

# THE CURRENT STATUS OF PARAGONIMIASIS IN JAPAN

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**Abstract.** Paragonimiasis was considered a disease of the past in Japan in the 1970s. However, new cases began to emerge from the late 1980s. During the years 1986 to 2002, we experienced over 200 cases. Although most of patients were Japanese, sporadic cases have been seen among immigrants living in Japan. To elucidate the clinical features of current paragonimiasis patients in Japan, we analyzed the relationship between parasite-specific IgM and IgG antibodies and the stage of disease. The results showed that the majority of Japanese patients had light grade infections and were diagnosed at a relatively early stage. On the other hand, immigrants had heavy infections, diagnosed at a late stage.

## INTRODUCTION

Paragonimiasis is a subacute to chronic inflammatory disease of the lung caused by infection with lung flukes of the *Paragonimus* species. The disease is common in Asia, some parts of Latin America, and Africa. Infection in humans occurs when the second intermediate hosts, freshwater crabs or crayfish, contaminated with metacercariae of *Paragonimus* spp, are ingested. As an unusual route of human infection, consumption of uncooked meat of wild boars, which serve as the paratenic host, was reported from Japan. Paragonimiasis is, therefore, a typical food-borne parasitic zoonosis closely related to unique eating habits in particular areas of the world (Nakamura-Uchiyama *et al*, 2002).

Japan is one of endemic areas for this disease. For instance, Miyazaki Prefecture in Kyushu has been a representative endemic nidus where over 300 cases were reported in the 1950s. After mass screening and prevention campaigns by the local government during the 1950-1960s, the prevalence of paragonimiasis drastically decreased in this area, to the extent that in the 1970s, paragonimiasis was considered a disease of the past (Hayashi, 1978). However, new cases have been re-emerging from the late 1980s. From 1986 till now, we have experienced over 200 cases of paragonimiasis, most of which were infections with *P. westermani* and a few with *P. miyazakii*. Particularly in the most recent 3 years, >30 cases have been found every year. Among those recent cases, we have found

18 cases of paragonimiasis *westermani* in immigrants now living in Japan. In this article, we will describe the current status, including the clinical features, of paragonimiasis in Japan.

## PARAGONIMIASIS IN JAPAN - THE PAST AND PRESENT

Classically, paragonimiasis was known as a disease occurring in the 10-25-year-old group without obvious sex difference and the major source of infection was freshwater crabs (Komaki, 1959). Since their symptoms were characterized by chronic cough with rusty-colored sputum and nodular/cavitating lesions on chest radiographs, pulmonary tuberculosis was the most important disease to be considered in differential diagnosis (Yokogawa, 1969). Diagnosis depended on egg detection from sputum specimen and/or skin test. However, the clinical features of paragonimiasis cases in Japan nowadays appear to have changed from those classical types in terms not only of age and sex distribution, but also in their clinical features (Uchiyama *et al*, 1999; Nakamura-Uchiyama *et al*, 2001). In brief, Japanese patients nowadays are mostly middle-aged males with food habits of ingesting raw wild boar meat. Although various findings, such as pneumothorax, pleural effusion, infiltration and nodular/cavitating lesions were seen in chest radiographs, nearly 70% of them had pleurisy. Due to such variance in radioimaging appearances of pleuroparenchymal lesions in paragonimiasis, it is difficult to differentiate this disease from lung cancer, tuberculosis, or fungal infections. Egg detection rates in the sputum/bronchoscopic aspirates were <50%. Thus, immunodiagnostic methods have become more important for diagnosing paragonimiasis than before (Uchiyama *et al*, 1999). The characteristics of paragonimiasis, between the present and past, are compared in Table 1.

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CLINICAL STAGE OF PARAGONIMIASIS AND PARASITE SPECIFIC-IgM/IgG ANTIBODY

Almost all immunodiagnostic methods to detect *Paragonimus*-specific antibodies have been designed to detect specific antibody of the IgG class in the sera or body fluids of patients (Slemenda *et al*, 1988; Ikeda *et al*, 1992; Dekumyoy *et al*, 1998; Ikeda, 1998). Recently, we encountered a patient showing seroconversion from IgM to IgG antibody during a follow-up study (Mukae *et al*, 2001). This case led us to recognize the importance of detecting IgM antibody. When we analyzed 30 cases of paragonimiasis referred to and diagnosed in our laboratory during 1999, pleurisy with eosinophilia and relatively high IgM antibody are characteristic features of the early stage of paragonimiasis, whereas parenchymatous lesions in the lungs, with relatively low eosinophilia and dominant IgG antibody, are of the late stage (Nakamura-Uchiyama *et al*, 2002). The clinical features of those 30 cases are summarized in Table 2. The age, sex distribution, and clinical features were similar, as we previously reported (Uchiyama *et al*, 1999). Taking these results together, paragonimiasis patients in Japan nowadays are mostly light-grade infections and/or are diagnosed at the early stage of disease. When we analyzed 97 cases between 1999 and 2001, similar results were obtained (Nakamura-Uchiyama and Nawa, 2002).

PARAGONIMIASIS AMONG IMMIGRANTS IN JAPAN

We had only one immigrant case with paragonimiasis until 1997. However, along with the

increase in the number of paragonimiasis cases diagnosed in our laboratory, immigrant cases gradually increased. In the 5 years 1998-2002, a total of 18 cases of immigrants were found among 152 paragonimiasis cases. Sixteen of them were from China and 2 from Thailand. Chinese patients included 4 small groups of family and/or compatriots. All but 2 patients had a history of eating freshwater crabs. Some patients were supposed to be infected in their home country. However, at least 4 group infections were assumed to have occurred in Japan by ingesting either imported Chinese freshwater crabs or locally-purchased Japanese freshwater crabs. The clinical features of immigrant cases are summarized in Table 3. When we compared the clinical features of the immigrants and the Japanese patients, we found several differences (Table 4). In brief, the mean age of the immigrant patients was younger than the Japanese patients, and 2/3 of them were females. Over 50% had multiple/bilateral lung lesions in chest radiogram. Peripheral blood eosinophilia and elevation of total serum IgE were observed in nearly 90%, and over 65%, of patients, respectively. The degree of eosinophilia was significantly higher in immigrants (mean  $\pm$  SD =  $43.5 \pm 23.3\%$ ) than Japanese patients ( $19.5 \pm 13.8\%$ ,  $p < 0.01$ ). However, IgE levels between immigrants (mean  $\pm$  SD =  $1,066.3 \pm 2,126.6$  IU/ml) and Japanese patients ( $1,871.6 \pm 1,400.1$  IU/ml) were not significantly different from each other ( $p > 0.1$ ). These results suggest that immigrants have high-density and/or severe infections compare to Japanese patients (Obara *et al*, 2003).

Because clinical stages are correlated to various parameters, such as the degree of eosinophilia and parasite specific-IgM/IgG antibody (Nakamura-

Table 1  
Characteristics of paragonimiasis in the past and present in Japan.

	Past	Present
Age	School children	Middle age
Sex	M=F	M>>F
Source	Crabs	Wild boar
Degree	Severe	Mild
Lung lesion	Parenchymal	Pleuro-parenchymal
Diagnosis	Egg detection Skin test	Immuno-serological test
Differential diagnosis	Tuberculosis	Malignancy Tuberculosis Other infectious diseases

Table 2  
Summary of paragonimiasis patients during 1999 (n=30).

<b>Age: 48 (13-72 years), M:F=19:11</b>			
<b>Symptoms (n=29)</b>		<b>Egg detection</b>	
Respiratory	24 (82.8%)	Positive	3
Meningitis	1 (3.3%)		
None	5 (17.2%)	<b>Eosinophilia (n=28)</b>	
<b>Chest radiograph abnormality (n=30)</b>		Yes	23 (82.1%)
Yes	28 (93.3%)	No	5 (17.9%)
Pleurisy	19	<b>Hyper IgE (n=17)</b>	
Parenchymatous lesions	9	Yes	15 (88.2%)
<b>Lesions</b>		No	2 (11.8%)
Single (unilateral)	27	<b>Ingestion of raw materials (n=24)</b>	
Multiple (bilateral)	1	Wild boar meat	19 (79.2%)
No	2 (6.7%)	Freshwater crabs	9 (37.5%)

Table 3  
Summary of immigrant patients, 1998-2002 (n=18).

<b>Age: 36 (15-65 years), M:F=6:12</b>			
<b>Symptoms (n=18)</b>		<b>Egg detection</b>	
Respiratory	16 (88.9%)	Positive	1
Subcutaneous nodule	2 (11.1%)		
None	2 (11.1%)	<b>Eosinophilia (n=18)</b>	
<b>Chest radiograph abnormality (n=18)</b>		Yes	16 (88.9%)
Yes	17 (94.4%)	No	2 (11.1%)
Pleurisy	11	<b>Hyper IgE (n=13)</b>	
Parenchymatous lesions	3	Yes	9 (69.2%)
Mixed lesions	4	No	4 (30.8%)
<b>Lesions</b>		<b>Ingestion of raw materials (n=24)</b>	
Single (unilateral)	6	Wild boar meat	0 (0%)
Multiple (bilateral)	11	Freshwater crabs	14 (87.5%)
No	2 (6.7%)		

Table 4  
Characteristics of immigrants and Japanese in patients with paragonimiasis.

	Immigrants	Japanese
Age	36	48
Sex	M<F (1:2)	M>F (2:1)
Source	Crabs	Wild boar
Group infection	Frequent	Rare
Lung lesions	Multiple (bilateral)	Single (unilateral)
Eosinophilia (+)	88.9%	82.1%
mean ± SD (%)	43.5 ± 23.3	19.5 ± 13.8
Hyper IgE (+)	64.3%	88.2%
mean ± SD (IU/ml)	1,066.3 ± 2,126.6	1,871.6 ± 1,400.5

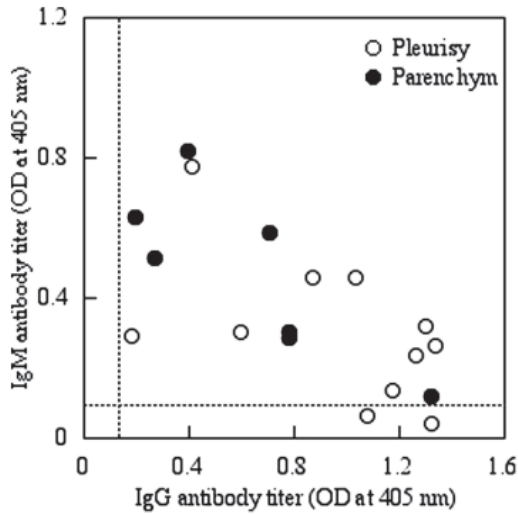


Fig 1- Scatter diagram of parasite-specific IgG and IgM antibody titers in the sera of immigrant paragonimiasis patients. ● : patients with parenchymatous lesion, ○ : patients with pleurisy, Dotted line: cut-off value.

Uchiyama *et al*, 2001), we performed such analysis for immigrant patients. The degree of eosinophilia in the pleurisy group (mean  $\pm$  SD = 39.6  $\pm$  20.2%) was lower than the parenchymatous lesion group (50.5  $\pm$  23.5%,  $p>0.1$ ), and serum IgE level in the pleurisy group (mean  $\pm$  SD = 2,099.1  $\pm$  3,538.7 IU/ml) was higher than the parenchymatous lesion group (313.0  $\pm$  3,24.9 IU/ml,  $p>0.05$ ). Unexpectedly, however, different from the clear results for Japanese patients, no statistically significant difference was observed in those parameters, between the pleurisy and parenchymal lesion groups in immigrants. Thus, in immigrant cases, it is hard to distinguish between early-stage and late-stage paragonimiasis by chest radiograph findings. From a scatter diagram of parasite-specific-IgM/IgG antibody titer of immigrant patients' sera, some patients in the parenchymal lesion group had dominant IgM antibody titer (Fig 1). Due to high-density infection in immigrants, *Paragonimus* worms pair off and enter the lung parenchyma earlier than single worms. As shown in Fig 2, IgM antibody titer correlated positively with degree of eosinophilia ( $r^2=0.30$ ), whereas IgG antibody titer showed an inverse relationship ( $r^2=0.10$ ) with degree of eosinophilia. We emphasize again that detection of IgM antibody should be considered for immunodiagnosing paragonimiasis-suspected patients.

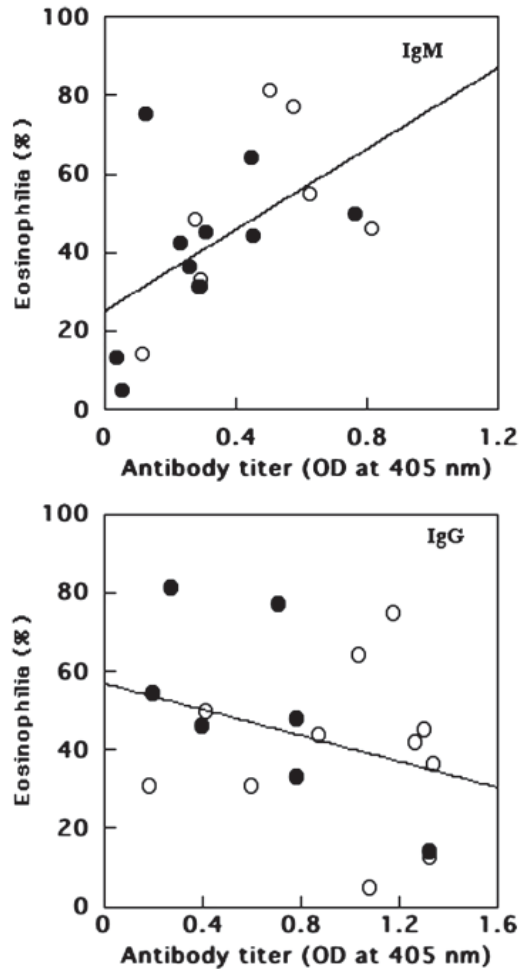


Fig 2- Relationship between IgG and IgM antibody titers and the degree of eosinophilia in paragonimiasis patients. ● : patients with parenchymatous lesion, ○ : patients with pleurisy.

CONCLUSIONS

The current status of paragonimiasis in Japan may be characterized as follows: 1) Japanese patients are mostly light-grade infections and/or are diagnosed at the early stage of the disease, 2) The number of immigrant patients is gradually increasing in Japan. They have high-density and/or severe infections, compared with Japanese patients, 3) Both wild boar and freshwater crabs (either domestic or imported) are important sources of infection. Along with the globalization of travelling and the food trade, and the popularization of ethnic dishes, paragonimiasis can be seen all over the world. This disease should always be

considered when patients have lung lesions with eosinophilia and/or hyper IgE.

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