Epstein–Barr virus: Dermatologic associations and implications

Part II. Associated lymphoproliferative disorders and solid tumors

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Learning objectives
After completing this learning activity, participants should be able identify lymphoproliferative disorders and malignant disorders associated with EBV, and describe the EBV-related diseases that occur in the immunocompromised host.

Disclosures
None declared.

Epstein–Barr virus (EBV) was the first human virus to be associated with oncogenesis. Over the past few decades, cumulative research has revealed that latent EBV infection may be implicated in the pathogenesis of a heterogeneous group of lymphoproliferative disorders and malignancies occurring in both immunocompetent and immunocompromised hosts. Many of these diseases have either primary or secondary cutaneous manifestations. Serologic studies and EBV-encoded RNA in situ hybridization stains have been used to show the association of EBV with disease; while these findings may imply a role, they do not equate with causation. In part II of this continuing medical education review, the salient features of EBV-associated lymphoproliferative disorders and solid tumors are detailed. (J Am Acad Dermatol 2015;72:21-34.)

Key words: angioimmunoblastic T-cell lymphoma; Burkitt lymphoma; diffuse large B-cell lymphoma; Epstein–Barr virus; gastric carcinoma; hemophagocytic syndrome; Hodgkin lymphoma; hydroa vacciniforme–like lymphoma; leiomyosarcoma; lymphomatoid granulomatosis; nasopharyngeal carcinoma; NK/T-cell lymphoma; posttransplant lymphoproliferative disorder.

INTRODUCTION

Epstein–Barr virus (EBV) has been associated with a range of lymphoproliferative disorders and solid tumors. It behooves both the dermatologist and dermatopathologist to understand these associations, because this knowledge may aid in the diagnosis, prognosis, and monitoring of disease. Serologic studies have been used to show an association with EBV, and for some diseases, titers may carry prognostic significance. EBV-encoded RNA (EBER) in situ hybridization (ISH) stains can be used to aid in the histologic diagnosis of EBV-associated malignancies. However, while these findings may imply a role and can aid in the diagnosis, they do not equate with causation. In part II of this continuing medical education article, the salient features of EBV-associated lymphoproliferative disorders and solid tumors are detailed (Table I).

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Abbreviations used:

AITL:	angioimmunoblastic T-cell lymphoma
BL:	Burkitt lymphoma
CAEBV:	chronic active Epstein–Barr virus
DLBCL:	diffuse large B-cell lymphoma
EBER:	Epstein–Barr virus–encoded RNA
EBNA:	Epstein–Barr virus nuclear antigen
EBV:	Epstein–Barr virus
ENK/T:	extranodal natural killer/T-cell lymphoma
HL:	Hodgkin lymphoma
HPS:	hemophagocytic syndrome
HRS:	Hodgkin and Reed–Sternberg-like
HV:	hydroa vacciniforme
HVLL:	hydroa vacciniforme–like lymphoma
ISH:	in situ hybridization
LMP1:	latent membrane protein-1
LYG:	lymphomatoid granulomatosis
MF:	mycosis fungoides
NHL:	non-Hodgkin lymphoma
PCR:	polymerase chain reaction
PTLD:	posttransplant lymphoproliferative disease
SPTCL:	subcutaneous panniculitis-like T-cell lymphoma
TIA-1:	T-cell intracellular antigen-1
VCA:	viral capsid antigen

MATURE B-CELL NEOPLASMS

Burkitt lymphoma

Key points

- **Burkitt lymphoma is an aggressive B-cell lymphoma that is subdivided into 3 categories: endemic, sporadic, and HIV-related**
- **Cutaneous involvement, presenting as erythematous nodules and plaques, is rare**
- **Endemic Burkitt lymphoma is the subtype that is most commonly associated with Epstein–Barr virus infection**

Burkitt lymphoma (BL) is an aggressive, poorly differentiated B-cell lymphoma.[1,2] It is the fastest growing tumor in humans, with an extremely short doubling time of 24 to 48 hours.[3] BL is classified as a non-Hodgkin lymphoma and is further subdivided into 3 categories: endemic, sporadic, and HIV-related BL.[3,4] Endemic BL most frequently arises in the head and neck, while sporadic BL usually presents with abdominal involvement, and HIV-related BL often affects the lymph nodes and bone marrow.[4] Infrequently, cutaneous involvement occurs, presenting as well demarcated erythematous nodules and plaques.[1,2] Skin disease results from both lymphatic and hematologic spread. Cutaneous lesions may also appear iatrogenically at sites of catheter insertion or previous surgical procedures.[2]

EBV was first discovered in cultured cell lines from endemic BL.[3,5-7] However, the exact mechanisms linking EBV infection to lymphomagenesis are not completely understood. EBV nuclear antigen 1 (EBNA1) is consistently expressed in endemic BL.[3] Endemic BL is most closely associated with EBV infection; in areas where malaria is holoendemic (ie, Africa, Brazil, and Papua New Guinea), virtually all cases of endemic BL are associated with EBV infection.[8] Coinfection with malaria increases the levels of circulating EBV, and children with antibodies against both EBV and *Plasmodium falciparum* have the highest risk of developing BL.[3,9,10] While both EBV and *P falciparum* are acknowledged as cofactors in the development of endemic BL, the exact mechanisms are not entirely clear.[11] In contrast, EBV is present in only 30% of sporadic BL, and only 25% to 40% of tumors in patients with HIV-related BL.[12] In addition, BL contains translocations that activate the c-myc protooncogene, a key factor in the pathogenesis of BL.[1,3,12]

Histologically, cutaneous BL is characterized by an atypical lymphocytic infiltrate in the dermis and subcutis composed of monomorphic, medium-sized, mitotically-active lymphocytes expressing CD20, CD79a, CD10, and BCL6.[1,3,8,13] Tingible body macrophages containing apoptotic lymphocytes result in a "starry sky" appearance.[3]

BL follows an aggressive disease course but is potentially curable.[12] Chemotherapy is the mainstay of treatment, with an overall cure rate of approximately 90% in developed countries.[3] Rituximab may be a useful adjunctive agent.[3]

Lymphomatoid granulomatosis

Key points

- **Lymphomatoid granulomatosis is an aggressive B-cell lymphoproliferative disorder that primarily affects the lungs**
- **Cutaneous findings include subcutaneous nodules, plaques, or ulcers, erythematous macular rashes, or erythroderma**

Lymphomatoid granulomatosis (LYG) is a rare, aggressive, angioinvasive lymphoproliferative disorder of EBV^+ B cells associated with a large population of reactive, infiltrating T cells.[14,15] Lung involvement is present in nearly all patients, but other organs may also be affected, including the kidneys, liver, central nervous system, or skin.[16,17] Cutaneous lesions occur in >40% of patients and include subcutaneous nodules, plaques, or ulcers, erythematous macular rashes, or erythroderma.[18-23] Not uncommonly, these cutaneous findings may represent the first sign of disease.[20-22] Middle-aged adults are most commonly affected.[24]