EBV Positive B-Cell Lymphoproliferative Disorder

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Epstein-Barr virus (EBV) is a gamma herpes virus that infects the majority of the world population. EBV induces B-cell transformation, and disruption of a finely balanced relationship between the virus and host immune system can lead to EBV+B-cell lymphoproliferative disorders (B-LPDs), which represent a wide and expanding clinicopathological spectrum ranging from indolent and self-limited disease to aggressive lymphoma.

Keywords: Epstein-Barr virus (EBV) ; mucocutaneous ulcer ; diffuse large B cell lymphoma (DLBCL) ; lymphoproliferative ; gastrointestinal lymphoma ; gastric lymphoma ; intestinal lymphoma ; programmed cell death ligand 1 (PD-L1)

1. Introduction

Epstein-Barr virus (EBV) is a gamma herpes virus that infects the majority of the world population. EBV induces B-cell transformation, and disruption of a finely balanced relationship between the virus and host immune system can lead to EBV + B-cell lymphoproliferative disorders (B-LPDs), which represent a wide and expanding clinicopathological spectrum ranging from indolent and self-limited disease to aggressive lymphoma.

EBV + DLBCL was initially described as senile EBV-associated B-LPD by Oyama et al. in 2003 [1] and was listed as DLBCL of the elderly in the 2008 WHO classification [2][3][4]. After the original study, the development of nodal EBV + DLBCL in young patients with no evidence of immunosuppression was reported by Nicolae et al. in 2015 [5]. As a result, the 2017 WHO classification of malignant lymphoma encompassed these diverse diseases and emphasized that EBV + DLBCL, NOS often affects both young and elderly immunocompetent patients. EBV + DLBCL often presents an aggressive clinical course with frequent extranodal disease. Primary EBV + DLBCL of the GI tract (giDLBCL) accounted for 5% to 10% of consecutively diagnosed giDLBCL in a series of 62, 107, and 240 cases [6][7][8]. Although contradictory conclusions on the significance of EBV in regards to clinical outcome have been reported [5][9][10][11][12], we recently documented the negative impact of EBV in the largest series of 156 patients with gDLBCL and 51 patients with iDLBCL in the rituximab era to date [6][7].

EBVMCU is an ulcerating EBV + B-LPD with a self-limited indolent course [13]. The disease is associated with advanced age and immunosuppression, such as primary immunodeficiency, post-transplantation, and other iatrogenic causes, including methotrexate (MTX), prednisolone (PSL), azathioprine (AZA), cyclosporin A (CYA), and TNF-α antagonists [13]. The disease often involves the oropharyngeal mucosa, skin, and GI tract. In particular, EBVMCU in the GI tract (giEBVMCU) is frequently detected in patients with inflammatory bowel disease or immune-related colitis, which is the specific disease in the intestine [13][14][15][16][17][18][19]. In general, giEBVMCU responds well to conservative management, but patients with immune-related colitis are distinct from others in the high frequency of perforation requiring surgery [19].

Recent advances in immune-oncology have expanded our knowledge of immune evasion, mostly by programmed cell death ligand 1 (PD-L1) and the PD-1 pathway has become an attractive therapeutic target in various malignancies [20][21][22][23][24]. We also showed that PD-L1 immunohistochemistry aids in the differential diagnostic approach for EBV + B-LPDs and their morphological analogues [25]. EBV + DLBCL is accompanied by high PD-L1 expression but the clinicopathological significance remains to be clarified [21][26]. We further revealed that PD-L1 expression on tumor cells and non-malignant immune cells has an opposite prognostic impact in patients with giDLBCL [7][27].

2. EBV Biology and the GI Tract

EBV was the first oncogenic virus identified and it persistently infects the B cells of >95% of adults, resulting in an asymptomatic life-long carrier status [28]. The EBV life cycle is biphasic, with phases of lytic replication and latency [29]. EBV is etiologically linked to a wide range of human tumors, including gastric carcinoma, nasopharyngeal carcinoma, and lymphoma, and three EBV latency patterns have been recognized [29][30][31]. Latency I is associated with Burkitt's lymphoma and a distinct subset of gastric carcinomas, whereas Latency II is associated with classic Hodgkin's lymphoma,

extranodal NK/T-cell lymphoma, and nasopharyngeal carcinoma [32]. Latency III is linked to immunodeficiency-associated LPDs arising in the setting of immunosuppression due to HIV infection, post-transplantation, and other iatrogenic causes, such as MTX and anti-TNF-α therapy.

Some studies have reported that the presence of EBV is restricted to lymphoid cells, not benign epithelial cells, in gastritis lesions and normal colonic mucosa [33][34]. In the stomach, a positive correlation between EBVDNA load and Helicobacter pylori positivity has been reported, which suggests that the H . pylori infection could trigger EBV to switch from the latent to lytic phase of its life cycle [35][36]. In addition, EBV infection of tumor cells is detected in approximately 9% of gastric cancer (GC) cases; it is categorized as one of the major GC types and characterized by a high frequency of amplification and elevated expression of PD-L1 [37][38][39]. Notably, EBV + GC is an attractive target for anti-PD-1/PD-L1 therapy in the current era [40][41].

In the intestine, EBV replication has been reported to be associated with severe inflammatory bowel disease and mucosal inflammation [42]. The presence of EBV-infected B lymphocytes in colonic lesions of IBD may indicate a potential role of EBV in colonic immune disturbances, which may be caused by the inflammatory process itself, immunosuppressive medication, or a combination of both. In contrast, Lopes et al. showed that mucosal EBV load does not correlate with the presence of inflammation or endoscopic severity despite a higher prevalence of EBV infection in IBD [43]. Whether EBV is involved in the pathogenesis or is an innocent bystander remains unclear, but active inflammation with intramucosal expansion of EBV-infected B-lymphocytes in IBD patients may cause local impairment. In IBD patients exposed to thiopurines or anti-TNF agents, particularly in combination, the risk of LPDs, mostly associated with EBV, is higher [44][45][46]. Thiopurines are cytotoxic for NK and cytotoxic T cells, which restrict proliferation of EBV-infected and immortalized B cells, which could be associated with lymphomagenesis [47].

3. EBV-Positive Mucocutaneous Ulcer (EBVMCU)

EBVMCU, first recognized by Dojcinov et al., is defined as an ulcerating EBV + B-LPD affecting the skin and mucosal surfaces, with a typically indolent course and spontaneous regression in some cases.

EBVMCU occurs in iatrogenic immunosuppressed patients with autoimmune disorders and inflammatory bowel disease receiving MTX, CYA, AZA, TNF-α antibody, tacrolimus (Tac), or steroid treatment, in solid organ or bone marrow transplant recipients, in HIV-positive patients, after other lymphoma or tumor treatment, and in elderly patients. Elderly subjects are markedly restricted and deficient in their epitope-specific T-cell repertoire, leading to an increased risk of infection for the host [13][48].

A handful of studies have reported PD-L1 expression in EBVMCU. Satou et al. described the lack of PD-L1 expression on tumor cells in seven cases with MTX-associated EBVMCU using two different clones (SP142 and E1J2J) [49], which is consistent with findings reported by Daroontum et al. in 13 cases of EBVMCU associated with treated lymphoma or MTX [50]. Interestingly, in their subsequent series, one possibly exceptional EBVMCU case in which multiple EBV-driven B-LPDs developed after spontaneous regression of the disease was found to have PD-L1 expression on tumor cells at the time of the initial onset of EBVMCU [51]. This PD-L1 expression detected by immunohistochemistry (clone SP142) may be related to unusual clinical behavior after the spontaneous regression of EBVMCU. In contrast, Prieto et al. reported that all three cases with EBVMCU were positive for PD-L1 on large cells and HRS-like cells when using clone 28-8 [18]. This discordance in PD-L1 expression between studies is thought to be due to the use of different anti-PD-L1 antibody clones (SP142 vs. 28-8). However, a definitive conclusion cannot be drawn because of a limited number of cases examined, and this issue is expected to be clarified in a larger study.

Six patients with EBVMCU in IBD consisted of three with Crohn’s disease, two with ulcerative colitis, and one without any available information. Except for the one with Crohn’s disease presenting with an anal lesion, all cases had rectal involvement, two of which were accompanied by synchronous involvement of the colon. Macroscopically, most cases had ulcerated lesions during treatment with immunosuppressive regimens, including AZA, IFX, MTX, 6-mercaptopurine, and CYA, whereas only one used mesalazine alone and had a non-specific erythematous lesion. Interestingly, two cases had multiple lesions, which is not typical for ordinal EBVMCU [15][17]. In most EBVMCU cases with IBD, the clinical course was benign with complete recovery by reduction of immune suppression or aggressive therapy. Two patients achieved complete remission upon reduction of immune suppression. One patient with ulcerative colitis received rituximab because colonic biopsies showed persistent necrotic ulceration with EBV-positive immunoblasts after 4 weeks, though the ulcer slightly decreased in size by reduction of immune suppression and achieved complete remission [17]. The other patient with Crohn’s disease finally underwent proctectomy with terminal colostomy due to an inability to control the rectal symptoms despite cessation of AZA and IFX [16]. The third patient using only mesalazine did not receive any therapy and

presented with stable persistent disease without symptomatology for 6 months [18]. The remaining patient with Crohn's disease treated with AZA and adalimumab in the past presented an aggressive clinical course, developing widespread classic Hodgkin lymphoma 18 months after cessation of IFX and MTX [15].

4. EBV-Positive Diffuse Large B-Cell Lymphoma (EBV+ DLBCL)

Among patients with common DLBCL, the frequency of PD-L1 expression has been reported to be 6% to 26% with different cut-off values and anti-PD-L1 monoclonal antibodies [26][52][53][54]. In general, an alteration in chromosome 9p24.1 is rarely found, and the structural variations disrupting the 3′ untranslated region of the PD-L1 gene, which correlates with PD-L1 expression, is detected in 8% of common DLBCL cases [52][55]. However, whether this PD-L1 expression on malignant tumor cells has an adverse prognostic impact is still controversial [26][53][56]. PD-L1 is also expressed on nonmalignant immune cells, such as macrophages and dendritic cells in DLBCL; thus, the prognostic significance is unproven because of the paucity of reports.

In EBV + cases, EBV-LMP1 increases PD-L1 promoter and enhancer activity [57]. EBV + DLBCL has a higher frequency of PD-L1 expression on tumor cells (19–100%) and immune cells (40–100%) compared to EBV-negative DLBCL [21][26][56]. Notably, 76% of young patients with EBV + DLBCL exhibit PD-L1 positivity in the tumor cells [5]. Takahara et al. recently reported that PD-L1 expression (clone SP142-positive staining) was present in more than 5% of tumor cells in only 6 (11%) of 57 cases (95% were >45 years old) [58], clearly contrasting the 77% reported in younger cases (<45 years old) [5]. The former also indicated that PD-L1 + cases had significantly shorter progression-free survival ($p = 0.002$) and relatively short overall survival ($p = 0.26$), compared to PD-L1-negative cases.

In our series of giDLBCL patients using PD-L1 (by clone SP142) immunohistochemistry, neoplastic cell staining was considered positive for PD-L1 (nPD-L1) when ≥5% of the lymphoid cells exhibited moderate to strong membrane staining. In addition, microenvironment immune cell staining was considered positive for PD-L1 (miPD-L1) when, among the total tissue cellularity, ≥20% comprised non-malignant cells with moderate or strong membrane or cytoplasmic PD-L1-specific staining.

Thus far in the English literature, researchers first documented that PD-L1 expression on non-malignant immune cells, such as macrophages and dendritic cells, contributes to better outcomes in giDLBCL patients treated with modern immunochemotherapy.

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