Epstein–Barr virus (EBV)

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Epstein–Barr virus (EBV) is one of the most common human virus; it belongs to the Herpes virus family and is also known as Herpes virus 4. EBV is ubiquitous and is transmitted through saliva. Most individuals develop the infection during childhood or adolescence and the infection generally remains clinically silent; when primary infection is symptomatic usually follows a self-limited course manifesting as infectious mononucleosis (IM).

Keywords: Epstein–Barr virus ; EBV-positive mucocutaneous ulcer ; classic Hodgkin lymphoma ; EBV-positive ; diffuse large B-cell lymphoma

1. Epstein–Barr Virus Biology

During EBV infection, there are two phases: a lytic phase and a latent phase [1][2][3]. EBV is capable of infecting both epithelial cells and B lymphocytes. During the lytic phase, the virus replicates in the oropharynx epithelium. During the latent phase, the viral genome persists in the oropharyngeal lymphoid tissue.

The mechanism of EBV entry into B lymphocytes is based on the interaction of the major viral surface glycoprotein (gp350) with its primary receptor on B lymphocytes, so-called complement receptor 2 (CR2/CD21) or CR1 (CD35). A second viral glycoprotein (gp42) binds the class II major histocompatibility complex molecules on B lymphocytes functioning as coreceptors.

In healthy hosts, lymphoid B-cells, particularly memory B-cells, represent the EBV reservoir. To escape T-cell immune-surveillance, latent viral proteins are not expressed in memory B-cells and EBV genome remains life-long within B-cells in the episomal form.

In the latent phase, EBV gene products upregulate the expression of various B-cell genes. EBV-infected cells express six types of EBV nuclear antigen (EBNA)—EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C and EBNA leader protein—and three types of latent membrane protein (LMP), LMP1, LMP2A and LMP2B.

Depending on the specific viral expression pattern, there are three types of latency phase of EBV infection [4]. In Latency I, only EBNA1 is expressed in all infected cells; EBNA1 is the cause of viral genome maintenance and replication. Latency II is a phase of transition characterized by the expression of various proteins such as LMP1, LMP2A and LMP2B. Latency II consists of Latency IIa and Latency IIb. Latency IIa is characterized by the expression of LMP1, LMP2A and EBNA1 and it is a phase of transition to Latency III. In Latency IIa, the infected cells acquire the ability to avoid cytotoxic T lymphocytes. In Latency IIb, there is EBNA2 expression, in absence of LMP1; in Latency IIb, infected cells prepare for transition to Latency III, in which all gene products are expressed.

The BamHI Z EBV replication activator (ZEBRA) mediates disruption of latency and induction of EBV early gene expression in latently infected lymphocytes.

EBV is etiologically related to several neoplasms, including gastric carcinoma, nasopharyngeal carcinoma and different types of lymphoma [5][4].

EBV employs different mechanisms to evade the host immune response system in order to survive. The programmed cell death protein 1 (PD-1) is an immune checkpoint regulating the host immune response. The binding of PD-1 ligand 1 (PD-L1) on neoplastic cells to PD-1 on T-lymphocytes produces inhibitory signals to T-cells, allowing the tumor cells to evade the host immune system [6][7][8][9][10][11]

Recent data have demonstrated that PD-L1 expression is a common feature of EBV-linked LPDs, supporting the concept that these diseases may benefit from checkpoint inhibitor treatment, blocking the interplay between PD-1 of T lymphocytes and PD-L1 on neoplastic cells and, hence, enhancing anti-tumor immune response [12][13].

It remains not completely elucidated which viral-encoded proteins may affect PD-L1 expression and how they act, although recent studies have shown that EBV alters PD-L1 expression mainly through EBNA2 [14]. Therefore, EBNA2-positive lymphomas may have a better prognosis with immune checkpoint blockers. Further studies are required to fully explore this interesting and therapeutically relevant issue.

2. EBVMCU

2.1. General Features and Etiology

EBVMCU was first described in 2010 by Dojcinov et al. [15] in a series of EBV-positive, circumscribed and superficial mucosal and cutaneous ulcers arising in different setting of IS, including old age.

EBVMCU involves extra-nodal sites, occurring in the oropharynx (52%), skin (29%) and GIT (19%) [15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32].

In the current 2017 WHO classification, EBVMCU is identified as a provisional clinicopathological entity strictly linked to EBV [33].

Although its histology can be reminiscent of more aggressive lymphomas, such as cHL and EBV-positive DLBCL-NOS, the disease course is mostly indolent, with regression upon removal of the immunosuppressive cause. The cell of origin of EBVMCU is considered to be an EBV-transformed lymphoid B-cell [15].

EBVMCU develops in the context of iatrogenic IS (56–66%), in advanced age favored by immunosenescence (27% to 40% of cases) or in primary immunodeficiency (2% to 4% of cases) [16]. It has been reported in patients on immunosuppressive treatments such as methotrexate (MTX), cyclosporin A (CYA), Tacrolimus (Tac), prednisolone (PSL), azathioprine (AZA) or TNF-alpha inhibitors for autoimmune conditions or for solid organ/bone marrow transplantation [5][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][34][35][36][37][38][39][40][41]. EBVMCU is also reported after another lymphoma or tumor treatment [32].

The disease may emerge when the virus overwhelms the host immune response. Its hallmark is the localized and superficial nature of the ulcer, in absence of a tumor-forming lesion.

Noteworthy, the presence of a mass and/or involvement of lymph nodes, liver, spleen and bone marrow (BM) substantially excludes the diagnosis of EBVMCU [15].

The frequent localization in the oropharynx (69.3% of cases) and, less commonly, in the skin and GIT, is probably due to the release of EBV into saliva.

In immunocompromised hosts, conditions favoring EBVMCU may be represented either by a local trauma (for instance, tooth extraction) or chronic mucosal irritation [15][17]. The superficial nature of the disease and its indolent course might be explained by the occurrence of a slight and localized lapse in immune-surveillance over EBV.

2.2. EBVMCU and GIT

The occurrence of EBVMCU in GIT is rather uncommon, with just about 30 cases reported so far [15][19][20][21][22][23][24][25][26][29][30][31][32][34][35][36][37][38][39][40][41].

The most common setting is iatrogenic IS in inflammatory bowel disease (IBD) patients [15][20][21][22][30], followed by solid organ-transplanted patients [15][18][19], immune-related colitis (irColitis) [31], rheumatoid arthritis [15] and treated lymphoma [32]. Occasional cases are reported in patients with autoimmune thrombocytopenia, HIV, post-hematopoietic stem cell transplantation, hypogammaglobulinemia and rheumatic polymyalgia [23][24][40]. In a minority of GIT cases, EBVMCU develops in advanced age, without other known causes of IS [18][25][26].

In the majority of cases, iatrogenic IS either by AZA, infliximab (IFX), 6-mercaptopurine, CYA, MTX, mycophenolate mofetil (MMF), PSL and Tac is present [40].

The colon is the most commonly involved site [40].

The local irritative stimulus favoring EBVMCU occurrence may be represented by chronic mucosal inflammation in IBD [15][20][21][22][30] and irColitis [31] and even by large bowel inflamed diverticula [23][26].

The lesions are typically single, although multiple lesions are reported in IBD [21][30], in irColitis [31] and in colon diverticula [26].

EBVMCU superimposed on IBD clinically presents as a refractory IBD [22]. Its correct identification is of paramount importance, as refractory IBD is usually treated with a strong immunosuppressive therapy, whereas EBVMCU may regress with removal of iatrogenic immunosuppression [27].

Interestingly, GI EBVMCU have been recently reported in the setting of irColitis, a type of colitis related to the use of immunotherapies targeting the immune checkpoints T-lymphocyte-associated protein 4 (CTLA-4) and PD-1.

irColitis-related EBVMCU often consists of multiple ulcerating lesions, which may be complicated by colon perforation, an uncommon event in patients with EBVMCU in other settings [31][40]. In the correct clinical context, ulcerating lesions leading to perforation may be considered the hallmark of irColitis-related EBVMCU [31][40].

2.3. Histology, Immunophenotype and Genetic Profile

The ulcers are superficial and circumscribed [15]; in rare cases, multiple ulcers are reported [26][31].

On histology, the ulcers consist of EBV-positive atypical cells in the context of a polymorphic infiltrate including inflammatory cells (granulocytes, histiocytes, plasma cells) and are often associated with necrosis and apoptotic bodies.

In situ hybridization for EBV-encoded RNA (EBER) is diffusely positive. Typically, the EBV-positive cells are of different sizes, from small to large cells with Hodgkin and Reed Sternberg-like features. Angioinvasion by EBV-positive cells is a frequent finding.

The histological spectrum of EBVMCU is variable; some cases, with a more polymorphic pattern, simulate cHL and others, with a monomorphic and diffuse pattern of growth, mimic EBV-positive DLBCL-NOS [17][28].

A rather characteristic rim of small CD8 positive T lymphocytes is usually present at the base of the ulcer.

The atypical EBV-positive cells usually show strong CD30 positivity with variable expression of B-cell markers such as CD20 and CD79 alpha. PAX5, MUM1/IRF4 and the transcription factor OCT2 are usually positive, whereas BOB1 is variably expressed. CD15 is positive in 50% of cases. CD10 and BCL6 are generally negative. LMP1 is usually positive with Latency pattern IIa or III.

Clonality may be detected. About 40% of cases may harbor clonal immunoglobulin heavy chain (IGH) gene rearrangement and/or T-cell receptor (TCR) gene rearrangement [15]. Cases with T-cell clonality are more often described in the setting of age-related IS [15][16]. The presence of clonality is supposed to be the consequence of the clonal selection caused by EBV.

2.4. Differential Diagnosis

EBVMCU may display features overlapping with cHL and EBV-positive DLBCL, NOS.

Primary GI cHL is a rare event and a diagnosis of primary cHL at extra-nodal sites, including GIT, should always be made with caution.

Unlike EBVMCU, which is superficial, primary GI cHL is generally a tumor-forming lesion with transmural GI involvement [15][23]. Morphology and immunohistochemical profile of cHL are similar to EBVMCU.

Helpful histological clues observed in EBVMCU and not in cHL are the high number of EBV-positive cells of variable sizes and the small rim of CD8-positive T lymphocytes at the base of the ulcer [15].

EBV-positive DLBCL, NOS may involve both lymph nodes and extra-nodal sites, including the GIT. It usually forms a mass, diffusely effacing the tissue architecture, unlike EBVMCU. Histologically, EBV-positive DLBCL, NOS can show a monomorphic appearance quite easy to identify due to similarity with conventional diffuse large B-cell lymphoma (DLBCL). Cases of EBV-positive DLBCL, NOS with a polymorphic pattern of growth, containing Hodgkin-like cells, display features reminiscent of both cHL and EBVMCU.

In EBV-positive DLBCL, NOS, CD30 is often positive, with less frequent co-expression of CD15. Unlike EBVMCU and cHL, EBV-positive DLBCL, NOS shows a full B-cell phenotype, with expression of CD20, CD19, PAX5, CD79alfa and the

transcription factors BOB1 and OCT2 are usually positive [33][42][15]. Similarly to EBVMCU, EBV-positive DLBCL, NOS has as an activated phenotype, with positivity for MUM1/IRF4 and negativity for CD10 [33]. In order to differentiate these EBV-positive LPDs, it is of paramount importance to know the whole clinicopathological picture and particularly, the extent of the disease.

For completeness, it has to be mentioned that angioinvasion and necrosis often observed in EBVMCU may histologically resemble the angiocentric features characteristic of lymphomatoid granulomatosis (LYG) [33]. Unlike EBVMCU, LYG usually presents with nodules and lung is the most commonly involved site.

2.5. Treatment and Outcome

EBVMCU is characterized by a self-limited course, with either spontaneous remission or regression upon reduction or removal of the immunosuppressive therapy [15][17].

Only in a few cases do the patients experience a recurrence or a progressive disease. Rare cases require a therapeutic intervention, including standard radiotherapy and chemotherapy [15][28][29][41]; rituximab as single agent is reported to be effective [15][19][30].

Patients with treated-lymphoma-associated EBVMCU have been observed to have a worse behavior than patients with MTX-associated EBVMCU due to lymphoma relapse or unrelated causes [32]; therefore, EBVMCU emergence in patients treated for lymphoma may predict an adverse clinical course [32][40].

Similarly to EBVMCU arising in other sites, GI EBVMCU often follows an indolent behavior, with remission upon reduction or suspension of IS.

Progression to overt lymphoma represents a rare event as in the report of Moran et al. presenting a case of EBVMCU arising in the setting of iatrogenic IS for Crohn’s disease, in which the patient experienced progression to widespread cHL [21].

In IBD patients, the treatment strategy for IBD itself after regression of EBVMCU is not well defined, as reintroduction of immunosuppressive treatment may cause relapse of the EBV-positive LPD [40]. irColitis-related EBVMCU often leads to perforation requiring surgical resection; however, the clinical course after surgery is usually favorable [31][40].

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