease (cyst with/without edema, nodule, calcification)	Ingestion of food or water contaminated by <i>T. solium</i> eggs Ingestion of uncooked pork Travel abroad Adult worm in intestine		ABZ (10 mg/kg/day for 4 weeks) PZQ ^f (50 mg/kg/day for 2 weeks) +Steroid
Echinococcosis	Encephalitis	Origin/Habitat (Hokkaido) Liver (/Lung) involvement		Surgical resection
Amebiasis	CT, MRI: single or multiple enhancing lesions	STD, Immunodeficiency (HIV) Liver involvement	Immunodiagnosis DNA diagnosis	MNZ (1,500 mg/day for 10 days)
Malaria	Sudden onset	Travel abroad Anemia Kidney failure	Blood smear	Quinine etc
Toxoplasmosis	CT, MRI: Multiple nodular lesions (ring enhancement with thin and smooth wall)	Immunodeficiency (HIV) Ingestion of uncooked chicken/pork History of cat parenting	Immunodiagnosis DNA diagnosis	Pyrimethamin Sulfamonomethoxine
A. suum-/T. canis-VLM	Myelitis	Ingestion of chicken/cattle liver or organic vegetables History of dog parenting Lung/Liver involvement	Immunodiagnosis	ABZ (10–15 mg/kg/day for 4–8 weeks)

^fDepending on the patient's state, drug resistance malaria. ^hIn case of tapeworm infection, most patients have an episode of release of worm segments (proglottids). ⁱIn case of *Taenia solium* (pork tapeworm) infection, elimination by "Gastrophilin" is better for preventing autoinfection. ^jIn case of inactive dirofilariasis, immunodiagnosis is not always useful. ^kIt is important to excise the entire parasites. ^lWhen the adult worm exists in small intestine, worm expulsion by "Gastrophilin" should be prior to PZQ treatment for preventing the autoinfection. MNZ: metronidazole, TBZ: thiabendazole, IVM: ivermectin, PZQ: praziquantel, PP: pyrantel pamoate, TCBZ: triclabendazole, ABZ: albendazole, DEC: diethylcarbamazine.

often misdiagnosed as malignant diseases resulting in excessive diagnostic tests or unnecessary surgery (2). These facts remind of us the vital importance of the correct diagnosis for parasitic diseases. Therefore we outlined the clinical features and tips for diagnosis and treatment of representative parasitic diseases in Japan to facilitate a better understanding of the parasitic diseases for correct diagnosis and more appropriate treatments (Table 3).

Fever

When patients with FUO (fever of unknown origin) have a history of traveling abroad especially to tropical developing countries, we have to think of the possibility of malaria, dengue fever or typhoid fever (23). Particularly *Plasmodium*

falciparum infection called malignant malaria progresses rapidly and shows a high mortality rate within a week or so. Since red blood cells infected with *P. falciparum* tend to cause obstruction in small vessels of brain and kidney, the patient show acute cerebral symptoms or renal failure (22). It should be noted that the fever pattern is not always typical even in the patients infected with *P. vivax* or *P. malariae*. It is important for the diagnosis of malaria to detect the malaria parasite in blood smear by Giemsa staining (pH 7.2) (Fig. 2). When fluorescence microscopy is available, rapid diagnosis of malaria can be obtained by acridine orange staining (24). Quinine and sulfadoxine/pyrimethamine are the commercially available anti-malarial drugs in Japan. However, the first choice of drugs depends on the patient's state. A combi-

Figure 2. Direct demonstration of *P. falciparum* in blood smear (arrowhead, Giemsa staining, pH 7.2).

nation of drugs having different pharmacological actions or having targeting the different of malaria parasite stages is necessary for complete cure. In addition drug-resistant malaria parasite are gradually increasing in almost all endemic areas (22). Various anti-malarial drugs are available from the Japan Health Science Foundation Orphan Drug Study Group under approval of Ministry of Health, Labor and Welfare (Table 4). Detailed information such as dosage and administration or pharmacological actions of drugs are available in the Study Group website (<http://www.ims.u-tokyo.ac.jp/didai/orphan/index.html>).

Abdominal symptom: diarrhea

Some parasitic infections cause diarrhea as seen in Table 3.2. Mucous and bloody stool is characteristic of intestinal entoamebiasis. Massive infection with *Metagonimus* or giardiasis, cryptosporidiosis and strongyloidiasis in immunocompromised hosts may present severe diarrhea leading to protein-losing enteropathy (23, 25). Therefore when a patient with severe diarrhea due to infection with opportunistic parasites is found, it is important to search for the underlying disease leading immunodeficiency. Definitive diagnosis can be obtained by direct demonstration of parasite trophozoites, cysts, oocysts, larva or eggs in feces.

Thiabendazole (TBZ) was the only approved therapeutic drug for strongyloidiasis in Japan. This drug usually requires at least a 3-day dosage but has a high frequency of side effects which interfere with compliance (26, 27). Instead of TBZ, ivermectin (IVM), a newly developed anti-*Strongyloides* drug, is now commercially available. This drug is significantly effective with a single dose of 200 µg/kg without severe side effects (28). Standard treatment protocol for cryptosporidiosis in patients with HIV has not been established yet. Although there are a few reports suggesting that azithromycin, clarithromycin or roxithromycin were effective for cryptosporidiosis in patients with HIV, the efficacy of these drugs are still controversial and reports of ineffective cases exist. Thus, the development of effective anti-

Table 4. Orphan Drug List Available from the Japan Health Science Foundation Orphan Drug Study Group Under Approval of Ministry of Health, Labor and Welfare*

Drug	Formula	Indication
Chloroquine sulfate	Tablet	Malaria
Atovaquone/Proguanil	Tablet	Malaria
Artesunate	Tablet/Suppository	Malaria
Quinine glyconate	Injectable	Malaria
Primaquine phosphate	Tablet	Malaria
Metronidazole	Injectable	Entoamebiasis
Diloxanide furoate	Tablet	Entoamebiasis
Sodium stibogluconate	Injectable	Leishmaniasis
Ivermectin	Tablet	Onchocerciasis (Strongyloidiasis) Scabies
Triclabendazole	Tablet	Fascioliasis Paragonimiasis
Ribavirin	Tablet	Viral Hemorrhagic Fever
Suramin	Injectable	Trypanosomiasis
Melasoprol	Injectable	Trypanosomiasis
Eflornithine	Injectable	Trypanosomiasis

*For dosage and administration refer to Study Group website (<http://www.ims.u-tokyo.ac.jp/didai/orphan/index.html>).

Cryptosporidium drugs is urgently needed (29). In case of severe intestinal entoamebiasis with peritonitis, metronidazole (MNZ) div is available from the Orphan Drug Study Group.

Abdominal symptom: acute abdomen

Some parasitic diseases cause acute abdomen (Table 3.3). Among them, gastric anisakiasis is probably the most prevalent one. Typical anisakiasis develops 5–6 hours after the ingestion of marine fish, mackerels or squids. Principle of diagnosis and treatment of this disease is to pick out the worms endoscopically (30). In the case of intestinal anisakiasis, patients may present ileus. Recently, *Spirurina* Type X larva infection has been emerged and patients develop ileus and/or creeping eruption (11). The major source of infection with *Spirurina* Type X larva is small schintillant squids. Special anthelmintic drugs are not found for *Anisakis* or *Spirurina*, and spontaneous cure of these diseases is often observed by conservative treatment alone. Therefore when the patient with acute abdomen is strongly suspected of having these parasitic infections based on the eating history, excessive examination or unnecessary surgery should be avoided.

As an extremely rare case, colonic ileuses due to nodular lesions caused by *Gnathostoma* migration was reported previously (31). Acute abdomen due to ectopic migration to the bile duct or pancreatic duct of *Ascaris lumbricoides* are often reported, suggesting that this classic parasite still exists sporadically in Japan (4). Massive infections with *A. lumbricoides*

Figure 3. Liver lesions in various parasitic diseases. These findings are similar to those of hepatocellular carcinoma, cholangiocellular carcinoma or metastatic tumor; Abdominal CT of fascioliasis (A), *A. suum*-VLM (B), abdominal echo and CT of echinococcosis granulosa (C, D) and CT of entoamebiasis (E). *E. histolytica* trophozoite in liver abscess drainage (F).

coides cause bolus obstruction in the intestine (32).

Abdominal symptom: lesions in the liver or biliary tract

The liver and biliary tract are involved in some parasitic diseases (Table 3.4). Bile duct is the target of *Fasciola* and *Clonorchis*. *Ascaris*, *Toxocara* and hookworm larvae are carried into liver via portal blood stream. Notably these liver-affecting parasitic diseases are often manifested as space

occupying lesions and misdiagnosed as malignant diseases such as hepatocellular carcinoma, cholangiocellular carcinoma or metastatic tumor because of similarity on diagnostic imaging (Fig. 3). Fascioliasis and *A. suum*-/*T. canis*-VLM are frequently associated with peripheral blood eosinophilia. Thus clinicians should be aware of the possibility of parasitic diseases especially when patients with liver lesions reveal eosinophilia. Immunodiagnostic methods such as multiple-dot ELISA to detect antibody against parasites are particu-

lary valuable for the rapid screening to diagnose these diseases (33).

Fascioliasis cases in Japan have been found mostly around small-scale cattle farms. Over 100 cases were found by 1992 (34) and more cases have been added year after year (35, 36). Praziquantel (PZQ) is the only available drug for chemotherapy for fascioliasis. However, the efficacy of PZQ for fascioliasis remains controversial, in spite of its broad trematocidal spectrum (36). Recently, triclabendazole (TCBZ) is recommended by WHO as an essential drug against fascioliasis (37), and TCBZ tablets for human use have become available since April 2001 through the Orphan Drug Study Group (38).

Larva migrans due to infection with *T. canis* is famous for its preferential ocular involvement in children in Western countries. The major route of infection is thought to be a direct oral infection from pet puppies. However in Japan the number of adult patients is far greater than that of children (16). Similarly the majority of *A. suum*-VLM patients in Japan are middle-aged males. In Japan, both *Toxocara*-VLM and *A. suum*-VLM are thought to occur mainly by ingesting chicken/cattle liver or organic vegetables contaminated by parasite eggs (16). Because of the nature of migration of *A. suum* and *T. canis* larvae, the liver (Fig. 3B) and lungs (Fig. 4E) are the commonest sites affected in *A. suum*-/*T. canis*-VLM (39, 40). It should be noted that *A. suum* as well as *T. canis* migrate occasionally into the CNS (41). Standard protocol for chemotherapy on VLM has not yet determined. Albendazole (ABZ) is assumed to be effective for VLM, but needs 4–8 weeks of continuous administration and has side effects causing transient liver dysfunction.

Echinococcosis is a slowly progressive and chronic disease caused by infection with *Echinococcus multilocularis* or *E. granulosus*. The former infection to humans is often lethal because of its metastatic nature and is emerging in Hokkaido (42). Whereas the latter infection is benign and only a few cases were sporadically found in Japan (Fig. 3C, D) (43). Though the diagnosis can be achieved by the serological test and findings on ultrasonography, habitat profile of the patient is the most important information to suspect of echinococcosis (44). Surgical resection is the only way to treat echinococcosis. Benzimidazole derivatives such as ABZ or mebendazole (MBZ) seem to be effective, however it is difficult to obtain complete cure (44). Thus early diagnosis and subsequent surgical treatment is essential to cure this disease.

Entamoebiasis is emerging in Japan, especially as STD. Though the parasite primarily causes colitis (amebic dysentery), abscess in the liver (Fig. 3E) is not rare. Amebic liver abscess is diagnosed directly by a demonstration of trophozoites in the drainage fluid from the abscess (Fig. 3F) or indirectly by immunodiagnostic methods (33). Intestinal involvement is not always evident. MNZ is a drug of choice. In severe cases, MNZ div is available from the Orphan Drug Study Group.

Although *Paragonimus* is a lung-seeking trematode, its

juvenile worms migrate from the small intestine to the lung through several tissue/organs including peritoneal organs. Thus, the liver, peritoneal cavity, abdominal skin, or urogenital organs are occasionally affected (45). Most of these patients having ectopic infection are asymptomatic and found by chance in a post-operative histopathological examination under the diagnosis of non-parasitic disease (46, 47). In patients with active ectopic paragonimiasis, immunodiagnosis is useful and, regardless of the site affected, patients can be cured by PZQ. Recently we encountered a case of active hepatic capsulitis due to infection with *P. westermani* (48).

Schistosomiasis japonicum and clonorchiasis are well known causes of liver cirrhosis, which sometimes becomes liver cancer. Once liver cirrhosis has developed, anthelmintic treatment is ineffective. Therefore, early diagnosis and treatment is essential for these diseases. No new cases of schistosomiasis and few cases of clonorchiasis have been reported in Japan. However, it should be noted that these diseases still exist all over the world especially in Asian countries and a few imported cases have been reported.

Respiratory symptoms or lesions

Possible parasitic diseases presenting respiratory symptoms or lesions are summarized in Table 3.5. Paragonimiasis patients often present respiratory symptoms with eosinophilia. Since radio-imaging appearances of paragonimiasis are variable, it is difficult to distinguish this disease from lung cancer, tuberculosis, or fungal infections (Fig. 4A–D) (45). It should be noted that despite remarkable chest radiological findings in the lung parenchyma and/or pleural cavity, about 20% of paragonimiasis patients are asymptomatic; the presence of lung lesion happens to be discovered by chest X-ray examination at a regular health screening (45). Recently, we demonstrated that pleurisy with a high degree of eosinophilia (>20%) is characteristic of the early stage of paragonimiasis, whereas parenchymatous lesions with relatively low eosinophilia (~10%) were characteristic of the late stage (49). Immunodiagnosis is quite useful for the diagnosis of paragonimiasis because egg detection rates in sputum or bronchoscopic aspirates were less than 50% (45). In the very early stage of this disease, detection of parasite-specific IgM rather than IgG antibody is useful and should be considered (49). Pulmonary paragonimiasis can be treated by oral administration of PZQ (75 mg/kg/day for 3 days) with an almost 100% cure rate (45).

A. lumbricoides, hookworm and *Strongyloides* infection cause Löffler's syndrome, an acute eosinophilic pneumonia with tracheitis. Pathogenesis of this syndrome is thought to be due to hypersensitive reaction to migrating larvae. Severe symptoms such as cough, wheezing and dyspnea last for 7–10 days and usually resolve spontaneously when larvae migrate out of the lungs (50). When the disease status is worsening rapidly or patients show the signs of septicemia and/or CNS involvement, we should consider the possibility of disseminated strongyloidiasis in which drastic increase in

Figure 4. Lung lesions in various parasitic diseases. Variance of paragonimiasis on chest radiography; nodular (A), mixed pattern (B), pleural effusion and pneumothrax (C, D). Chest CT findings of *A. suum*-VLM (E) and *dirofilaria* (F). (A–D: Reprinted from Clinics in Chest Medicine, 23, Nakamura-Uchiyama F et al, “Paragonimiasis: A Japanese perspective”, 409–420, Copyright 2002, with permission from Elsevier Science).

number of *Strongyloides* larvae occurs from autoinfection associated with the invasion of intestinal bacteria. Larvae can be seen in the sputum smear of disseminated strongyloidiasis patients. Such a condition is frequently seen in patients with immunodeficiency (51). Whenever we see disseminated strongyloidiasis patients in Japan, we must consider the possibility of ATL/HTLV-1 infection.

In cases of *A. suum*-*T. canis*-VLM presented with respi-

ratory symptoms, lesions may be seen not only in the lungs (Fig. 4E) but also in the liver, eyes and CNS. As the nature of ascarid larvae, they migrate first into the liver via portal blood flow, then migrate into lungs via blood stream, and then disseminated by systemic circulation. Thus it is important to perform systematic examinations of all possible organs affected in patients with *A. suum*-*T. canis*-VLM (16). Treatment for VLM has been described in the liver lesion

Figure 5. Skin lesions. Creeping eruption due to infection with *Gnathostoma* (A) and larval dog hookworm (C). *Gnathostoma* exists in deep site (B, $\times 25$) whereas larval hookworm is in the epidermis (D, $\times 200$).

section above.

Dirofilaria immitis is known as a zoonotic parasite causing pulmonary dirofilariasis in humans. Typical dirofilariasis is asymptomatic and characteristic of coin lesion in the chest radiography (Fig. 4F). Therefore, patients with pulmonary dirofilariasis have been often misdiagnosed as malignancy and received unnecessary examinations and/or surgical treatments. We have reported three cases of pulmonary diro-

filariasis successfully diagnosed with serological tests (52). Diethylcarbamazine (DEC) is a recommended drug for pulmonary dirofilariasis, though it is ineffective for chronic cases.

As extremely rare cases, various parasites such as *Gnathostoma* (53), *Spirometra* (54, 55) and *Anisakis* (56) unexpectedly migrate into the pleural cavity causing pleuropulmonary lesions. All of these cases were serologically

Figure 6. CNS lesions in various parasitic diseases. Various lesions of neurocysticercosis depending on the stage of the diseases (A, B). MRI findings of spinal lesion of *A. suum*-VLM (C). (B: Reprinted from Rinsho Shinkeigaku, 42, Nakajima M et al, "A case of neurocysticercosis suggestive of a reinfection, 20 years after the initial onset", 18–23, 2002, with permission from Japanese Society of Neurology. C: Reprinted from J Neurol Neurosurg Psychiatry, 70, Osoegawa M et al, "Localised myelitis caused by visceral larva migrans due to *Ascaris suum* masquerading as an isolated spinal cord tumor", 265–266, 2001, with permission from BMJ publishing Group).

diagnosed. In cases of pulmonary sparganosis (*Sparganum mansonii*, larval form of *S. erinaceieuropaei*, infection), PZQ treatment at the dose of 75 mg/kg/day for 3 days is highly effective. At the present, standard protocol for pleuro-pulmonary nematodiasis due to ectopic migration of *Gnathostoma* or *Anisakis* larvae has not been established yet. Symptomolytic treatment with anti-inflammatory drugs is the only practical way to treat these patients.

Mobile skin lesions

Mobile skin lesions strongly suggest the presence of parasitic infection, and causative parasites can be predicted, though not definitely, from the type of skin lesions (creeping eruption or mobile nodular lesion) and the eating history (Table 3.6) (57). Gnathostomiasis (Fig. 5A, B) occurs by ingestion of freshwater fish (brook trout, domestic or imported

loach and snakehead fish) or snakes (12, 13, 15) and presents both types of lesions depending on its species (58). Sparganosis due to infection with the *S. mansonii*, larval form of *S. erinaceieuropaei*, occurs by ingestion of raw or undercooked chicken, snake or frog meat and presents with a slowly moving nodular lesion (14). Skin involvement is well known in paragonimiasis (45). *Spirurina* Type X larvae were identified to cause creeping eruption more often than ileus (11). Recently we reported 7 cases of creeping eruption due to infection with dog hookworm larvae overseas (Fig. 5C, D) (59). As can be seen in those pictures, creeping eruption due to dog hookworm larvae is usually limited to the epidermal layer.

The surgical removal of the larva is the best way for treatment as well as leading to definitive diagnosis. However the rate of resection is usually low. Thus immunodiagnosis is im-

portant for the diagnosis of these diseases (57). Several reports have documented that ABZ is effective for gnathostomiasis and larval animal hookworm infection (58, 59). Recently Wear et al (60) recommended a single oral dose of IVM (12 mg/adult or 200 µg/kg B.W. at once) for hookworm infection.

CNS symptoms

Possible parasitic diseases affecting CNS are summarized in Table 3.7. Human infection with *Angiostrongylus cantonensis* occurs by ingesting contaminated snails and slugs, or green vegetables, and appears as eosinophilic meningitis/meningoencephalitis. Though the severity of symptoms depends on worm burden, the patients may present cranial nerve involvement (especially facial palsy), ocular manifestations (mainly diplopia), psychosis, and sensory impairment in addition to headache with fever (61). This parasite is widely distributed in Okinawa but sporadically found around the international trading harbors of main lands of Japan (62). Some cases of *Angiostrongylus* infection by ingesting raw slugs as medical treatment have been reported (18, 19). Although the standard protocol has not yet been established, consecutive administration of ABZ is reported to be effective for treatment of angiostrongyliasis.

Larval form of *Taenia solium*, *Cysticercus cellulosae*, frequently causes cerebral, ocular, and subcutaneous cysticercosis (63). CT and MRI findings of neurocysticercosis vary depending on the stage of the disease (Fig. 6A, B) (64). Infection to humans occurs by ingestion of food or water contaminated with *T. solium* eggs or by cysticerci-contaminated pork meat. The eggs release the larvae that invade the intestinal mucosa, enter blood vessels, and travel to various organs and tissues, where they develop into cysticerci and cause human cysticercosis. When the cysticerci are ingested, they develop into adult *T. solium* in the intestine. Then the worm segments (proglottids) rupture and release eggs in the intestine. Cysticercosis results from intestinal autoinfection (63). It is important to determine whether the patients with neurocysticercosis have adult worms in their intestine. This is because if patients have adult *T. solium* infection in their intestine, treatment of cysticercosis with PZQ leads to the autoinfection by the rupture of the proglottids. Thus, worm expulsion by gastrographin must be preceded to the administration of PZQ in cysticercosis co-infected with adult *T. solium*. Treatment of cysticercosis itself can be done successfully by the administration of PZQ or ABZ with steroid.

As a rare form of neuroparasitoses, *A. suum*/*T. canis*-VLM occasionally involves CNS including the spinal cord (Fig. 6C) (41, 65). CNS is a target organ of acquired toxoplasmosis, especially in the compromised hosts like AIDS/HIV infection, as well as congenital toxoplasmosis. Not only *Entamoeba histolytica* but also *Naegleria fowleri* causes amebic meningoencephalitis. Recently the first case of primary amebic meningoencephalitis due to *N. fowleri* was reported in Japan (66). While entamoebic abscess in

CNS can be treated successfully with MNZ, chemotherapy for meningoencephalitis due to free-living amoeba like *Naegleria* has not been established.

Conclusion: We Are Still Living in This Wormy World

From the global point of view, helminth infections are still threatening to human health and current numbers of helminth infections are estimated as about 4,500 million which number is beyond Stoll's estimate in 1964 (67). Parasitic diseases in Japan will remain to exist and recent rapid globalization is a warning alarm us to pay more attention not only to domestic but also to the imported parasitic diseases in Japan. We should be aware of the possibility of parasitic diseases because we are still living in this wormy world.

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