Detection of Antibodies to *Fasciola* and *Anisakis* in Japanese Patients With Intravascular Lymphomatosis

To the Editor:

Recently, we reported five Japanese patients with large B-cell lymphoma associated with hemophagocytic syndrome, ie, malignant histiocytosis-like B-cell lymphoma, and suggested that they might be regarded as an aggressive variant of intravascular lymphomatosis (IVL) based on the localization of tumor cells within the sinus and vessels of the involved organs. Phenotypically, these lymphomas were CD5⁺, CD10⁺, CD19⁺, CD20⁺, and HLA-DR⁺, with monoclonal rearrangement of the Ig heavy chain gene in two cases. They were also clinically characterized by onset in middle age or old age, fever, anemia, thrombocytopenia, hepatosplenomegaly, initial involvement of the bone marrow, hemophagocytosis, and a rapidly aggressive clinical course. Lymphadenopathy, skin lesions, neurological abnormalities, or peripheral blood lymphocytosis were rarely observed during the entire clinical course. Laboratory examinations showed elevated levels of D-D dimer, lactate dehydrogenase, C-reactive protein, interleukin-6 (IL-6), and the soluble IL-2 receptor isoforms, but not IL-1β, IL-2, or tumor necrosis factor-α, with serologic evidence of abnormal immune function such as circulating antinuclear antibody. Interestingly, more than 30 cases of malignant histiocytosis-like B-cell lymphoma or IVL with hemophagocytic syndrome have been reported exclusively in Asian patients, with only a few cases in Western patients, and their clinical features appeared to differ considerably from those of typical IVL in Western countries. We therefore proposed that this group should be called an Asian variant of IVL (AIVL). In our series, antibodies against human T-cell lymphotropic virus type-I were negative, and Epstein-Barr virus was not detected by in situ hybridization. Notably, in one of the autopsied cases (case no. 5 in our previous report), circumscribed egg granulomas of *Schistosoma japonicum* were observed to be distributed among the lymphoma cells in the liver (Fig 1). This unusual finding prompted us to perform a seroimmunological survey for helminthious infections associated with AIVL, because some parasites, as well as viruses, most likely play an important role in the etiology of several endemic lymphoproliferative diseases.

In the present study, all five patients with AIVL had lived for at least 20 years in suburban areas of Toyota, which is located in the central part of Japan. No patient showed eosinophilia or a high titer of total IgE. Informed consent was obtained from all patients or their families. Enzyme immunoassays for the detection of antibodies to *Echinococcus* (IgG and M), *Fasciola* (IgG and M), *Toxocara* (IgG and M), *Trichinella* (IgG, M, and A), and *Anisakis* (IgG and M) were performed at Specialty Laboratories (Santa Monica, CA). The titers of anti-*Fasciola* IgG and anti-*Anisakis* IgE were judged as positive in four (3.2 to 5.3 SD) and three (1.03 to 11.2 kU/L) of five patients with AIVL, respectively. Among these, anti-*Fasciola* IgM was also positive in the case with the highest titer of anti-*Fasciola* IgG. Anti-*Toxocara* IgG and M, together with anti-*Fasciola* IgG and anti-*Anisakis* IgE, was detected in another patient. All other antibodies were negative in the AIVL patients. As a control, the sera of 19 age- and habitat-matched patients with conventional large B-cell lymphoma were tested for anti-*Fasciola* IgG and anti-*Anisakis* IgG (Table 1). The percentage of anti-*Fasciola* IgG in the patients with AIVL (4/5 [80%]) was significantly higher than that in the control patients (1/19 [5%]). The presence of anti-*Anisakis* IgE in patients with AIVL (3/5 [60%]) tends to be more frequent than that in the control group (7/19 [37%]), but not at a significant level.

The present seroimmunological study indicates a positive relationship between *Fasciola* infection and AIVL. Although we could not find studies regarding carcinogenicity of *Fasciola*, the tumor promoting activity of the flukes in related genera, such as the genus *Schistosoma*, has been well reported. In addition, *S. mansoni* was reported recently to be a possible pathogenic cofactor of Burkitt’s lymphoma in Brazil.

Fig 1. A circumscribed egg granuloma of *Schistosoma japonicum* among the lymphoma cells in a portal area of the liver. Sinusoidal involvement of the lymphoma cells is also evident. Hematoxylin and eosin stain; original magnification × 200.
**Table 1. Detection of Antibodies to Fasciola and Anisakis in Patients With DLBL**

<table>
<thead>
<tr>
<th></th>
<th>AIVL</th>
<th>DLBL Other Than AIVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>44-75 (65 yr)</td>
<td>49-78 (60 yr)</td>
</tr>
<tr>
<td>Male:female</td>
<td>3:2</td>
<td>10:9</td>
</tr>
<tr>
<td>Anti-Fasciola IgG</td>
<td>4/5*</td>
<td>1/19*</td>
</tr>
<tr>
<td>Anti-Anisakis IgE</td>
<td>3/5*</td>
<td>7/19*</td>
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</tbody>
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*According to the continuously adjusted $\chi^2$ test and $P = .0021$ according to Fisher’s exact test (two-tailed).

**REFERENCES**


Detection of Antibodies to *Fasciola* and *Anisakis* in Japanese Patients With Intravascular Lymphomatosis

Takuhei Murase, Kazuhiro Tashiro, Takashi Suzuki, Hidehiko Saito and Shigeo Nakamura