ATYPICAL LYMPHOPROLIFERATIVE DISORDERS

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Introduction

Over 90% of humans are infected with the Epstein-Barr virus (EBV) and the infection persists for life. Most persons have a chronic asymptomatic infection with EBV, but the virus has been associated with a number of malignancies, and can infect B-cells, T-cells, NK-cells, and epithelial cells. Patients with iatrogenic, congenital, or acquired immunodeficiency are at increased risk for EBV-associated lymphomas, which are in nearly all instances of B-cell lineage. HHV-8 is another virus that has more recently been identified as associated with both clonal and polyclonal lymphoproliferative disorders (LPDs).

Chronic active EBV disease (CAEBV) has been defined as a systemic EBV-positive LPD characterized by fever, lymphadenopathy, and splenomegaly developing after primary virus infection in patients without known immunodeficiency[1]. Affected patients have high levels of EBV DNA in the blood, histological evidence of organ disease, and elevated levels of EBV RNA or viral proteins in affected tissues. While initially proposed as a progressive EBV infection of B-cells as the primary target, the term as used in the recent literature refers to an aggressive EBV-positive T-cell, NK-cell, or B-cell LPD, mainly affecting persons of Asian origin[2].

EBV-associated hemophagocytic syndrome (HPS), which can appear with CAEBV, or as a complication of other EBV-associated LPD, is due to excessive macrophage activation and hemophagocytosis[3,4]. Patients present with fever, lymphadenopathy, pancytopenia, and hepatosplenomegaly, and have marked elevation of cytokines including tumor necrosis factor [TNF]-a and interferon [IFN]-g [5,6]. The disease is often fatal, despite therapy directed at the virus-infected T-cells or NK-cells. In addition to corticosteroids or cyclosporine to inhibit cytokine production, bone marrow or hematopoietic stem cell transplant may be effective in some cases.

In recent years it has been appreciated that otherwise healthy adults of advanced age are at risk for EBV-associated B-cell lymphomas, initially reported as "senile EBV-associated B-cell LPD"[7]. Clinical series have identified a high risk of treatment failure[8,9]. This process was incorporated in the 4th Edition of the WHO classification of lymphomas as EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly[10].

Acute and chronic EBV syndromes of B cells

CAEBV infection was first identified by Straus as a disease related to chronic or persistent EBV infection of B cells[1]. It was defined as a severe illness greater than 6 months' duration that (a) begins as a primary EBV infection, or is associated with markedly abnormal EBV antibody titers (e.g. anti-EBV viral capsid antigen IgG$\geq$5,120, anti-EBV early antigen IgG$\geq$640, or anti-EBNA < 2, and (b) histological evidence of major organ involvement such as interstitial pneumonia, hypoplasia of the bone marrow, uveitis, lymphadenitis, persistent hepatitis or splenomegaly, and (c) increased EBV RNA or proteins in affected tissues. Patients who have CAEBV of B cells usually develop a progressive cellular and humoral immunodeficiency and other complications including HPS and B cell LPD. The etiology of B cell CAEBV remains uncertain.

Adult - late onset EBV-associated B-cell LPD

In recent years it has been appreciated that defective immune surveillance may develop late in

life, probably related to immune senescence, and be associated with the development of EBV-positive B-cell LPD in individuals who otherwise have no apparent immune deficiency. Aggressive EBV-positive B-cell lymphomas that occur in older individuals are often extranodal, frequently involving the skin, gastrointestinal tract, or lung[7,11,12]. Termed EBV-positive DLBCL of the elderly in the 2008 WHO classification, it is characterized by proliferation of atypical large B-cells including immunoblasts and Reed-Sternberg-like cells. Some cases have a more varied cytological composition and resemble the EBV-positive B cell lymphomas that occur in iatrogenically immunosuppressed patients. Necrosis is prominent. Patients with EBV-positive DLBCL have a worse prognosis than patients with EBV-negative DLBCL or EBV-positive classical Hodgkin lymphoma (CHL)[9,13]. Most cases occur after the age of 60 with a median age of 70-79 years, and the incidence continues to increase with age.

A novel recently identified syndrome is mucocutaneous ulcer, which is also seen in the elderly, often associated with immunosuppressive therapy. The most common sites of presentation are oropharynx, lips, gingiva, and skin. Histologically it has Hodgkin-like features and a self-limited, indolent course, generally responding well to conservative management. Association with various forms of immunosuppression implies a common pathogenetic mechanism. The localized nature of the disease may be owing to a minimal and localized lapse in immunosurveillance over EBV.

Lymphomatoid granulomatosis (LYG) is an EBV-related B-cell LPD that can affect patients with known immunodeficiency, but it also occurs in adults without any known predisposing risk factors[14]. The lungs are the most frequent site of involvement by disease (95% of patients); about 30% of patients have lesions in the kidneys, liver, skin, or central nervous system[15]. The number of EBV-infected B-cells is relatively low, in proportion to the number of T-cells identified within the lesions (T-cell rich rather than T-cell poor). However, there is evidence of defective immune surveillance, as the mean CD4 and CD8 T cell counts are below normal in most patients at diagnosis. The EBV viral load in the blood is usually not elevated. A clinical trial at the National Cancer Institute has used dose-adjusted IFN-alpha for patients with grade 1 or 2 lymphomatoid granulomatosis, and dose-adjusted EPOCH with rituximab for patients with grade 3 disease[16]. Preliminary data indicate that IFN-alpha

results in complete remissions in about 60% of patients; about 20% of patients progressed to grade 3 disease. The overall complete response rate with dose-adjusted chemotherapy was about 68%. The overall survival in patients with grades 1-3 disease was about 70% at a follow-up of about 4 years.

Acute and chronic EBV syndromes of T cells and NK cells

While CAEBV was first described as a persistent EBV infection targeting B cells, over the years the syndrome has been primarily associated with EBV infection of T cells, and less often NK cells[2]. It has a strong racial predisposition, with most cases occurring in Japan and Korea, and some cases in Native American populations in the Western Hemisphere from Mexico, Peru, and Central America. It is rare in Caucasians and African Americans. The term T/NK-cell CAEBV has been used in the literature to encompass a very broad spectrum of diseases, including a systemic form which may be polyclonal, fulminant and systemic EBV-positive T-cell LPDs that are clonal, HV of T-cell derivation, and severe mosquito bite allergy (usually of NK-cell origin). The 2008 WHO classification has recognized the following disease entities that are considered neoplasms: systemic EBV-positive T-cell LPD of childhood (a clonal T-cell LPD) and HV-like lymphoma[10].

The pathogenesis of T-cell and NK-cell CAEBV is uncertain. EBV-positive T/NK cells have been identified in the tonsils and peripheral blood from patients with infectious mononucleosis [17], and the virus has been shown to infect NK cells in vitro[18]. NK cells can acquire the EBV receptor, CD21, by synaptic transfer from B cells[19], allowing EBV binding to NK cells. T and NK cells from patients with CAEBV often have latency 2 phenotype with expression of EBV EBNA-1, LMP1, and LMP2[20]. There is evidence that defective T-cell and NK-cell responses to EBV may play a role in the pathogenesis[21,22].

While a number of therapies have been tried for CAEBV including antiviral agents (acyclovir, ganciclovir), immunomodulators (IFN-α, IL-2), chemotherapy (etoposide, corticosteroids), cyclosporine, and EBV-specific CTLs, the most effective therapy for severe CAEBV is hematopoietic stem cell transplantation. [23, 24.]

The CAEBV study group has proposed a subclassification of CAEBV based on cytological atypia and clonality. [25]. They divided cases into four categories: A1 (polymorphic and polyclonal), A2

(polymorphic and generally monoclonal), A3 (mono-morphic and monoclonal proliferation of T-cell or NK-cell origin, and B (monomorphic and monoc-lonal T-cell LPD with fulminant clinical course). The clinical course in groups A1-A3 was generally protracted with most patients surviving for several years. Group B was defined as equivalent to ful-minant EBV-positive LPD of childhood[26]; patients were under the age of five, had a fulminant clinical course that emerged soon after EBV infection, and morphology and phenotype that overlapped with Group A3. Patients with the clinical syndromes of mosquito bite allergy and HV were distributed in Groups A2 and A3. All patients had very high viral loads at presentation. Anti-EBV antibody titers were highest in A1 (VCA IgG 2560), and lowest in B (VCA IgG 160). Interestingly, antibody titers to EBV also were reported to be low in fulminant EBV-positive LPD of childhood [26] (now designated "systemic EBV-positive T-cell LPD of childhood" in the WHO classification of 2008[10]. It will be of interest to apply this classification system prospec-tively to CAEBV cases to determine its applicability as a diagnostic and prognostic system.

An unanswered issue is the distinction of HV from HV-like T-cell lymphoma, if such a distinc-tion exists. Based on the published experience, EBV and T-cell clonality have been reported in both types of cases. Some patients with HV have eventual resolution of their disease in adult life, whereas other patients develop progressive dise-ase with worsening of cutaneous symptoms and eventual systemic dissemination[27-30]. In addition, some patients with HV-like symptomatology have severe CAEBV early in the course of the disease. Thus, criteria for the distinction of HV and HV-like lymphoma remain to be defined and it is likely that these terms have not been used consistently in the literature. . The entity of HV-like lymphoma as included in the WHO classification likely encom-passes the full spectrum[31]. A related issue is severe mosquito bite allergy, which is usually of NK-cell derivation, but shows overlap with HV[32,33]. Both HV and severe mosquito bite allergy are considered part of the spectrum of CAEBV, with a broad spect-rum of clinical aggressiveness.

Lymphoproliferative Disorders associated with HHV-8

Human herpesvirus type 8 (HHV8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), was first identified as the causative agent of Kaposi's

Sarcoma[34]. Subsequently HHV8 has been iden-tified in cases of primary effusion lymphoma[35], in a majority of cases of multicentric Castleman's disease (MCD)[36] [37], in the plasmablastic prolifera-tions that arise in the setting of MCD[38], and the entity known as germinotropic LPD[39]. The majority of these cases arise in the setting of HIV-infection, with the exception of germinotropic lymphoproli-ferative disorder. More recently the spectrum of HHV-8 associated LPDs is expanding, with both monoclonal and polyclonal lesions identified [40,41]. The cells may be confected with EBV in PEL and in the germinotropic LPD, but with very different cli-nical sequelae. Additionally, there are solid forms of PEL, presenting without effusions, in both nodal and extranodal sites[42].

References

1. Straus SE. The chronic mononucleosis syndrome. J Infect Dis. 1988;157:405-412.

2. Kimura H, Hoshino Y, Kanegane H, et al. Clini-cal and virologic characteristics of chronic active Epstein-Barr virus infection. Blood. 2001;98:280-286.

3. Risdall RJ, McKenna RW, Nesbit ME, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant his-tiocytosis. Cancer. 1979;44:993-1002.

4. Su IJ, Hsieh HJ, Lee CY. Histiocytic medullary reticulosis: a lethal form of primary EBV infecti-on in young children in Taiwan [letter]. Lancet. 1989;1:389.

5. Lay JD, Tsao CJ, Chen JY, Kadin ME, Su IJ. Upre-gulation of tumor necrosis factor-alpha gene by Epstein-Barr virus and activation of macrophages in Epstein-Barr virus-infected T cells in the patho-genesis of hemophagocytic syndrome. J Clin Invest. 1997;100:1969-1979.

6. Teruya-Feldstein J, Setsuda J, Yao X, et al. MIP-1alpha expression in tissues from patients with hemophagocytic syndrome. Lab Invest. 1999;79:1583-1590.

7. Oyama T, Ichimura K, Suzuki R, et al. Senile EBV+ B-Cell Lymphoproliferative Disorders: A Clinico-pathologic Study of 22 Patients. Am J Surg Pathol. 2003;27:16-26.

8. Shimoyama Y, Oyama T, Asano N, et al. Senile Epstein-Barr virus-associated B-cell lymphoprolife-rative disorders: a mini review. J Clin Exp Hematop. 2006;46:1-4.

9. Park S, Lee J, Ko YH, et al. The impact of Epstein-Barr virus status on clinical outcome in diffuse large B-cell lymphoma. Blood. 2007;110:972-978.

10. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon, France: Internati-onal Agency for Research on Cancer; 2008.

11. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. Clin Cancer Res. 2007;13:5124-5132.

12. Shimoyama Y, Yamamoto K, Asano N, Oyama T, Kinoshita T, Nakamura S. Age-related Epstein-Barr virus-associated B-cell lymphoproliferative disorders: special references to lymphomas surrounding this newly recognized clinicopathologic disease. Cancer Sci. 2008;99:1085-1091.

13. Asano N, Yamamoto K, Tamaru J-I, et al. Age-related EBV-associated B-cell lymphoproliferative disorders: comparison with EBV-positive classical Hodgkin's lymphoma in elderly patients. Blood. in press.

14. Guinee DJ, Jaffe E, Kingma D, et al. Pulmonary lymphomatoid granulomatosis. Evidence for a proliferation of Epstein-Barr virus infected B-lymphocytes with a prominent T-cell component and vasculitis. Am J Surg Pathol. 1994;18:753-764.

15. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology, and clinical implications. Cancer Surveys. 1997;30:233-248.

16. Wilson WH, Kingma DW, Raffeld M, Wittes RE, Jaffe ES. Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. Blood. 1996;87:4531-4537.

17. Anagnostopoulos I, Hummel M, Kreschel C, Stein H. Morphology, Immunophenotype, and Distribution of Latently and/or Productively Epstein-Barr Virus-Infected Cells in Acute Infectious-Mononucleosis - Implications for the Interindividual Infection Route of Epstein-Barr-Virus. Blood. 1995;85:744-750.

18. Isobe Y, Sugimoto K, Yang L, et al. Epstein-Barr virus infection of human natural killer cell lines and peripheral blood natural killer cells. Cancer Res. 2004;64:2167-2174.

19. Tabiasco J, Vercellone A, Meggetto F, Hudrisier D, Brousset P, Fournie JJ. Acquisition of viral receptor by NK cells through immunological synapse. J Immunol. 2003;170:5993-5998.

20. Kimura H, Hoshino Y, Hara S, et al. Differences between T cell-type and natural killer cell-type chronic active Epstein-Barr virus infection. J Infect Dis. 2005;191:531-539.

21. Aoukaty A, Lee IF, Wu J, Tan R. Chronic active Epstein-Barr virus infection associated with low expression of leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) on natural killer cells. J Clin Immunol. 2003;23:141-145.

22. Kimura H. Pathogenesis of chronic active Epstein-Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? Rev Med Virol. 2006;16:251-261.

23. Okamura T, Hatsukawa Y, Arai H, Inoue M, Kawa K. Blood stem-cell transplantation for chronic active Epstein-Barr virus with lymphoproliferation. Lancet. 2000;356:223-224.

24. Kawa K, Okamura T, Yasui M, Sato E, Inoue M. Allogeneic hematopoietic stem cell transplantation for Epstein-Barr virus-associated T/NK-cell lymphoproliferative disease. Crit Rev Oncol Hematol. 2002;44:251-257.

25. Ohshima K, Kimura H, Yoshino T, et al. Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children and young adults: overlap with chronic active EBV infection and infantile fulminant EBV T-LPD. Pathol Int. 2008;58:209-217.

26. Quintanilla-Martinez L, Kumar S, Fend F, et al. Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood. 2000;96:443-451.

27. Iwatsuki K, Xu Z, Takata M, et al. The association of latent Epstein-Barr virus infection with hydroa vacciniforme. Br J Dermatol. 1999;140:715-721.

28. Barrionuevo C, Anderson VM, Zevallos-Giampietri E, et al. Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. Appl Immunohistochem Mol Morphol. 2002;10:7-14.

29. Iwatsuki K, Ohtsuka M, Akiba H, Kaneko F. Atypical hydroa vacciniforme in childhood: from a smoldering stage to Epstein-Barr virus-associated lymphoid malignancy. J Am Acad Dermatol. 1999;40:283-284.

30. Katagiri Y, Mitsuhashi Y, Kondo S, Kanazawa C, Iwatsuki K, Tsunoda T. Hydroa vacciniforme-like eruptions in a patient with chronic active EB virus infection. J Dermatol. 2003;30:400-404.

31. Quintanilla-Martinez L, Kimura H, Jaffe ES. EBV-positive T-cell lymphoproliferative disroders of childhool. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th edition). Lyon, France: International Agency for Research on Cancer; 2008:278-280.

32. Satoh M, Oyama N, Akiba H, Ohtsuka M, Iwatsuki K, Kaneko F. Hypersensitivity to mosquito bites with natural-killer cell lymphocytosis: the possible implication of Epstein-Barr virus reactivation. European Journal of Dermatology. 2002;12:381-384.

33. Zhang Y, Nagata H, Ikeuchi T, et al. Common cytological and cytogenetic features of Epstein-Barr virus (EBV)-positive natural killer (NK) cells and cell lines derived from patients with nasal T/NK-cell lymphomas, chronic active EBV infection and hydroa vacciniforme-like eruptions. British Journal of Haematology. 2003;121:805-814.

34. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266:1865-1869.

35. Nador RG, Cesarman E, Chadburn A, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood. 1996;88:645-656.

36. Dupin N, Fisher C, Kellam P, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Proc Natl Acad Sci U S A. 1999;96:4546-4551.

37. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood. 1995;86:1276-1280.

38. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood. 2000;95:1406-1412.

39. Du MQ, Diss TC, Liu H, et al. KSHV- and EBV-associated germinotropic lymphoproliferative disorder. Blood. 2002;100:3415-3418.

40. Seliem RM, Griffith RC, Harris NL, et al. HHV-8+, EBV+ multicentric plasmablastic microlymphoma in an HIV+ Man: the spectrum of HHV-8+ lymphoproliferative disorders expands. Am J Surg Pathol. 2007;31:1439-1445.

41. Ferry JA, Sohani AR, Longtine JA, Schwartz RA, Harris NL. HHV8-positive, EBV-positive Hodgkin lymphoma-like large B-cell lymphoma and HHV8-positive intravascular large B-cell lymphoma. Mod Pathol. 2009;22:618-626.

42. DePond W, Said JW, Tasaka T, et al. Kaposi's sarcoma-associated herpesvirus and human herpesvirus 8 (KSHV/HHV8)-associated lymphoma of the bowel. Report of two cases in HIV-positive men with secondary effusion lymphomas. Am J Surg Pathol. 1997;21:719-724.