Paragonimiasis in Japan: A Twelve-year Retrospective Case Review (2001-2012)

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Abstract

Objective Paragonimiasis, or lung fluke infection, is a food-borne parasitic disease caused by infection with trematodes belonging to the genus Paragonimus. Although paragonimiasis was once considered successfully controlled in the 1970s, new cases began to emerge in the late 1980s. To apprehend the current-day situation of the re-emergent cases of paragonimiasis in Japan, we conducted a retrospective review of 443 patients who were referred to our laboratory and diagnosed as having paragonimiasis during 2001-2012.

Methods Patients were diagnosed as having paragonimiasis based primarily on immunodiagnostic methods in addition to clinical, laboratory, and radiographic findings. Patient data were extracted from consultation sheets from attending physicians and were analyzed.

Results Majority of the patients were residents of Kyushu Island. However, a substantial number of cases were also from other parts of Japan. Immigrants (mostly from China, Thailand, and Korea) accounted for a quarter of the cases. Native Japanese contracted paragonimiasis by consuming wild boar meat or freshwater crabs, whereas immigrants contracted the infection almost exclusively by consumption of freshwater crabs. Eosinophilia and elevated serum IgE levels were found in around 80% of the patients. Parasite egg detection was documented only in 11.7% of the cases, showing the reliance on serological tests for diagnosing paragonimiasis in current clinical practice.

Conclusion Paragonimiasis remains a public health issue in Japan, and the situation should be closely monitored.

Key words: paragonimiasis, lung fluke, immunodiagnosis, eosinophilic pneumonia, immigrants, re-emergence


Introduction

Paragonimiasis, or lung fluke infection, is a food-borne parasitic disease caused by infection with a number of trematode species belonging to the genus Paragonimus. In Japan, two species, P. westermani and P. skrjabini miyazakii, are pathogens causing human paragonimiasis, with the former being tremendously dominant (1-3). Human infections occur by consuming freshwater crustaceans (second intermediate host) or wild boar meat (paratenic host) (4). In Japan, Eriocheir japonica (Japanese mitten crab), Geothelphusa dehaani (Japanese freshwater crab) and Sus scrofa leucomystax (Japanese wild boar) are important sources of human infections (2).

Previously, paragonimiasis was endemic in most parts of Japan. In the late 1950’s, it was estimated that more than 300,000 people were infected with the disease (5). However, intensive mass screening and treatment campaigns performed in endemic areas from the 1950’s to 1960’s successfully reduced the number of new cases, and paragonimiasis was considered to be a rare local disease of the past by the 1970’s (6, 7).

However, new cases began to emerge in the late...
Table 1. Multiple Logistic Regression Analysis for White Blood Cell Count and Percentage of Eosinophil

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>WBC counts ≤10,000 (0), &gt;10,000 (1)</th>
<th>Eosinophil (%) ≤7.0 (0), &gt;7.0 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Odds ratio (95% CI) p value</td>
<td>Odds ratio (95% CI) p value</td>
</tr>
<tr>
<td>≤50 years old (0)</td>
<td>0.647 (0.327-1.281) 0.212</td>
<td>1.040 (0.519-2.085) 0.912</td>
</tr>
<tr>
<td>&gt;50 years old (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1.133 (0.559-2.298) 0.729</td>
<td>1.807 (0.795-4.112) 0.158</td>
</tr>
<tr>
<td>male (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female (1)</td>
<td>1.679 (0.746-3.778) 0.195</td>
<td>0.931 (0.336-2.578) 0.890</td>
</tr>
<tr>
<td>Ethnicity (Birth origin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>native Japanese (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>immigrants (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wild boar meat (1)</td>
<td>2.935 (1.366-6.308) 0.006*</td>
<td>1.694 (0.764-3.753) 0.194</td>
</tr>
<tr>
<td>freshwater crab (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1980’s (8), and a gradual increase in the annual number of paragonimiasis cases was observed during the 1990’s (1, 8). Detailed analyses of the clinical features of “re-emergent” cases were reported using clinical records collected between 1986 and 1998 (1) and 1999 and 2001 (9). Among these “re-emergent” cases, the majority of patients were middle- to old-aged men, and the major source of infection was the consumption of raw wild boar meat.

A gradual increase in the number of immigrant cases attracted attention from 1998 to 2002 (10). Clinical features of paragonimiasis in immigrant patients were found to be different from those observed in native Japanese patients. For example, the mean age of the immigrant patients was lower, with the majority of affected individuals being women, than that of the Japanese patients. In addition, the major source of infection was freshwater crabs consumed either in Japan or their home countries.

In the present study, we analyzed patient records collected between 2001 and 2012. The number of patients diagnosed as having paragonimiasis in our laboratory totaled 443. We summarized the demographic and clinical characteristics of these patients. Our records likely represent a substantial portion of the paragonimiasis cases that occurred nationwide within the past 12 years and provide the opportunity to elucidate the clinical features of current cases of paragonimiasis.

**Materials and Methods**

**Subjects and samples**

A total of 443 of approximately 5,200 cases referred to our laboratory were diagnosed as paragonimiasis based on the patient’s information, as provided by the attending physicians in the form of consultation sheets; this information included clinical symptoms, eating history, radiographic findings and laboratory data in addition to the results of immunodiagnostic tests performed in our laboratory. This study was approved by the Institutional Review Board of the Faculty of Medicine at the University of Miyazaki.

**Immunodiagnostic methods**

The details of the immunodiagnostic methods have been previously described (11). A multiple-dot enzyme-linked immunosorbent assay (ELISA) was used as a routine primary screening procedure.

**Statistical analysis**

The patients were categorized according to their age, sex, ethnicity (based on their birth place described on the consultation sheets) and eating history. Depending on the purpose of the analysis, the patients were also categorized based on
either the presence or absence of particular symptoms, abnormal chest radiograph findings or abnormal laboratory data.

Differences in the number of patients who exhibited various abnormalities were assessed using the chi-square test with Yates’ correction or Fischer’s exact test (when any of the expected cell frequencies were less than 5).

Multiple logistic regression analyses were conducted using the SPSS 22 software program (IBM Corp, Armonk, USA) to assess the factor(s) potentially affecting the frequency of a particular clinical symptom (chest/chest-back pain) or the absence of symptoms, as described in the Results section, and identify factor(s) potentially affecting the frequency of patients with a high white blood cell count (>10,000 cells/μL) or eosinophilia (>7.0% of white blood cells). For the analyses, all categorical variables were dummy-coded, as shown in Table 1 (male/female = 0/1, for example).

**Results**

Of approximately the 5,200 cases referred to our laboratory during the period of 2002-2012 for the serodiagnosis of various parasitic diseases, a total of 443 were diagnosed as paragonimiasis. The annual number of native Japanese patients with paragonimiasis was relatively consistent until 2009, ranging from 25 to 30, followed by a gradual decrease until 2012 (Fig. 1). The annual number of immigrant patients with the disease exhibited more marked fluctuation, ranging from 4 (in 2003) to 23 (in 2007) cases. Overall, immigrant cases represented 25.5% (113 of 443) of the total number of cases during the observation period. Among the immigrants, China (50 patients) was the most common country of origin, followed by Thailand (34 patients) and Korea (26 patients). These three countries accounted for 97% of all immigrant cases.

The geographical distribution of the cases is shown in Fig. 2. The majority (63.4%) of the patients were residents of Prefectures on Kyushu Island (Fukuoka, 71; Saga, 7; Nagasaki, 5; Kumamoto, 31; Oita, 32; Miyazaki, 56; and Kagoshima, 79), the most southwesterly of Japan’s four main islands. Outside Kyushu Island, Tokyo (18 cases), Kanagawa (15), Gifu (17) and Osaka (18) each had a relatively large number of patients. Only a few cases were referred to us from Prefectures in northern Japan (Tohoku district and Hokkaido). More immigrant cases were seen outside Kyushu Island (65 of 162, 40.1%) compared with that observed on Kyushu Island (48 of 281, 17.0%). Prefectures with large
populations, such as Tokyo and Osaka, tended to have a high percentage of immigrant cases (12 of 18, 66.7%, for both).

Among the native Japanese patients, there were more men than women in every age group, with the exception of patients over 80 years of age (Fig. 3A). Furthermore, there was a marked difference in the peak age of disease presentation between the sexes. In men, the peak was seen in the age group of 60-69 years (mean age: 55), compared to the age group of 30-39 years in women (mean age: 45). This difference with respect to gender was particularly marked in the age groups over 50 years. Regarding the immigrant patients, there were more women than men in every age group (Fig. 3B). The difference with respect to gender in the peak of disease presentation was not very clear, with men peaking at 40-49 years of age (mean age: 39) and women peaking at 30-39 years of age (mean age: 40).

In order to make comparisons between the “younger” and “older” age groups in terms of symptoms, chest radiographic findings and laboratory data, which will be presented later in this paper, we set an arbitrary cut-off of 50 years of age. As expected according to the age distribution graphs (Fig. 3), there were more patients over 50 years of age among the native Japanese than in the immigrant groups. In men, 175 (68.6%) patients were over 50 years of age among the native Japanese compared to two (7.4%) patients among the immigrants, a statistically significant difference (p<0.0001, χ² test). Similarly in women, more patients belonged to the older age group among the native Japanese (43 patients, 64.2%), compared to the only eight (9.4%) immigrants (p=0.0002, χ² test).

The patients’ eating history of consuming freshwater crab and wild boar is summarized in Table 2. Approximately half (45.8%) and one-third (32.8%) of male and female native Japanese patients, respectively, had a history of consuming wild boar meat, although only a fraction of patients informed the physicians that they ate these foods raw. Among the immigrant cases, the majority of patients had a history of consuming freshwater crab, whereas wild boar meat was consumed by only three patients. Freshwater crab tended to be consumed raw more frequently by immigrants (34.6% for men and 32.5% for women) than native Japanese (6.2% and 11.9%, respectively). Twenty-four patients informed the attending physicians that they did not consume either freshwater or wild boar meat. Among these subjects, 19 had history of consuming raw deer meat.

Frequent symptoms documented on the consultation sheets are shown in Table 3. Coughing (28.9% of the patients), sputum, including hemopto.sputum (27.3%), chest/chest-back pain (18.5%), fever (11.7%) and dyspnea (10.4%) were the most frequently observed symptoms. Other relatively common, but less frequent, symptoms included subcutaneous nodules (4.9%), rash/pruritus (3.1%), gastrointestinal (GI) symptoms (abdominal pain, vomiting and diarrhea, 6.5%) and back pain (2.3%).

Sixty-six (17.2%) of the patients were asymptomatic (Table 3). These patients were referred to us due to abnormal chest radiograph findings (50 patients), eosinophilia (seven patients) or both (one patient) at their annual check-up or upon visiting the physician for other medical reasons. Nine patients were referred to us in the absence of symptoms because their family members or close friends, who potentially had consumed the same food source of infection, were diagnosed with paragonimiasis.

The percentage of patients who exhibited each symptom was compared according to age groups (≤50 or >50 years old), sex (male or female), ethnic group (native Japanese or immigrant) and possible food source of infection (freshwater crab or wild boar meat). In these comparisons, we found the following differences with statistical significance: 1) chest/chest-back pain and GI symptoms appeared more frequently in the patients belonging to the younger age group; 2) chest/chest-back pain was more frequent in women than in men; 3) asymptomatic cases were more frequent in the older age group and native Japanese than in the younger patients and immigrants, respectively; 4) subcutaneous nodules were more frequent in the immigrants than in the native Japanese; 5) the potential food source of infection (freshwater crab or wild boar meat) did not affect the proportion of patients who presented with these symptoms.

Because these initial comparisons indicated that the presentation of chest/chest-back pain and “no symptoms” was affected by multiple factors, we performed multiple logistic regression analyses to identify factor(s) independently asso-
associated with the presence or absence of symptoms. For the analysis of chest/chest-back pain, the age group and sex were used as independent variables. For the analysis of “no symptoms,” the age group and ethnicity (native Japanese or immigrant) were used as independent variables. In these analyses, only the age group was found to be associated with the presentation of chest/chest-back pain and “no symptoms.” Between the younger and older age groups, the odds ratio of having chest/chest-back pain was 3.23 [95% confidence interval (CI): 1.69-6.25], while that of having no symptoms was 0.31 (95% CI: 0.16-0.60).

We analyzed the chest radiographic findings documented on the consultation sheets. This information was available in 355 of 443 cases (80.1%). The most frequent observation was the presence of pleural effusion (in 208 or 47.0% of cases), followed by pneumothorax (75, 16.9%), nodular shadows (51, 11.3%), infiltrative shadows (39, 8.8%) and mass shadows (29, 6.5%). These findings were compared between the sexes, age groups, ethnic groups and possible food sources of infection. In these comparisons, we found that more patients 50 years of age or younger exhibited pleural fluid than the older patients (53.7% vs. 39.6%, p=0.0039, χ^2 test). The comparisons between the sexes, ethnic groups and possible food sources of infection did not yield any statistically significant differences.

It is known that peripheral blood eosinophilia and elevated levels of serum immunoglobulin E (IgE) are frequently observed in patients with paragonimiasis, as in other parasitic helminth infections (12, 13). On the other hand, it has been documented that the total while blood cell (WBC) count usually remains in the normal range or is moderately elevated (12, 13). In the present study, the total WBC, peripheral blood eosinophil and serum IgE levels were available in 422, 412 and 264 cases, respectively. Overall, 29.9% of the patients showed an elevated WBC count, defined as being greater than 10,000 cells/μL. Likewise, 75.5% of the patients exhibited eosinophilia (>7% of the total white blood cell count) and 79.9% demonstrated an elevated (>170 IU/mL) serum IgE level.

These laboratory data were compared between the sexes, age groups, ethnic groups and possible food sources of infection. As shown in Table 4, more patients belonging to the younger age group (<50 years old), women, immigrants and those who ate fresh water crab exhibited a high WBC count (>10,000/μL) compared to that observed among the older patients (>50 years old), men and those who ate wild boar meat (χ^2 test). More women and patients who ate freshwater crab exhibited eosinophilia than did men and patients who ate wild boar meat (χ^2 test). As for the serum total IgE level, such comparisons did not yield any statistically significant differences.

In order to isolate factor(s) independently affecting these laboratory data, we performed a multiple logistic regression analysis with the age group, sex, ethnicity and food source of infection as independent variables and the presence or absence of a high WBC count (>10,000/μL) or eosinophilia (>7.0% of the total WBC count) as dependent variables. As shown in Table 1, only the food source of infection was found to affect the presentation of a high WBC count with statistical significance, with freshwater crab consumption being associated with a 2.9-fold greater chance of a high WBC count. No single factor was proven to affect the incidence of eosinophilia in this analysis.

According to the clinical records, the detection of paragonimus eggs was documented in 52 of 443 cases (11.7%). Bronchoscopic techniques were most commonly used (in 18 cases), followed by examinations of sputum (17 cases), pathological inspection of surgically removed tissue (seven cases) and examinations of pleural fluid (three cases). Egg detection in feces was documented in only one case.

### Discussion

The re-emergence of paragonimiasis in Japan attracted attention in the late 1980’s (1). Initially, cases diagnosed as paragonimiasis in our laboratory were almost restricted to residents of Kyushu Island. However, currently, a substantial number of patients (36.6% of total cases) living outside of
Kyushu Island are also diagnosed as having paragonimiasis. One factor contributing to this phenomenon may be the sophistication of the distribution system of fishery products in Japan. Today, it is common to see live freshwater crab being sold at supermarkets in big cities. One study showed that 17% of freshwater crabs (G. dehaani) purchased in Tokyo contain Paragonimus metacercariae (14).

An age difference between native Japanese and immigrants has been noticed previously (immigrants are younger on average) (10) based on the clinical records collected in the period of 1986-1998 for native Japanese (1) and 1998-2002 for immigrants (10). In the present study, although the trend was the same, the mean age had increased from 48 to 53 for native Japanese and 36 to 40 for immigrants.

Among male native Japanese, paragonimiasis occurs predominantly in middle- and old-aged individuals who consume wild boar meat or freshwater crab. Among female native Japanese, paragonimiasis in the elderly is less common than that observed in men. Wild boar meat is also a less common suspected source of infection in female native Japanese. Regarding immigrants, paragonimiasis is diagnosed most frequently in middle-aged individuals. In contrast with native Japanese patients, more female patients were found among the immigrants in this study. The suspected food source of infection in this group is almost exclusively freshwater crab.

It is interesting to determine the source of infection in immigrants. In many cases, occasional visits to the immigrant’s home country obscures the true source of infection. However, in a case of group infection among Thai patients presented to us in 2007, it was clear that the patients acquired the infection in Japan after eating the same dish containing raw freshwater crab (data not shown). In contrast, we also observed a case of a woman who developed symptoms two months after visiting Thailand. If she was truly infected in Thailand, the etiological agent should have been P. heterotremus, the only Paragonimus species affecting humans in Thailand (15). Although such a distinction does not directly affect treatment per se, it is expect to help construct a better public health strategy for controlling this disease.

We found that patients over 50 years of age were 3.18 times more likely to be asymptomatic compared to the patients belonging to the younger age group. The patients in this age group may have more occasions to receive health check-ups than those in the younger age group and therefore may have more opportunities to have paragonimus infection detected while symptoms are not apparent. Although a simple comparison showed that more Japanese patients than immigrants were asymptomatic (Table 3), this finding is most likely to reflect the fact that the Japanese group included more patients belonging to the older age group than the immigrant group, based on the results of the multiple logistic regression analysis in which only age group, and not ethnicity, was found to be associated with the absence of symptoms.

Likewise, although the initial comparisons indicated that the frequency of patients presenting with chest/chest-back pain was affected by sex, with women more often exhibiting this symptom, this finding may be due to the fact that the female group included more patients belonging to the younger age group based on the results of the multiple log-
Significantly more cases of subcutaneous nodules were observed among the immigrants than among the native Japanese (Table 3). Subcutaneous nodules are one manifestation of extrapulmonary paragonimiasis, which is caused by the aberrant migration of juvenile worms. We suspect that high-density infections tend to occur more frequently in immigrants than in native Japanese, as suggested by Obara et al. (2004) (10), which may account for the higher occurrence of subcutaneous nodules, as it has been proposed that this manifestation is likely to occur more frequently in patients with heavy infections (16).

On the analysis of the chest radiograph findings, we observed pleural effusion and pneumothorax in the older age group more frequently than in the younger age group (Table 5). Because it has been reported that pleural manifestations are characteristic features of the early stage of paragonimiasis (17, 18), this finding again leads to the speculation that cases of paragonimiasis are detected earlier in older patients than in younger patients.

It is intriguing to find that more patients who ate freshwater crab exhibited a high WBC count than those who consumed wild boar meat (Table 1). The immune reactions elicited by paragonimus infection may differ quantitatively or qualitatively depending on the food source of infection. Because there is no nationwide surveillance system for this disease in Japan, we believe that the present study provides an important basis for such monitoring.

The number of native Japanese patients with paragonimiasis has been decreasing over the past three years (since 2009). This may be due to a change in attitude toward eating raw meat, particularly after a widely broadcast food poisoning outbreak caused by eating raw beef tainted with enterohemorrhagic Escherichia coli (EHEC) in 2011 (20).

Traditionally, game meats, such as wild boar and venison, have been consumed locally by hunters and their families in Japan. However, in recent years, there have been efforts by some local governments to distribute such meats through consumer markets. In addition, several internet shopping sites are now selling game meats, propelled by the growing popularity of gibier dishes in Japan. The effects of the current easy access of general consumers to game meats on the pattern of paragonimiasis infection should be monitored closely. Because there is no nationwide surveillance system for this disease in Japan, we believe that the present study provides an important basis for such monitoring.

Although a treatment regimen with praziquantel (oral dose, 75 mg/kg body weight daily for three consecutive days) is recommended (21), we encountered at least 12 cases of underdosing. Therefore, there is still a need to increase awareness of this disease and its treatment among clinicians.

The authors state that they have no Conflict of Interest (COI).

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### Table 4. Laboratory Data of Patients

<table>
<thead>
<tr>
<th>Classifications</th>
<th>WBC count</th>
<th>Eosinophil count (%)</th>
<th>Serum total IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n &gt;10,000/μL</td>
<td>p</td>
<td>n &gt;7.0%</td>
</tr>
<tr>
<td>&lt;=50 y/o</td>
<td>131</td>
<td>43.5</td>
<td>0.0003*</td>
</tr>
<tr>
<td>&gt;50 y/o</td>
<td>108</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>149</td>
<td>24.8</td>
<td>0.0009*</td>
</tr>
<tr>
<td>female</td>
<td>90</td>
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<td></td>
</tr>
<tr>
<td>Native Japanese</td>
<td>165</td>
<td>23.0</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Immigrants</td>
<td>74</td>
<td>55.4</td>
<td></td>
</tr>
<tr>
<td>Freshwater crab</td>
<td>130</td>
<td>47.7</td>
<td></td>
</tr>
<tr>
<td>Wild boar meat</td>
<td>109</td>
<td>15.6</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

The sum of each classifications are less than 443 due to exclusion of cases that lack the information necessary for the classification or laboratory data.

Values are presented as percent.
p values were calculated using chi-square test with Yates’ correction.

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The detection of eggs in feces was documented in only one case. Many of the remaining cases. We expect that the detection rate would be low on fecal examinations based on a past publication that reported the detection of paragonimus eggs in feces in only 1.9% of 365 individuals with a positive skin reaction against a paragonimus antigen (19).

We do not have information regarding the number of cases in which fecal examinations were performed. Only three records mentioned negative results on fecal examinations. It is most likely that fecal examinations were not performed in many of the remaining cases. We expect that the detection rate would be low on fecal examinations based on a past publication that reported the detection of paragonimus eggs in feces in only 1.9% of 365 individuals with a positive skin reaction against a paragonimus antigen (19).

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Although a treatment regimen with praziquantel (oral dose, 75 mg/kg body weight daily for three consecutive days) is recommended (21), we encountered at least 12 cases of underdosing. Therefore, there is still a need to increase awareness of this disease and its treatment among clinicians.

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Table 5. Chest Radiograph Findings of Patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Symptoms</th>
<th>Overall (n=443)</th>
<th>Native Japanese Immigrants (n=322)</th>
<th>Japanese Immigrants (n=222)</th>
<th>Male (n=284)</th>
<th>Female (n=159)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50y/o</td>
<td>Pleural effusion</td>
<td>19.9</td>
<td>17.7</td>
<td>22.6</td>
<td>0.0078•</td>
<td>17.7</td>
<td>23.9</td>
</tr>
<tr>
<td>&gt;50y/o</td>
<td>No data available</td>
<td>20.0</td>
<td>18.0</td>
<td>21.3</td>
<td>0.0078•</td>
<td>18.0</td>
<td>23.9</td>
</tr>
</tbody>
</table>

Data are presented in percentage. Note that the sum of each categories such as male and female do not total 443 due to exclusions of cases that lack the information necessary for the categorization. P values were calculated using chi-square test with Yates' correction or Fisher's exact test when necessary.

References