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Commentary

Lingual and Lamina- EBV+ Muco-cutaneous Ulcer

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Muco-cutaneous ulcer infected with and immune reactive to Epstein Barr virus (EBV+MCU) is a contemporary clinico-pathological entity, as denominated by World Health Organization (WHO) diagnostic criteria revised in 2017. The disorder was previously designated as a lymphoproliferative lesion accompanied with isolated cutaneous or mucosal ulcerative lesions.

Generally, EBV+ muco-cutaneous ulcer incriminates elderly population or immunosuppressed individuals. Majority (~90%) of adult population is infected with Epstein Barr virus through the oral route wherein infections predominantly occur within early life.

Epstein Barr virus may persistently infect B cells in adults. Viral genes may upregulate several cellular antigens and pathways as nuclear factor kappa B (NF-κB). Generally, proliferation of B cells induced by Epstein Barr viral infection is regulated by immune system wherein a variety of factors contributing to immunosuppression may disrupt aforesaid mechanisms. Besides, Epstein Barr virus may engender diverse B cell lymphoproliferative disorders (LPDs).

Nevertheless, varying aetiologies as primary immunodeficiency, human immunodeficiency virus (HIV) infection, post-transplantation, immuno-senescence due to aging and iatrogenic factors as administration of methotrexate and tumour necrosis factor-alpha (TNF-α) antagonists may contribute to disease emergence [1,2].

Additionally, age related EBV+ lymphoproliferative disorders may ensue within elderly population in the absence of immunosuppression.

Characteristically, the contemporary EBV+ muco-cutaneous ulcer manifests as a solitary, localized, sharply circumscribed, ulcerative lesion. Generally, lesions appear within the oropharynx, cutaneous surfaces or sites within gastrointestinal tract as colon, oesophagus, rectum or terminal ileum. Cutaneous lesions may arise upon torso, dorsum and upper or lower gingiva.

A female preponderance is observed. Mean age of disease emergence is 77 years. Although systemic manifestations are absent, isolated regional lymphadenopathy may accompany the ulcer [1,2].

Of obscure aetiology, EBV+ muco-cutaneous ulcer is posited to arise as a consequence of decimated immuno-surveillance against Epstein Barr virus, especially within sites permeated with B cells infected with Epstein Barr virus as Waldeyer's ring. Alternatively, EBV+ muco-cutaneous ulcer may arise as a result of chronic irritation with subsequent decreased immune resistance and localized proliferation of B cells infected with Epstein Barr virus [1,2].

Characteristically, EBV+ muco-cutaneous ulcer manifests an ulcerated lesion unaccompanied by regional lymph node enlargement, hepatomegaly, splenomegaly or bone marrow involvement and may undergo spontaneous retrogression. The condition is commonly associated with immunodeficiency and preponderantly represents with an indolent clinical course [1,2].

Appropriate disease discernment and cogent therapy may be achieved with an amalgamation of comprehensive clinical history, morphological features, pertinent immunohistochemistry and phenotypic assessment.

The self-limiting EBV+ muco-cutaneous ulcer demonstrates monoclonal immunoglobulin heavy chain or kappa light chain and monoclonal T cell receptor (TCR) genetic rearrangements, as discerned by genotypic assays with polymerase chain reaction (PCR).

Typically, undetectable peripheral blood levels of Epstein Barr virus deoxyribonucleic acid (EBV DNA) are encountered in EBV+ muco-cutaneous ulcer, in contrast to diverse Epstein Barr virus associated lymphoproliferative disorders [1,2].

EBV+ muco-cutaneous ulcer compromises of ulcers confined to oral mucosa and various cutaneous surfaces wherein ulceration may arise due to concomitant immunosuppressive therapy. Incriminated subjects may depict weight loss or associated autoimmune diseases as Sjogren's syndrome [1,2].

Ulcerative lesions of variable magnitude appear as painful, sharply demarcated lesions with raised edges, scarring and a yellowish, fibrin imbued centric zone. Ulcerated lesions arising within oral mucosa and cutaneous surfaces may undergo spontaneous retrogression [1,2].

Characteristically, EBV+ muco-cutaneous ulcer depicts localized, mucosal or cutaneous ulcers pervaded with EBV+ atypical lymphoid cells which appear intermingled with a dense, polymorphic infiltrate of inflammatory cells as plasma cells, histiocytes and granulocytes.

Upon microscopy, EBV+ muco-cutaneous ulcer demonstrates a well circumscribed mucosal or cutaneous ulcer infiltrated with a polymorphous inflammatory infiltrate composed of histiocytes, eosinophils and plasma cells. The inflammatory exudate is admixed with enlarged, pleomorphic blasts simulating Hodgkin's Reed Sternberg (RS)-like cells, T cells of intermediate magnitude and plasmacytoid apoptotic bodies. Atypical, miniature to enlarged EBV+ cells may exhibit characteristics of B lymphocytes [1,2].

Few instances may morphologically simulate diffuse large B cell lymphoma (DLBCL) or classic Hodgkin's lymphoma (cHL). Foci of angio-invasion and disseminated necrotic debris are encountered. Histological examination depicts a sharply circumscribed cutaneous ulcer with expansion into hypodermis. The ulcer is permeated with enlarged, pleomorphic, mononuclear or binuclear, atypical lymphoid cells simulating Hodgkin's Reed Sternberg cells. The atypical lymphoid cells appear admixed with an inflammatory exudate of miniature lymphocytes, eosinophils, plasma cells and histiocytes. Apoptotic cells appear intermingled with foci of necrosis [3,4].

The mucosal ulcer delineates focal necrosis. Foci of angio-invasion are infiltrated by enlarged cells or Hodgkin's Reed Sternberg-like cells, miniature lymphocytes and occasional eosinophils.

Contingent to diverse histological features, EBV+ muco-cutaneous ulcer demonstrates cogent morphological subtypes as:

- Polymorphous subtype is a predominant category of EBV+ muco-cutaneous ulcer which manifests varying quantities of miniature to enlarged, clustered or disseminated atypical EBV+ lymphoid cells occasionally intermingled with few Hodgkin's Reed Sternberg-like cells.
- Large cell-rich subtype represents with a dense proliferation of enlarged, monomorphic, atypical EBV+ lymphoid cells, akin to cellular constituents of diffuse large B cell lymphoma [3,4].

- Classic Hodgkin's lymphoma-like subtype exemplifies a significant quantification Hodgkin's Reed Sternberg-like EBV+ cells admixed with EBV+ atypical lymphoid cells of variable magnitude. Occasionally, epithelioid cell granulomas or eosinophilic infiltration may ensue. Hodgkin's Reed Sternberg-like cells appear immune reactive to CD30.
- Mucosa associated lymphoid tissue (MALT) lymphoma-like subtype enunciates miniature to intermediate atypical lymphoid cells demonstrating centrocyte-like or plasmacytic morphological features. Cellular proliferation occurs within expanded inter-follicular zone.

Additionally, plasmablastic lymphoma (PBL)-like subtype is accompanied by superior prognostic outcomes, especially within subjects devoid of concurrent human immune deficiency virus (HIV) infection [3,4].

However, distinction of EBV+ muco-cutaneous ulcer from diverse lymphoproliferative disorders as EBV+ diffuse large B cell lymphoma, singularly upon pathological features may be challenging [3,4].

B cell lymphoproliferative disorders
EBV+ diffuse large B cell lymphoma-not otherwise specified
EBV+ muco-cutaneous ulcer
Diffuse large B cell lymphoma associated with chronic inflammation
Lymphomatoid granulomatosis
Plasmablastic lymphoma
Burkitt's lymphoma
Classic Hodgkin's lymphoma
Immunodeficiency associated lymphoproliferative disorders
Lymphoproliferative disorder associated with primary immune deficiencies
Lymphomas associated with human immune deficiency virus (HIV)
Post transplant lymphoproliferative disorders
Iatrogenic immunodeficiency associated lymphoproliferative disorders
T cell/NK cell associated lymphoproliferative disorders
EBV+ T cell/NK cell lymphoproliferative diseases of childhood
Aggressive NK cell leukaemia
Extra-nodal NK/T cell lymphoma, nasal type
Primary EBV+ nodal T or NK cell lymphoma
Chronic active EBV infection
Malignant epithelial neoplasms
Carcinoma (nasopharynx, salivary, lung, thymus, stomach, breast, urinary bladder, kidney, uterine cervix, colon)
Mesenchymal neoplasms
Smooth muscle tumour (leiomyoma/leiomyosarcoma)
Inflammatory pseudo-tumour
Inflammatory pseudo-tumour-like follicular dendritic cell sarcoma

Table: *Epstein Barr virus associated disorders [2,3].*

Enlarged pleomorphic cells appear immune reactive to CD15, CD30, OCT-2, CD20, CD79a, MUM-1, CD45, PAX5, BOB-1 and Epstein Barr virus latent membrane protein-1 (EBV LMP1). Reactive, miniature lymphocytes amalgamated upon base of ulcer appear immune reactive to CD3, CD4, CD8 and CD45 with few cells immune reactive to OCT-2, CD45 and EBV LMP-1. Also, CD8+ T lymphocytes are abundant, in contrast to CD4+ T lymphocytes.

Ki67 proliferative index may be elevated [4,5].

Ulcers arising secondary to immunosuppressive therapy may be alleviated with cessation of therapy or administration of rituximab. Although an estimated 30% instances represent with monoclonal immunoglobulin and T cell receptor (TCR) genetic rearrangements, prognostic outcomes are excellent [4,5].

EBV+ muco-cutaneous ulcer requires segregation from neoplasms such as EBV+ diffuse large B cell lymphoma (DLBCL) associated with or unaccompanied by Epstein Barr virus infection, Epstein Barr virus associated malignant lymphoproliferative disorders, classic Hodgkin's lymphoma (cHL), plasmablastic lymphoma, aggressive post-transplant lymphoproliferative disorder (PTLD), primary cutaneous anaplastic large cell lymphoma or lymphomatous granulomatosis (LyG) [4,5].

In the absence of recommended therapeutic guidelines, conservative management of EBV+ muco-cutaneous ulcer is optimal. Relevant instances may be managed with withdrawal or decimation of immune-suppressants [4,5].

Majority (~65%) of immunosuppressive-associated EBV+ muco-cutaneous ulcers may progress to complete clinical remission singularly with reduction of dosage and a median duration of lesion resolution of 4 weeks although clinical regression may occur within 2 weeks to 12 weeks. Lack of therapeutic response towards withdrawal or decimated doses of immunosuppressant within three months mandates re-evaluation of diagnosis [4,5].

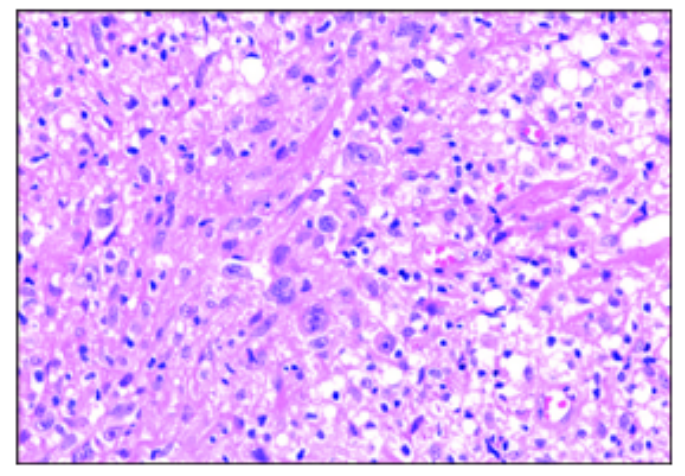

Figure 1: *EBV+ muco-cutaneous ulcer depicting ulcerated mucosa imbued with enlarged, atypical lymphocytes admixed with an inflammatory infiltrate of small lymphocytes, plasma cells, histiocytes and few eosinophils [6].*

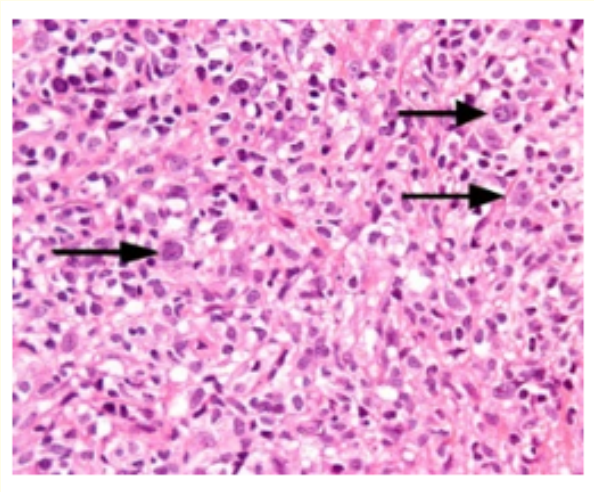

Figure 2: *EBV+ muco-cutaneous ulcer delineating an ulcerated lesion incorporated with enlarged, atypical lymphocytes with commingled inflammatory cells as small lymphocytes, histiocytes, plasma cells and few eosinophils [7].*

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6. Image 1 Courtesy: Research gate.
7. Image 2 Courtesy: Science direct.

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