Epstein-Barr Virus–associated Lymphoproliferative Disorders in the Skin

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KEYWORDS

• Skin • EBV • Mucocutaneous ulcer • Lymphomatoid granulomatosis
• Diffuse large B-cell lymphoma • Hydroa vacciniforme • Extranodal NK/T-cell lymphoma
• Immunosuppression

Key points

- Epstein-Barr virus (EBV)–associated lymphoproliferations involving the skin are rare, may be of B, T, or natural killer (NK) cell lineage, and encompass a spectrum of clinical behavior requiring different approaches to treatment.
- EBV-positive B-cell lymphoproliferations that frequently involve the skin include EBV-positive mucocutaneous ulcer, lymphomatoid granulomatosis, and EBV-positive diffuse large B-cell lymphoma.
- These show overlapping pathologic features but can be separated with close attention to pathologic detail and clinical features.
- The most frequently encountered cutaneous EBV-positive lymphoproliferations of T or NK cell type are hydroa vacciniforme–like lymphoproliferative disorder and extranodal NK/T-cell lymphoma, nasal type.
- These disorders also share many pathologic features and clinical correlation is essential in differentiating the more indolent from the more aggressive forms of disease.

ABSTRACT

Epstein-Barr virus (EBV)–associated lymphoproliferations involving the skin are a rare but important group of diseases with a broad spectrum of behavior, ranging from self-limiting spontaneously resolving disorders to highly aggressive malignancies. They may be of B, T, or natural killer (NK) cell type and include EBV-positive mucocutaneous ulcer, lymphomatoid granulomatosis, EBV-positive diffuse large B-cell lymphoma, hydroa vacciniforme–like lymphoproliferative disorder, and extranodal NK/T-cell lymphoma of nasal type. Recognition and distinction of these entities is important in view of their differing prognoses and treatments. An association with EBV may be the first indication that a patient is immunosuppressed.

OVERVIEW

Epstein-Barr virus (EBV), formally designated human herpesvirus 4, is a ubiquitous gamma herpes virus that infects approximately 90% of the population worldwide.[1] In most cases, infection occurs in childhood and is asymptomatic, although a minority who are infected in adolescence or adulthood present with infectious mononucleoisis.[2,3] Following acute infection the virus assumes a latent state in which it persists in circulating B lymphocytes without active viral production. In the

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latent state EBV is maintained through expression of a limited number of viral transcripts and proteins that affect the host cell cycle, promoting cellular proliferation and inhibiting apoptosis. In healthy individuals this proliferation is limited by the host immune system. However, when host immunity is compromised, EBV-driven cell division can go unchecked, producing a variety of lymphoproliferative disorders (LPDs).[2–4]

Immune dysregulation leading to EBV-associated LPDs is well documented in association with organ transplant, iatrogenic immunosuppression for a variety of autoimmune diseases, congenital immune deficiency, and human immunodeficiency virus (HIV) infection,[4] and age-related immune senescence has more recently been recognized as a predisposing factor.[5–7] In addition, EBV is implicated in a variety of other LPDs in apparently immune-competent patients, including classic Hodgkin lymphoma, Burkitt lymphoma, some cases of diffuse large B-cell lymphoma (DLBCL) in young patients, and extranodal natural killer (NK)/T-cell lymphoma of nasal type.[2–4,8–10]

EBV-associated LPDs encompass a broad spectrum of disease and include disorders of B, T, and NK cells. These disorders range in severity from benign self-limiting conditions to aggressive, rapidly fatal malignancies. Although most commonly encountered and recognized in lymph nodes and noncutaneous extranodal sites, the skin too may be the site of presentation, although this fact is often under-recognized. Although virtually any lymphoma can involve the skin, often as a consequence of disseminated disease, this article focuses on EBV-associated lymphoproliferations that preferentially or frequently present at cutaneous sites and that illustrate the range of behavior within this enigmatic group of diseases, highlighting the importance of accurate diagnosis to facilitate appropriate management.

EPSTEIN-BARR VIRUS–ASSOCIATED B-CELL LYMPHOPROLIFERATIVE DISORDERS IN THE SKIN

Well-defined EBV-associated lymphomas of B-cell origin, such as Burkitt lymphoma and classic Hodgkin lymphoma, only rarely involve the skin and, when present, this is usually the result of direct extension from underlying nodal disease or a late manifestation of extensive dissemination.[11–13] This article focuses on 3 entities that are either localized to the skin at presentation or represent conditions that frequently present in the skin, or involve cutaneous sites during the course of the disease.

EPSTEIN-BARR VIRUS–POSITIVE MUCOCUTANEOUS ULCER

EBV-positive (EBV+) mucocutaneous ulcer (MCU) is a recently described disorder that arises on a background of immune senescence in apparently healthy elderly individuals, in patients receiving immunosuppressive therapy after organ transplant, or following treatment of autoimmune disease.[14–18] In the context of autoimmune disease, methotrexate is the most commonly implicated drug.[14,16,17,19] The pathogenesis of EBV+ MCU is not fully established but it is hypothesized that immune surveillance is reduced to a level that is only just sufficient to maintain EBV in a dormant state systemically. Additional localized factors are then thought to tip the balance toward an EBV-driven lymphoproliferation at the affected site, often corresponding with locations where EBV-infected cells are prevalent, such as Waldeyer's ring.[14]

The disease is characterized by the development of a solitary, well-circumscribed, often painful ulcerating lesion at a mucosal or cutaneous site. Oropharyngeal mucosa is the most frequent site of presentation. Cutaneous involvement is often perioral but other acral sites or the trunk may be affected.[14,16,19,20] Any part of the gastrointestinal tract may be involved and patients occasionally present with a variety of abdominal symptoms, including as abdominal emergencies.[18] There is no detectable underlying mass lesion, either on clinical examination or imaging, and no associated lymphadenopathy or splenomegaly.[18] EBV DNA is typically undetectable in peripheral blood, in contrast with many other types of EBV-associated LPDs.[18]

Biopsy reveals a circumscribed shallow ulcer, the base of which contains a polymorphous infiltrate comprising variable numbers of immunoblasts and large atypical Reed-Sternberg–like cells. An admixture of small lymphocytes, plasma cells, histiocytes, and eosinophils is present and plasmacytoid apoptotic cells are usually prominent. Vascular invasion with thrombosis and sometimes necrosis is present in a significant proportion. The base of the lesion is sharply defined by a rim of small lymphocytes (**Figs. 1** and **2**). In squamous mucosa and skin there may be reactive epithelial atypia, and pseudoepitheliomatous hyperplasia is often present.[14,18] The immunoblasts and Reed-Sternberg–like cells are EBV-positive B cells that are uniformly CD30 and, in some, CD15 positive. Although CD20 is downregulated in a proportion of cases, these blast cells typically