these cells may predict response to chemotherapy.[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

1. Dvorak HF. Angiogenesis: update 2005. J Thromb Haemost 2005;3:1835-42.
2. Folkman J. Role of angiogenesis in tumor growth and metastasis. Semin Oncol 2002;29 Suppl 16:15-8.
3. Garmy-Susini B, Varner JA. Circulating endothelial progenitor cells. Br J Cancer 2005;93:855-8.
4. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964-7.
5. Asahara T, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circ Res 1999; 85:221-8.
6. Kalka C, Masuda H, Takahashi T, Kalka-Moll WM, Silver M, Kearney M, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci USA 2000;97:3422-7.
7. Ribatti D. The involvement of endothelial progenitor cells in tumor angiogenesis. J Cell Mol Med 2004;8:294-300.
8. Rafii S, Lyden D, Benezra R, Hattori K, Heissig B. Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy? Nat Rev Cancer 2002;2:826-35.
9. Lyden D, Hattori K, Dias S, Costa C, Blaikie P, Butros L, et al. Impaired recruitment of bone-marrow-derived endothelial and hematopoietic precursor cells blocks tumor angiogenesis and growth. Nat Med 2001;7:1194-201.
10. Bailey AS, Jiang S, Afentoulis M, Baumann CI, Schroeder DA, Olson SB, et al. Transplanted adult hematopoietic stems cells differentiate into functional endothelial cells. Blood 2004;103:13-9.
11. Bagley RG, Walter-Yohrling J, Cao X, Weber W, Simons B, Cook BP, et al. Endothelial precursor cells as a model of tumor endothelium: characterization and comparison with mature endothelial cells. Cancer Res 2003;63:5866-73.
12. Kawamoto A, Tkebuchava T, Yamaguchi J, Nishimura H, Yoon YS, Milliken C, et al. Intramyocardial transplantation of autologous endothelial progenitor cells for therapeutic neovascularization of myocardial ischemia. Circulation. 2003;107:461-8.
13. Losordo DW, Dimmeler S. Therapeutic angiogenesis and vasculogenesis for ischemic disease: part II: cell-based therapies. Circulation 2004;109:2692-7.
14. Siepe M, Heilmann C, von Samson P, Menasche P, Beyersdorf F. Stem cell research and cell transplantation for myocardial regeneration. Eur J Cardiothorac Surg 2005; 28: 318-24.
15. Rigolin GM, Fraulini C, Ciccone M, Mauro E, Bugli AM, De Angeli C, et al. Neoplastic circulating endothelial cells in multiple myeloma with 13q14 deletion. Blood 2006; 107: 2531-5.
16. Leibundgut EO, Horn MP, Brunold C, Pfanner-Meyer B, Marti D, Hirsiger H, et al. Hematopoietic and endothelial progenitor cell trafficking in patients with myeloproliferative diseases. Haematologica 2006;91:1465-72.
17. Dentelli P, Rosso A, Balsamo A, Colmenares Benedetto S, Zeoli A, Pegoraro M, et al. c-Kit by interacting with the membrane-bound ligand recruits endothelial progenitor cells to inflamed endothelium. Blood 2007;[Epub ahead of print].
18. Igreja C, Courinha M, Cachaco AS, Pereira T, Cabecadas J, da Silva MG, et al. Characterization and clinical relevance of circulating and biopsy-derived endothelial progenitor cells in lymphoma patients. Haematologica 2007;92;469-76.
19. Dome B, Timar J, Dobos J, Meszaros L, Raso E, Paku S, et al. Identification and clinical significance of circulating endothelial progenitor cells in human non-small cell lung cancer. Cancer Res 2006;66:7341-7.
20. Zhang H, Vakil V, Braunstein M, Smith EL, Maroney J, Chen L, et al. Circulating endothelial progenitor cells in multiple myeloma: implications and significance. Blood 2005;105:3286-94.
21. Bertolini F, Paul S, Mancuso P, Monestiroli S, Gobbi A, Shaked Y, et al. Maximum tolerable dose and low-dose metronomic chemotherapy have opposite effects on the mobilization and viability of circulating endothelial progenitor cells. Cancer Res 2003;63:4342-6.

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

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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.[1] However, since

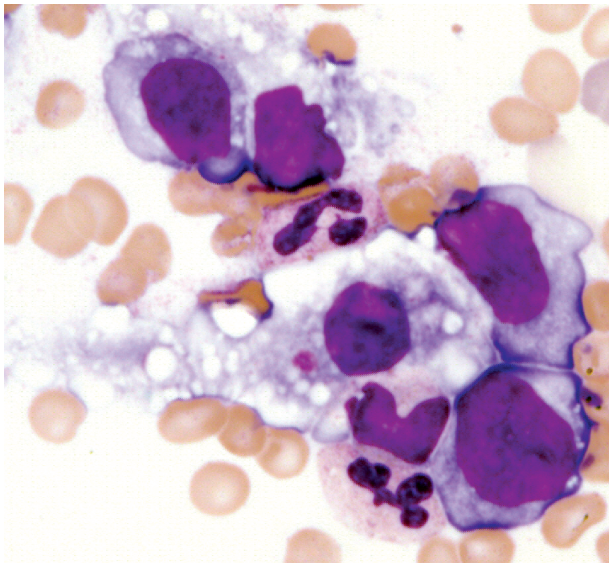

Figure 1. Asian variant of intravascular lymphoma. Bone marrow smear showing lymphoma cells and seemingly benign histiocytes with hemophagocytosis (May-Grünwald-Giemsa stain, ×1000)

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.[2-7]

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.[8,9] 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.[3] 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.[7] 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.[10] It should also be emphasized that hemo-erythrophagocytosis is not a mandatory morphological marker of Asian variant of IVL, indicating that clinical findings of bicytopenia or pancytopenia are extremely important.[4]

Heterogeneous symptoms of IVL

Dermatological signs specific to IVL patients were first described by Pfleger and Tappeiner in 1959.[2] 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.[11] 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.[5] 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.[12] 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.[7,13]

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 CD5 expression, despite histological differences, such as angiotropic and intravascular patterns.[14,15] 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.[16,17]

References

1. Gatter KC, Warnke RA. Intravascular large B-cell lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization: Pathology and Genetics of Tumors of Heamatopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 177-8.
2. Pfleger VL, Tappeiner J. Zur Kenntnis der systemisierten Endotheliomatose der cutanen Blutgef(ass)e (Reticuloendotheliose?). Der Hautarzt 1959;10:363-9.
3. Murase T, Nakamura S, Tashiro K, Suchi T, Hiraga J, Hayasaki N, et al. Malignant histiocytosis-like B-cell lymphoma, a distinct pathologic variant of intravascular lymphomatosis: a report of five cases and review of the literature. Br J Haematol 1997;99:656-64.
4. Murase T, Nakamura S, Kawauchi K, Matsuzaki H, Sakai C, Inaba T, et al. An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol 2000; 111:826-34.
5. Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol 2004;127:173-83.
6. Wu S-J, Chou W-C, Ko B-S, Tien H-F. Severe pulmonary complications after initial treatment with rituximab for the Asian-variant of intravascular lymphoma. Haematologica 2007;92:141-2
7. Murase T, Yamaguchi M, Suzuki R, Okamoto M, Sato Y, Tamaru JI, et al. Intravascular large B-cell lymphoma (IVL-BCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood 2007;109:478-85.
8. Majluf-Cruz A, Sosa-Camas R, Perez-Ramirez O, Rosas-Cabral A, Vargas-Vorackova F, Labardini-Mendez J. Hemophagocytic syndrome associated with hematological neoplasias. Leuk Res 1998;22:893-8.
9. Takahashi N, Chubachi A, Kume M, Hatano Y, Komatsuda A, Kawabata Y, et al. A clinical analysis of 52 adult patients with hemophagocytic syndrome: the prognostic significance of the underlying diseases. Int J Hematol 2001; 74: 209-13.
10. Dufau JP, Le Tourneau A, Molina T, Le Houcq M, Claessens YE, Rio B, et al. Intravascular large B-cell lymphoma with bone marrow involvement at presentation and haemophagocytic syndrome: two Western cases in favour of a specific variant. Histopathology 2000;37:509-12.
11. Bogomolski-Yahalom V, Lossos IS, Okun E, Sherman Y, Lossos A, Polliack A. Intravascular lymphomatosis-an indolent or aggressive entity? Leuk Lymphoma 1998;29: 585-93.
12. Ferreri AJM, Dognini GP, Campo E, Willemze R, Seymour JF, Bairey O, et al. Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographic regions. Hematologica 2007;92:485-91.
13. Hans CP, Weisenburger DD, Greiner TC, Gascoyne D, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-82.
14. Kanda M, Suzumiya J, Ohshima K, Tamura K, Kikuchi M. Intravascular large cell lymphoma: clinicopathological, immuno-histochemical and molecular genetic studies. Leuk Lymphoma 1999;34:569-80.
15. Yamaguchi M, Seto M, Okamoto M, Ichinohasama R, Nakamura N, Yoshino T, et al. De novo CD5$^+$ diffuse large B-cell lymphoma: a clinicopathologic study of 109 patients. Blood 2002;99:815-21.
16. Rubenstein JL, Fridyland J, Shen A, Aldape K, Grinzinger D, Batchelor T, et al. Gene expression and angiotropism in primary CNS lymphoma. Blood 2006;107:3176-23.
17. Ponzoni M, Arrigoni G, Gould VE, Del Curto B, Maggioni M, Scapinello A, et al. Lack of CD 29 (β1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Hum Pathol 2000;31:220-6.