Clinicoradiologic Features of Pleuropulmonary Paragonimus westermani on Kyusyu Island, Japan*

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Study objective: Recently, the number of new cases of Paragonimus westermani in humans has gradually increased, and paragonimiasis is a re-emerging public health issue in Kyusyu, Japan. We review our recent experience with pleuropulmonary Paragonimus westermani.

Patients: Pulmonary paragonimiasis was diagnosed in 13 patients at the Third Department of Internal Medicine, Miyazaki Medical College between 1993 and 1999.

Results: Both sputum and bronchoscopic examinations revealed ova in four of nine patients; bronchoscopy yielded ova in two additional patients. Twelve patients (92%) had respiratory symptoms, including cough (92%), sputum and/or hemoptysis (92%), and chest pain (46%). Chest radiography and CT showed pleural lesions (62%) and parenchymal lesions (92%). Of note was the high frequency of solitary nodular lesions (62%), mimicking lung cancer, tuberculosis, or fungal diseases. Immunodiagnosis and bronchoscopic examination were also useful for diagnosis. Praziquantel treatment was very effective and had minimal side effects. One patient required surgical decortication for empyema in spite of treatment with praziquantel. Eosinophilia was noted in peripheral blood and body fluids, which was probably due to increased levels of interleukin-5.

Conclusions: Our findings indicate that our patients with Paragonimus westermani presented with a wide variety of radiographic findings, which were different from the classic presentations reported earlier. Bronchoscopic examination and serologic tests are very useful for accurate diagnosis. As dietary habits change and international transportation increases, it appears likely that paragonimiasis will also increase in frequency in various parts of the world.

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Key words: clinicoradiologic feature; interleukin-5; Paragonimus westermani

Abbreviations: BALF = BAL fluid; ELISA = enzyme-linked immunosorbent assay; IL = interleukin

Paragonimiasis is a food-born parasitic disease common in southeast Asia, especially in Japan, Korea, the Philippines, Taiwan, and parts of China. Furthermore, a highly increasing incidence of paragonimiasis was observed in eastern Nigeria in from 1967 to 1970; in the late 1970s, immigration of southeast Asian refugees resulted in an increased number of reported cases in the western world.

In Japan, two species, Paragonimus westermani and Paragonimus miyazakii, are known as the pathogens of human paragonimiasis and a majority of paragonimiasis was infection due to P westermani. Kyusyu Island is the southernmost of the four major islands of Japan (Fig 1). Miyazaki prefecture is located in Kyusyu Island (Fig 1) and has long been known as one of endemic areas for P. westermani, where > 300 cases were found in the 1950s. The inhabitants of Miyazaki prefecture have a custom of eating freshwater crabs, Eriocheir japonicus, a famous second intermediate host of P. westermani, or the flesh of wild boars, Sus scrofa leucomystax, a proven paratenic host. After an extensive survey and treatment by the local government during the 1950s and 1960s, the number of new reported cases rapidly decreased; by the late 1970s, paragonimiasis was declared a disease of the past in this area.

However, since the late 1980s, the number of new cases of paragonimiasis has gradually increased in
southern Kyusyu,7,9,10 and 13 cases of pulmonary *P. westermani* have been diagnosed at the Third Department of Internal Medicine, Miyazaki Medical College during the last 7 years. Thus, paragonimiasis is a re-emerging public health issue in Kyusyu, Japan. We summarize our recent experience of 13 patients with pulmonary *P. westermani*.

**Materials and Methods**

All 13 patients with pulmonary *P. westermani* diagnosed at the Third Department of Internal Medicine, Miyazaki Medical College between 1992 to 1999 were included in the study. They consisted of 10 men and 3 women (median age, 49 years; range, 25 to 77 years). Six patients were smokers, and two were ex-smokers. All patients were confirmed to have *P. westermani* by immunodiagnosis. Briefly, a multiple-dot enzyme linked immunosorbent assay (ELISA) was used for routine primary screening of parasite diseases, and binding inhibition ELISA and/or Ouchterlony’s method were also used for identification of pathogens (performed in the Department of Parasitology, Miyazaki Medical College, Miyazaki). Details of the immunodiagnostic methods have been described previously.9 A full clinical evaluation was performed in all patients before and repeatedly after treatment. A systemic review of the chest radiographs and CT scans was performed in all patients. In some cases, new lesions developed into three types: pleural lesions, such as nodular and infiltrative opacity; and a combination of pleural and intrapulmonary parenchymal lesions (Table 2). Pleural effusion was present unilaterally in nine patients (69%). Of these, two patients also had pneumothorax on the same side of the lung. One patient (patient 6) had also transient pericardial effusion (Fig 2). Intrapulmonary parenchymal lesions were present in 12 patients (92%). A nodular shadow (2 to 3 cm in diameter) was present in eight patients (62%), and small nodular lesions (< 1 cm) were seen in four patients (31%). Cavitation with a nodule was present in two patients was bound to microtiter plates by incubation at 4°C overnight. The wells were washed with phosphate-buffered saline solution containing 0.05% Tween 20. After blocking with phosphate-buffered saline solution/10% fetal calf serum for 2 h, samples and recombinant human IL-5 (Pharmingen) were added to each well and incubated at 4°C overnight. After washing, secondary antibody (biotinylated antihuman IL-5 monoclonal antibody) was added to each well and incubated at room temperature for 1 h, followed by an additional 1-h incubation with peroxidase-conjugated streptavidin. Wells were subsequently washed and incubated with 0.11 mol/L sodium acetate buffer containing tetramethylbenzidine for 15 min or until the development of a suitable color. Reaction was terminated by adding 1.8 mol/L H2SO4 to each well. Absorbance was read at 450 nm in an ELISA reader. The detection limit was 20.0 pg/mL.

**Results**

**Clinical Features**

Table 1 summarizes the clinical and laboratory data of each patient. Almost all patients (92%) reported eating raw foods, especially wild boar meat. Twelve patients (92%) presented with respiratory symptoms (cough, n = 12; 92%), sputum and/or hemoptysis (n = 12; 92%), chest pain (n = 6; 46%), dyspnea (n = 3; 23%), and fever (n = 3; 23%). Subcutaneous paragonimiasis was seen in one patient (patient 8), and one patient (patient 5) suffered from repeated bacterial pneumonia in the right lower lobe for 4 years before hospital admission. Another patient (patient 13) had been treated for tuberculosis at another hospital. Calcification was seen in the brain (patient 2) and liver (patient 6) on CT scan. WBC count was within the normal range in 12 patients (92%), but eosinophilia was detected in peripheral blood of 11 patients (85%). Serum IgE levels were also elevated in 7 of 11 patients (64%).

**Chest Radiograph and CT Findings**

Patients presented with a variety of radiographic and CT findings (Table 2), probably depending on different stages of migration of the fluke. All patients had abnormal findings in the lungs that were classified into three types: pleural lesions, such as pleural effusion and pneumothorax; intrapulmonary parenchymal lesions, such as nodular and infiltrative opacity; and a combination of pleural and intrapulmonary parenchymal lesions (Table 2). Pleural effusion was present unilaterally in nine patients (69%). Of these, two patients also had pneumothorax on the same side of the lung. One patient (patient 6) had also transient pericardial effusion (Fig 2). Intrapulmonary parenchymal lesions were present in 12 patients (92%). A nodular shadow (2 to 3 cm in diameter) was present in eight patients (62%), and small nodular lesions (< 1 cm) were seen in four patients (31%). Cavitation with a nodule was present in two patients.
(patients 1 and 7; Fig 3). Two patients showed a reticular shadow (patient 2 [Fig 4, bottom] and patient 8). One patient showed an infiltrate in the right lower lobe because of obstructive pneumonia (patient 5). Three patients showed atelectasis: compression atelectasis by massive pleural effusion in two patients (patients 10 and 13) and atelectasis by stenosis of the orifice of the associated bronchus in one patient (patient 5). Mediastinal lymphadenopathy was seen in four patients. Interestingly, radiographic and CT findings changed in four patients during intermittent examinations before diagnosis. Enlargement of a nodule was noted in two patients (patients 1 and 2; Fig 4, top, middle) within 2 months. In two patients, a nodule (2 to 3 cm) developed after transient pleural effusion and pneumothorax (patient 9) or pericardial and pleural effusion (patient 6; Fig 2).

**Examination of Sputum, Pleural Effusion, and BAL Fluid**

As shown in Table 2, *P. westermani* eggs were detected in six patients. Ova were found in the sputum of four patients who had a solitary nodule and in six BAL fluid (BALF) and/or brushing samples obtained by bronchoscopy from nine patients (Fig 5). In three of four patients with positive findings for ova in the sputum, eggs were found in the sputum just 1 day after bronchoscopic examination (patients 2, 4, and 6). Furthermore, ova were detected in two patients (patients 1 and 3) only in BALF and/or brushing samples harvested during bronchoscopy (Table 2). Ova were not found in any pleural effusion samples examined in four patients (Table 2). Bronchoscopic examination showed stenosis of congested and edematous bronchi in seven patients (78%) with intrapulmonary parenchymal lesions (Table 2). No malignant cells were found by bronchial brushing and/or biopsy in these lesions. Marked eosinophilia was detected in body fluids of these patients (Table 2).

**Treatment**

All patients were treated with a high dose (75 mg/kg/d for 2 or 3 days) of praziquantel. One patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Eating Custom</th>
<th>Symptoms</th>
<th>Leukocytes, No. (% Eosinophil)</th>
<th>IgE, IU/mL</th>
<th>Eosinophils in Body Fluid, %</th>
<th>IL-5, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>M</td>
<td>Unknown</td>
<td>Cough, hemoptysis, chest pain, fever</td>
<td>8,700 (4.7)</td>
<td>ND</td>
<td>20 (serum)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>F</td>
<td>Freshwater crabs</td>
<td>Cough, hemoptysis</td>
<td>5,400 (7.4)</td>
<td>2,338.5†</td>
<td>29 (serum)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Cough, hemoptysis</td>
<td>6,400 (17.4)</td>
<td>3,120.7†</td>
<td>&lt;20 (serum)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Asymptomatic</td>
<td>7,200 (7.4)</td>
<td>125.9</td>
<td>20 (serum)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Cough, sputum, fever, repeated pneumonia (right lower)</td>
<td>5,800 (8.0)</td>
<td>27,378.1†</td>
<td>69 (BALF)</td>
<td>32.3 (serum)</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>F</td>
<td>Freshwater crabs</td>
<td>Chest pain, cough—6 mo—cough, hemoptysis</td>
<td>5,400 (9.8)</td>
<td>1,832.9†</td>
<td>57 (BALF)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Cough, hemoptysis</td>
<td>6,200 (12.0)</td>
<td>866.0†</td>
<td>34 (BALF)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>F</td>
<td>Freshwater crabs</td>
<td>Cough, sputum</td>
<td>10,900† (45.0)</td>
<td>ND</td>
<td>95 (PF)</td>
<td>2400 (BALF)</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Cough, chest pain—6 mo—cough, hemoptysis</td>
<td>5,800 (22.8)</td>
<td>31.8</td>
<td>15 (BALF)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Cough, sputum</td>
<td>7,100 (8.6)</td>
<td>659.6†</td>
<td>ND</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>M</td>
<td>Flesh of wild boars, freshwater crabs</td>
<td>Cough, hemoptysis, chest pain, dyspnea, fever</td>
<td>7,200 (0.4)</td>
<td>192.1</td>
<td>2 (PF)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>12</td>
<td>41</td>
<td>M</td>
<td>Freshwater crabs</td>
<td>Cough, dyspnea, sputum, chest pain</td>
<td>6,800 (17.4)</td>
<td>365.0</td>
<td>87 (PF)</td>
<td>&lt;20 (serum)</td>
</tr>
<tr>
<td>13</td>
<td>44</td>
<td>M</td>
<td>Flesh of wild boars</td>
<td>Cough, exertional dyspnea, chest pain, sputum</td>
<td>8,000 (38.6)</td>
<td>2,918.9†</td>
<td>94 (PF)</td>
<td>38.8 (serum)</td>
</tr>
</tbody>
</table>

*ND = not done; PF = pleural fluid.
†Normal range = 5,000 to 9,000.
‡Normal range = <394 IU/mL.
§Normal range = 0.7 to 7.0.
with empyema (patient 11) was additionally treated with bithionol. No serious side effects were noted, with the exception of mild urticaria in two patients. In patients with a solitary nodular lesion, treatment resulted in the resolution of respiratory symptoms and abnormal findings on chest radiography. Furthermore, IgG antibody titers and peripheral blood eosinophilia also significantly decreased in these

Table 2—Chest Radiographic and Bronchoscopic Findings*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Radiographic and CT Findings</th>
<th>Bronchoscopic Findings</th>
<th>Ova</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nodule (left upper, 2.5 cm, transient cavity), mediastinal lymphadenopathy, pleural thickness→2 mo→enlargement of nodule</td>
<td>Normal finding</td>
<td>Sputum</td>
</tr>
<tr>
<td>2</td>
<td>Nodule (right upper, 3 cm), small nodule (right middle, 0.3 cm), mediastinal lymphadenopathy→2 mo→plus infiltrate (right upper), enlargement of nodule (right upper)</td>
<td>Stenoses of right B1 and B2 with edematous and reddish mucosa</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Nodule (left lower, 2 cm), transient PE</td>
<td>Stenosis of left B6 with edematous and reddish mucosa</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Nodule (right upper, 3 cm)</td>
<td>Stenosis of right upper bronchus with edematous and reddish mucosa</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Nodule (right lower, 3 cm), atelectasis (right middle), infiltrate (right lower)</td>
<td>Stenoses of right B5a and B6 with edematous and reddish</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Pericardial effusion, PE (left)→6 mo→nodule (right upper, 3 cm)</td>
<td>Stenosis of right upper bronchus with edematous and reddish mucosa</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Nodule (right middle, 3 cm), mediastinal lymphadenopathy</td>
<td>Stenosis of right B4 with edematous and reddish mucosa</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>Reticulonodular (right upper); PE (left)</td>
<td>Normal finding</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>PE, pneumothorax (left), small nodules (right, &lt; 1 cm)→6 mo→nodule (right upper, 3 cm), mediastinal lymphadenopathy</td>
<td>Stenosis of right B2 with edematous and reddish mucosa</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>Right PE, compression atelectasis (right lower)</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>PE (right)</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>PE, pneumothorax (right), small nodules (right &lt; 1 cm), mediastinal lymphadenopathy</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>PE, compression atelectasis (right), small nodule (right upper, &lt; 1 cm)</td>
<td>ND</td>
<td>–</td>
</tr>
</tbody>
</table>

*PE = pleural effusion; + = positive; – = negative; BF = bronchofiberscope; see Table 1 for expansion of other abbreviation.

Figure 2. Chest CT scan of patient 6 showing pericardial effusion and mild pericardial thickening, and left pleural effusion. Six months later, an irregular nodular opacity appeared in the right upper lung in this patient (Table 2).

Figure 3. Chest CT scan of patient 7 showing a well-defined nodule with cavitation in the right middle lobe. This shadow also makes contact with the pleura and with satellite lesions and ectatic changes of draining bronchi.
patients within a few months after treatment with praziquantel. However, associated bronchiectatic changes were still present after treatment in some cases. Praziquantel treatment also resulted in resolution of pleural effusion in all but one patient (patient 11) who required surgical decortication. However, pleural thickening (n = 3) and/or atelectasis (n = 2) remained after treatment in some cases.

Serum levels of IL-5

We also measured IL-5 levels in serum samples from 12 patients and body fluid samples from 7 patients (Table 1). Three of 12 patients showed elevated levels of IL-5 in the serum as compared to levels below the detection limit found in 8 healthy volunteers. In BALF samples, IL-5 levels were also elevated in three of four patients. Three of four patients showed marked elevation of IL-5 levels in pleural effusion.

Discussion

We report here the clinicoradiologic features of 13 patients with pulmonary *P. westermani*. Diagnosis of paragonimiasis can be established readily in most patients by identifying the typical operculated ova in the sputum, stools, or pleural fluid. However, in our patients, eggs in the sputum were found only in four patients (31%); in three of these patients, eggs were found in their sputum only after bronchoscopic examination. In addition, no ova were detected in pleural fluid samples. The diagnosis was, therefore, made serologically by a dot-ELISA method to detect parasite-specific IgG antibody. More than 100 new cases of paragonimiasis have been diagnosed mainly by this method between 1986 and 1998 in the Department of Parasitology, Miyazaki Medical College, indicating that the dot-ELISA method for the detection of IgG antibody is very useful for the diagnosis of paragonimiasis.

To our knowledge, there are no previous studies that have examined the validity of fiberoptic bron-
choscopy for the diagnosis of P westermani. Our finding that six of nine patients with intrapulmonary paragonimiasis were found to have ova on cytologic examination of bronchial brushing and/or BALF indicates that bronchoscopic examination is also useful for the diagnosis of intrapulmonary paragonimiasis. Bronchoscopy also showed bronchial stenosis of bronchi with congested and edematous mucosa in seven of nine patients. In addition, one patient (patient 5) had repeated obstructive pneumonia of the right lower lung and atelectasis of the right middle lobe due to stenosis of segmental bronchi. In some patients, bronchiectatic changes were also seen (Fig 3, 4, middle). In this regard, previous reports also indicated that cystic changes were the main manifestations of paragonimiasis on chest radiography.2,13,14 Taken together, P westermani seems to cause marked damage to the bronchi.

To our knowledge, there are few comprehensive reports of the CT findings in pulmonary P westermani.14 In our series, patients exhibited a variety of radiographic and CT findings. Of interest was the high frequency of pleural lesions (69%). A comprehensive report of the radiographic changes in pulmonary paragonimiasis by Ogakwu and Nwokolo,2 who studied 100 cases in eastern Nigeria, did not emphasize the presence of pleural lesions. However, consistent with our data, other reports3,6,14 described the presence of pleural effusion as one of the clinical manifestation of P westermani. One possible explanation for this difference in the incidence of pleural lesions is that patients reported by Ogakwu and Nwokolo2 included only ova-positive patients, whereas our data emphasize the diagnostic importance of serologic tests. Our results indicate that pleural lesions are a common manifestation of P westermani.

With respect to intrapulmonary lesions in paragonimiasis, four patterns were described by Ogakwu and Nwokolo2: the most common shadows were well-defined patches of cavitation, ill-defined “cotton wool” lesions, “streaky” shadows, or “bubble” cavities. These patterns were predominantly in the mid-zones of the lungs. A somewhat different radiographic presentation was, however, observed by Johnson and Johnson,6 which included diffuse (44%) and segmental (24%) infiltrates, nodules (20%), and cavities (20%). Ring shadow was the most prominent lesion in a study of 38 cases in Thailand,13 and airspace consolidation (45%) and cyst(s) (46%) were most common in Korea.14 Interestingly, in our series, the most common lesion was a nodular shadow (62%), a pattern different from the above-mentioned studies. Chest CT scans revealed that each nodule was subpleural and occasionally accompanied by ectatic changes in associated bronchi. Differential diagnosis of pulmonary paragonimiasis should, therefore, include lung cancer, tuberculosis, and fungal infection.

A typical route of migration of P westermani in human or other natural final host is as follows: when metacercariae, the infective stage of the parasite, are ingested by the final host, they excyst in the intestine and penetrate the abdominal cavity. The larvae migrate through the peritoneum, liver, diaphragm, and pleura into the lung, where they mature to adult flukes.1 Two patients presented here showed a typical clinical feature of paragonimiasis with transient pleural effusion and pneumothorax (patient 9) or pericardial and pleural effusion (patient 6) followed by a nodular shadow in the lung about 6 months later, which was consistent with the migratory route of Paragonimus worms. Because of the complexity of the migration route in the final host, this parasite often causes an ectopic infestation at various sites, such as the skin, liver, kidney, peritoneum, spinal cord, or brain.1 In this study, subcutaneous paragonimiasis was seen in one patient (patient 8). In addition, calcified lesions were found in the liver (patient 6) and brain (patient 2), which might be manifestations of extrapulmonary paragonimiasis.

Studies evaluating the usefulness of bithionol for paragonimiasis, a drug initially developed as an anthelminthic for veterinary use, confirmed its effectiveness against paragonimiasis.1 Unfortunately, however, the pharmaceutical company has recently stopped production of this drug. The alternative agent, praziquantel, has proven to be effective for paragonimiasis.15,16 Headache, nausea, and urticaria have been reported as adverse effects during its use.15 Our study confirmed that praziquantel treatment, 75 mg/kg/d for 2 to 3 days, was very useful and safe. However, ectatic changes in associated bronchi, pleural thickening, or passive atelectasis were still present after treatment in some patients. In addition, one patient in our study required decortication for chronic empyema. This was consistent with a previous report17 documenting the need for a similar surgery for chronic empyema in 16 of 58 patients infested with P westermani. Thus, early diagnosis and treatment with praziquantel is necessary for paragonimiasis.

IL-5, a potent eosinophil chemotactic and growth factor,18,19 seems to play a major role in parasite-induced eosinophilia. However, there are only few studies20–22 that have examined the relationship between IL-5 and paragonimiasis. In this study, eosinophilia was noted in the serum and/or other body fluids. In addition, high levels of IL-5 also were detected in the serum and/or other body fluids, particularly in pleural effusion in some patients. These findings suggest that IL-5 may play an impor-
tant role in the pathogenesis of eosinophilic infiltration in the lung of patients with paragonimiasis.

In conclusion, our patients with *P. westermani* presented with a wide variety of radiographic findings of intrapulmonary and pleural lesions, which were different from the classic presentations reported earlier by other investigators. Our results also indicated that bronchoscopic examination and serologic tests are very useful for accurate diagnosis. Eosinophilia noted in the serum and body fluids could be relevant to IL-5 in paragonimiasis. Although paragonimiasis is rarely seen in Europe and North America, our speculation is that it will be encountered in the future more frequently in various parts of the world due to changing dietary habits and increasing international transportation.

**REFERENCES**