these cells may predict response to chemotherapy.\textsuperscript{21} While this observation is intriguing, simpler and more reproducible predictive markers have been used. However, this observation may be further explored in selecting patients for anti-angiogenesis clinical trials.

**Future issues concerning EPC**

While it has been years since anti-angiogenic therapy has been introduced for the treatment of cancer, such therapy remains only marginally effective and is associated with significant potential toxicity. Characterization of tumor-associated EPC may provide clues for more specific anti-angiogenesis therapy that may selectively target tumor vasculature, thus minimizing toxicity to normal vessels. The study by Igreja and colleagues is another step in the right direction.

### References


**Intravascular large B-cell lymphoma: the heterogeneous clinical manifestations of its classical and hemophagocytosis-related forms**

Shigeo Nakamura, Takuehi Murase, Tomohiro Kinoshita

Department of Pathology and Clinical Laboratories, Nagoya University Hospital, Nagoya, Japan (SN); Department of Internal Medicine, Nishio Municipal Hospital, Nishio, Japan (TM); Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan (TK). E-mail: snakamu@med.nagoya-u.ac.jp

In this issue, Ferreri and the International Extranodal Lymphoma Study Group document that the clinical features of patients with intravascular lymphoma (IVL) vary based on the presence or absence of hemophagocytosis (HPC), rather than geographical region, differentiating IVL into classical and HPC-related forms. IVL is defined morphologically by the distribution of tumor cells exclusively in the lumina of blood vessels. IVL has unique clinical characteristics due to massive involvement of extranodal sites, without lymphadenopathy or leukemic manifestations, and is currently regarded as a rare entity listed in the category of diffuse large B-cell lymphomas of the World Health Organization (WHO) classification.\textsuperscript{1} However, since
most of the literature on IVL is formed of single case reports or small series of patients, the broad clinical spectrum of the disease is underappreciated. In the last decade, an increasing number of reports have shed light on this disease and have led to the recognition of Asian and cutaneous variants of IVL.

IVL and HPC

HPC is accompanied by fever, cytopenia, and hepatosplenomegaly, frequently occurs in patients with infectious or autoimmune disorders, as well as malignant lymphoma, and appears to be prevalent in Asians. Therefore, the hemophagocytic syndrome often presents diagnostic and therapeutic challenges for pathologists and clinicians, in Asia. Lymphoma-associated HPC develops rapidly and, in most cases, is fatal within several months of onset, despite intensive chemotherapy. In children and young adults, HPC tends to occur with Epstein-Barr virus (EBV)-associated lymphoproliferative disorders, including nasal type NK/T-cell lymphoma. In elderly patients, HPC is more commonly seen in B-cell lymphomas. Interestingly, the majority of B-cell lymphomas with HPC as a main clinical symptom are reported in Asian patients, and it remains to be determined whether those patients constitute a clinicopathologically distinct population. In 1997, Murase et al. suggested that malignant histiocytosis-like B-cell lymphoma, a symptomatically descriptive diagnostic term, may fall within the framework of IVL, and they proposed the term Asian variant of IVL for this peculiar disease. Since then, despite considerable skepticism, Japanese clinicians have regarded HPC as a key sign of the Asian variant of IVL, providing a nation-wide group of 96 IVL patients, which to our knowledge represents the largest series of patients, for our recent analysis in Japan. In that series, bone marrow was the most frequently involved organ and this involvement was usually accompanied by HPC (Figure 1), causing symptomatic anemia (66% of the cases), thrombocytopenia (58%), and leukocytopenia (27%). However, it was rarely accompanied by neurological abnormalities or cutaneous lesions, providing additional support for our assertion that clinicopathological features in many Japanese IVL patients are consistent with the Asian variant of the disease. Of note, the Asian variant of IVL has been observed almost exclusively in Asian countries, especially Japan, with a few observations in Western countries. It should also be emphasized that hemophagocytosis is not a mandatory morphological marker of Asian variant of IVL, indicating that clinical findings of bicytopenia or pancytopenia are extremely important.

Heterogeneous symptoms of IVL

Dermatological signs specific to IVL patients were first described by Pfleger and Tappeiner in 1959. While most of those cases had a fatal course, some exceptional cases of untreated long-term survival were documented as indolent lymphomas for IVL, although the diagnosis was often incidental. Based on these traditional ideas about IVL, Ferreri and the International Extranodal Lymphoma Study Group (IELSG) highlighted a distinct IVL subgroup, the cutaneous variant, primarily diagnosed in Europeans. The cutaneous variant is characterized by skin tumors. It is predominant in females and associated with a normal platelet count; it is regarded as a favorable prognostic factor. Subsequently, the same group investigated the frequency of HPC among IVL patients in different geographical regions, including Western countries, Japan, and other Asian countries. They concluded that clinical features of IVL patients vary according to the presence or absence of HPC rather than to geographic region. There is a paucity of HPC in Western countries, where IVL is characterized as classical or HPC-related. Japanese patients with IVL and HPC frequently have advanced disease (i.e., stage IV) and related symptoms, although IVL with HPC is usually considered to be a disseminated disease, and there are few technologies and methods available to delineate the clinical stages precisely. On the other hand, the analysis by Ferreri et al. as well as our own analysis, demonstrated that, beyond clinical forms or variants, the prognosis of IVL is poor even when the age of onset, gender, and lactate dehydrogenase levels are considered. Of note, nearly all of the tumor cells are characterized by a B-cell immunophenotype with B-cell lymphoma-2 (Bcl-2) and multiple myeloma oncogene-1/interferon regulatory factor 4 (mum1/IRF4) proteins, indicating that they should be classified as non-germinal center B-cell type lymphomas.

Figure 1. Asian variant of intravascular lymphoma. Bone marrow smear showing lymphoma cells and seemingly benign histiocytes with hemophagocytosis (May-Grünwald-Giemsa stain, ×1000)
Future issues regarding aggressive extranodal lymphomas

Anatomic localization is now appreciated as a parameter for classifying diffuse large B-cell lymphomas, as exemplified by primary mediastinal large B-cell lymphoma. Of course, distinct groups of extranodal lymphomas exist, which are defined by heterogeneous presentation syndromes related to the preferentially involved organs, such as primary central nervous system lymphoma and primary testicular lymphoma, in addition to IVL. These lymphomas are consistently characterized by an aggressive clinical course and predominant or exclusive extranodal distribution, with or without mass formation and sometimes with CDS expression, despite histological differences, such as angiotropic and intravascular patterns. Concerning IVL, Ferreri et al. state, “Extensive phenotypic and molecular characterization is needed to test whether these different clinical forms may also have different biological backgrounds, and, therefore, international co-operative studies are warranted”. We agree with their proposal and believe that such trials should be extended to aggressive extranodal lymphomas, since there are few perspectives concerning the distinct clinicopathological profiles of such diseases or the basis of their mechanisms of lymphomagenesis, adhesion, and dissemination.

References