Human oncoviruses: Mucocutaneous manifestations, pathogenesis, therapeutics, and prevention

Hepatitis viruses, human T-cell leukemia viruses, herpesviruses, and Epstein–Barr virus

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Learning objectives
After completing this learning activity, participants should be able to recognize mucocutaneous manifestations of cancers associated with hepatitis B, hepatitis C, Epstein-Barr virus, human T-cell lymphotropic virus-1, and human herpesvirus-8 and describe risk factors, key pathogenic events, prevention, and therapies for these cancers.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

In 1964, the first human oncovirus, Epstein–Barr virus, was identified in Burkitt lymphoma cells. Since then, 6 other human oncoviruses have been identified: human papillomavirus, Merkel cell polyomavirus, hepatitis B and C viruses, human T-cell lymphotropic virus-1, and human herpesvirus-8. These viruses are causally linked to 12% of all cancers, many of which have mucocutaneous manifestations. In addition, oncoviruses are associated with multiple benign mucocutaneous diseases. Research regarding the pathogenic mechanisms of oncoviruses and virus-specific treatment and prevention is rapidly evolving. Preventative vaccines for human papillomavirus and hepatitis B virus are already available. This review discusses the mucocutaneous manifestations, pathogenesis, diagnosis, treatment, and prevention of oncovirus-related diseases. The first article in this continuing medical education series focuses on diseases associated with human papillomavirus and Merkel cell polyomavirus, while the second article in the series focuses on diseases associated with hepatitis B and C viruses, human T-cell lymphotropic virus-1, human herpesvirus-8, and Epstein–Barr virus. (J Am Acad Dermatol 2019;81:23-41.)

Key words: adult T-cell leukemia/lymphoma; Epstein–Barr virus; hepatitis B virus; hepatitis C virus; hepatocellular carcinoma; human herpesvirus-8; human T-cell lymphotropic virus-1; Kaposi sarcoma; oncovirus.

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication October 2, 2018.
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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.10.072
Date of release: July 2019
Expiration date: July 2022

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Abbreviations used:

ATLL:	adult T-cell leukemia/lymphoma
DAA:	direct acting antiviral
EBV:	Epstein–Barr virus
FDA:	Food and Drug Administration
GCS:	Gianotti–Crosti syndrome
HBV:	hepatitis B virus
HCC:	hepatocellular carcinoma
HCV:	hepatitis C virus
HHV-8:	human herpesvirus-8
HPV:	human papillomavirus
HTLV-1:	human T-cell lymphotropic virus 1
IDH:	infective dermatitis
KS:	Kaposi sarcoma
LMP:	latent membrane protein
LP:	lichen planus
LPD:	lymphoproliferative disorders
MC:	mixed cryoglobulinemia
NA:	nucleos(t)ide analogue
NAE:	necrolytic acral erythema
PAN:	polyarteritis nodosa
PCT:	porphyria cutanea tarda
peg-IFN:	pegylated interferon
PTLD:	posttransplant lymphoproliferative disorders
SSLR:	serum sickness–like reaction
UROD:	uroporphyrinogen decarboxylase

HEPATITIS B VIRUS

Key points

- **Hepatitis B virus induces hepatocarcinogenesis through viral genome integration, actions of oncogenic proteins (surface and hepatitis B virus X proteins), and chronic inflammation**
- **Plasma-derived and recombinant hepatitis B virus vaccines provide similar immunogenicity and cost-effectiveness**
- **Serum sickness–like reaction, polyarteritis nodosa, and Gianotti–Crosti syndrome are hepatitis B virus–associated dermatologic manifestations caused by immune complex deposition**

Hepatitis B virus (HBV) is a DNA virus that is transmitted through percutaneous or mucosal contact with infected body fluids.[1] Chronic HBV infection is a risk factor for multiple mucocutaneous diseases and hepatocellular carcinoma (HCC), which develops decades after the initial infection.[2] HBV-induced oncogenesis primarily occurs because of viral genome integration into the host genome, causing mutations in 80% to 90% of HBV-related HCC.[3] HBV oncogenic proteins (surface and hepatitis B virus X proteins) also contribute to tumor development by inducing high cellular proliferation and mutation rates.[4-6] In addition, HBV-induced chronic inflammation can contribute to hepatocarcinogenesis.[2]

Serologic tests are useful in confirming HBV infection. Hepatitis B surface antigen (HBsAg), total antibody to hepatitis B core protein, and anti-HBc-immunoglobulin M are positive during acute infection.[7] Early in the infection during the window period, anti-HBc-immunoglobulin may be the only marker detected.[7] In addition, alanine aminotransferase and aspartate aminotransferase are markedly elevated in acute HBV infection, typically in the range of 1000 to 2000 IU/L.[8]

The current treatment recommendations for HBV infection are influenced by patient and virologic factors, such as HBV genotype, disease chronicity, treatment history, the presence of cirrhosis, and the presence of extrahepatic manifestations.[9] Treatment options include pegylated interferon (peg-IFN) or nucleos(t)ide analogues (NAs), which are similarly effective. Peg-IFN, entecavir, or tenofovir

Table I. Pegylated-interferon versus nucleos(t)ide analogues for chronic hepatitis B virus infection*

Therapy	Mechanism of action	Advantages	Disadvantages
Pegylated-interferon	Induces long-term immunologic response	Finite duration of therapy; absence of viral resistance; response durable posttherapy; increase in HBsAg seroconversion rate	Highly variable response rate; frequent side effects; expensive; weekly subcutaneous injection; frequent laboratory monitoring on treatment
Nucleos(t)ide analogues: lamivudine, telbivudine, emtricitabine, entecavir, adefovir, and tenofovir	Inhibits viral replication	Daily oral dosing; minimal side effects in the short term; proven efficacy in patients with advanced liver disease; less expensive during first year, possibly equally or more costly after long-term therapy	Risk of resistance; limited increase in HBsAg seroconversion rate; response less durable posttherapy; long-term or indefinite therapy may be required

HBsAg, Hepatitis B surface antigen.
*Adapted with modifications from Sonneveld and Janssen.[10]

Table II. Formulations of hepatitis B vaccine*

	Single-antigen vaccines						Combination vaccines					
	Recombivax HB			Engerix-B			Pediarix†			Twinrix		
Age group	Dose (mcg)	Volume (mL)	Schedule	Dose (mcg)	Volume (mL)	Schedule	Dose (mcg)	Volume (mL)	Schedule	Dose (mcg)	Volume (mL)	Schedule
Infants (<1 y)	5	0.5	0, 1, and 6 months	10	0.5	0, 1, and 6 months	10	0.5	2, 4, and 6 months	N/A	N/A	N/A
Children (1-10 y)	5	0.5	0, 1, and 6 months	10	0.5	0, 1, and 6 months	10	0.5	2, 4, and 6 months	N/A	N/A	N/A
Adolescents (11-19 y)	5‡	0.5	0, 1, and 6 months	10	0.5	0, 1, and 6 months	N/A	N/A	N/A	N/A	N/A	N/A
Adults (>20 y)	10	1.0	0, 1, and 6 months	20	1.0	0, 1, and 6 months	N/A	N/A	N/A	20§	1.0	0, 1, and 6 months
Hemodialysis patients and other immunocompromised persons	40	1.0	0, 1, and 6 months	40	2.0	0, 1, 2, and 6 months	N/A	N/A	N/A	N/A	N/A	N/A

*Adapted from the Centers for Disease Control and Prevention.[16]
†May be given as early as 6 weeks of age through 6 years of age (before the seventh birthday).
‡Alternative dosing for adolescents 11-15 years is a series of 2 doses (1.0 mL) on a 0- and 4- to 6-month schedule.
§Accelerated dosing given as a series of 4 doses (1.0 mL each) on days 0, 7, and 21 to 30 followed by a booster dose at month 12.

monotherapy is preferred because of its lower resistance with long-term use (Table I).[9,10] Long-term combined treatment with peg-IFN and NAs may be more effective in select patient populations.[11] However, the disadvantages of combination therapy include higher cost, higher rates of side effects, lower adherence rates because of regimen complexity, and the risk of multidrug-resistant HBV.[12]

HBV infection is a preventable disease. Two types of hepatitis B vaccines are available, plasma-derived and recombinant, with no differences in reactogenicity, efficacy, duration of protection, or cost.[13-15] Recombinant vaccines are generally favored because they provide less exposure to foreign antigens and are available as monovalent formulations or in combination with other vaccines (Table II).[16]

Dermatologic manifestations

While HBV infection primarily affects the liver, causing symptoms such as malaise, nausea, vomiting, dark urine, and jaundice, the skin may also be affected. Table III provides an overview of HBV-associated dermatologic conditions including serum sickness–like reaction (SSLR), polyarteritis nodosa (PAN), and Gianotti–Crosti syndrome (GCS).

A transient SSLR develops in approximately 10% to 20% of patients with acute HBV infection.[17] The condition presents with fever, skin rash (pruritic, erythematous, macular, maculopapular, urticarial, nodular, or petechial lesions), and polyarthritis. Symptoms often precede jaundice by days to weeks and subside shortly after the onset of jaundice but can persist throughout the duration of acute HBV infection. In contrast to true serum sickness, significant decreases in serum complement levels rarely occur.[17] Patients with SSLR often have normal or mild decreases in serum complements and high-level circulating immune complexes composed of hepatitis B surface antigen and complement components.[17]

PAN is an immune-mediated necrotizing vasculitis that affects approximately 30% of HBV carriers.[18,19] The kidneys, heart, nervous system, and skin are most frequently involved. Generalized symptoms often develop early in the course of illness and include high fever, weakness, malaise, and weight loss. Skin involvement occurs as palpable purpura, tender subcutaneous nodules, livedo reticularis, erythematous rashes, or ulcers (Fig 1, *A*). The diagnosis is primarily clinical because histopathologic findings are nonspecific. Untreated PAN has a 5-year survival rate of 13%, but treatment with high-dose corticosteroids improves the survival rate to 80%.[18]

GCS is a benign skin reaction to acute HBV in childhood, although other reported pathogens

Table III. Hepatitis B virus–associated dermatologic manifestations, skin findings, diagnosis, and therapy

Manifestation	Skin findings	Diagnosis	Therapy
Serum sickness–like syndrome	Erythematous, macular, maculopapular, urticarial, nodular, or petechial lesions that are often intensely pruritic[17]	Diagnosis is frequently based on clinical findings; obtaining a biopsy is generally not warranted; histopathologic features: dermal edema, perivascular lymphocytic infiltrate, and other urticarial/dermal hypersensitivity–like changes[122]; laboratory findings: normal or mild decreases in serum C3, C4, and CH50 levels, mild proteinuria, leukocytosis, and elevated ESR[122]	Withdrawal of the inciting agent and symptomatic treatment with antihistamines or corticosteroids[122]
Polyarteritis nodosa	Palpable purpura, tender subcutaneous nodules, livedo reticularis, erythematous rashes, or ulcers[17]	Diagnosis is based on clinicopathologic correlation; histopathologic features: leukocytoclastic vasculitis involving small- and medium-sized blood vessels with or without fibrinoid necrosis, occasionally with a surrounding panniculitis[18]	Treat the underlying HBV infection; cutaneous PAN can be treated with NSAIDs while systemic PAN is usually treated with high-dose corticosteroids; immunosuppressive agents may be helpful in refractory cases[123]
Gianotti–Crosti syndrome	Symmetric small, flat, erythematous, papular eruptions frequently found on the face, buttock, and extensor surfaces of arms and legs, usually occurring in infants and young children[17]	Diagnosis is frequently based on clinical findings; obtaining a biopsy specimen is generally not warranted; histopathologic features: epidermal spongiosis with marked papillary dermal edema in a background of a mixed mononuclear cell infiltrate consisting of lymphocytes and histiocytes[20]	Spontaneous resolution over several weeks; symptomatic treatment with antihistamines or soothing lotions[20]

ESR, Erythrocyte sedimentation rate; *HBV*, hepatitis B virus; *NSAID*, nonsteroidal antiinflammatory drug; *PAN*, polyarteritis nodosa.

include Epstein–Barr virus (EBV), hepatitis A virus, hepatitis C virus (HCV), cytomegalovirus, coxsackievirus, adenovirus, enterovirus, HIV, and others.[17,20] The condition is characterized by nonpruritic, small, erythematous, papular eruptions on the face and extremities (Fig 1, *B*). GCS precedes or follows the onset of jaundice and lasts 2 to 3 weeks.[17]

HEPATITIS C VIRUS

Key points

- **Chronic inflammation is the principal mechanism of hepatocarcinogenesis in hepatitis C virus infection**
- **Hepatitis C virus testing should be considered in patients who present with associated dermatologic manifestations**
- **Hepatitis C virus genetic variability and viral escape from neutralizing antibodies contribute to the slow progress of hepatitis C vaccine development**

HCV is an RNA virus that is transmitted through the same routes as HBV.[4,21] In the United States, chronic HCV infection is the greatest risk factor for HCC.[22] HCV-related HCC primarily occurs as a result of inflammation and fibrosis, rather than viral genome-induced transformation of cells.[21] The inflammatory process is mediated by reactive oxygen species and cytokines released during hepatocyte death that activate key transcription factors to drive protumorigenic processes.[2]

Treatment options for chronic HCV infection are direct acting antivirals (DAAs) and IFN-based therapies (Table IV). DAAs are preferred over IFNs because of their superior efficacy and fewer side effects. Possible adverse effects include flu-like symptoms, neuropsychiatric effects, and transient mild cutaneous reactions early in treatment. Severe

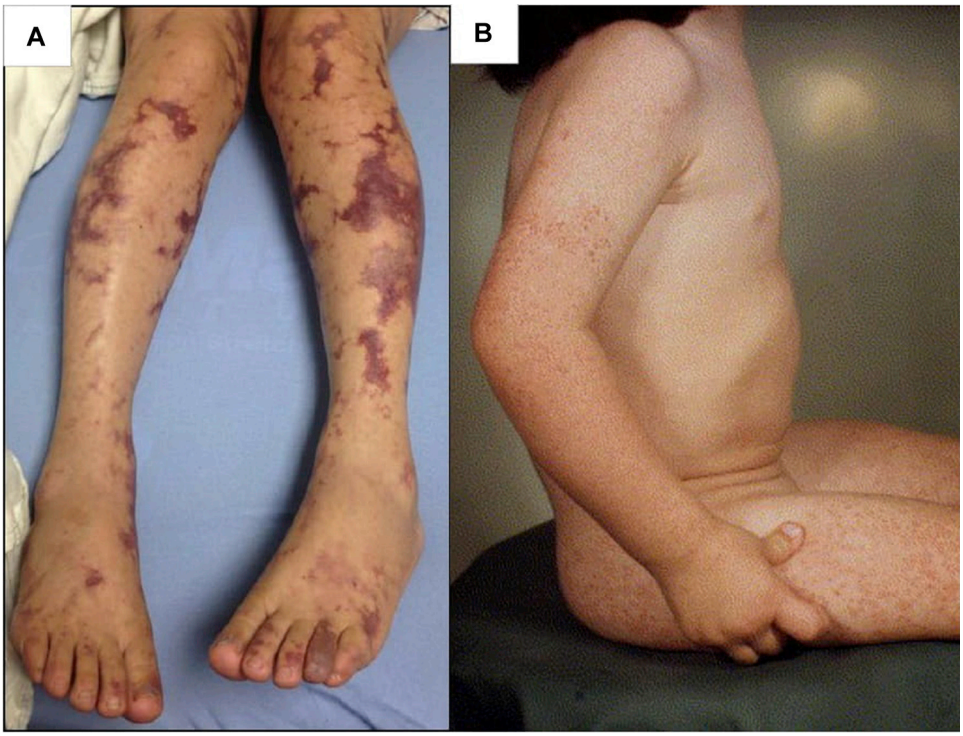


Fig 1. Cutaneous manifestations associated with hepatitis B infection. **A**, Polyarteritis nodosa. Reprinted with permission from Parperis and Rast.[130] **B**, Gianotti–Crosti syndrome. Reprinted with permission from Brandt et al.[20]

ulceration and skin necrosis have also been reported.[23] Potentially life-threatening side effects, such as autoimmune thyroiditis, pulmonary interstitial fibrosis, and liver, renal, and cardiac impairment, occur in 0.1% to 1% of patients.[24] Despite the considerable side effects, IFN-based therapies remain important adjuncts to DAAs in recalcitrant cases.

No HCV vaccine is currently available. Challenges to vaccine development include genetic variability and viral escape from neutralizing antibodies. Recent progress in the understanding of virus–host interaction will help identify highly conserved epitopes and cross-neutralizing antibodies to aid in the development of a prophylactic vaccine.[25]

Dermatologic manifestations

HCV-associated dermatologic manifestations include mixed cryoglobulinemia (Fig 2, *A*), necrolytic acral erythema (NAE; Fig 2, *B*), lichen planus (Fig 2, *C*), and porphyria cutanea tarda (PCT; Table V). Mixed cryoglobulinemia (MC) is the most common dermatologic manifestation of chronic HCV infection.[26] MC is a systemic vasculitis caused by deposition of circulating immune complexes in small- and medium-sized vessels. The typical presentation is a triad of purpura, weakness, and arthralgias. Purpura often begins on the legs and can involve the buttocks, trunk, and arms, but rarely the face. Progression to deep ulcers occurs in 10% of patients.[27]

MC affects 30% to 50% of individuals with chronic HCV, but only 10% to 30% of patients develop clinical symptoms. Conversely, 90% of patients with MC are positive for anti-HCV antibody.[28] Other laboratory findings of MC include serum mixed cryoglobulins, decreased C4 levels, and positive rheumatoid factor. Treatment of HCV-related MC depends on disease severity. Mild to moderate cases are treated with anti-HCV therapy plus ribavirin. Severe or refractory cases may require immunosuppressive or plasma exchange therapy. Rituximab should also be considered in refractory cases to reduce the expansion of B cells, a probable source of cryoglobulins. IFN should be avoided because it can stimulate the immune system and cause further damage in severe cases.[26]

PCT is a blistering photosensitivity disorder caused by dysfunction of hepatic uroporphyrinogen decarboxylase (UROD).[28] Approximately 20% of PCT is inherited (autosomal dominant), while the remainder results from acquired UROD dysfunction.[29] Risk factors for acquired PCT include HCV infection, HIV infection, smoking, alcohol abuse, exogenous estrogen, and hemochromatosis gene

Table IV. Therapies for chronic hepatitis C virus infection

Therapy	Mechanism of action	Advantages	Disadvantages
Interferon-based regimen	Inhibit fibrogenesis and angiogenesis and induce fibrinolysis and tumor cell apoptosis	Absence of viral resistance	Highly variable response rate; frequent side effects
Direct acting antivirals NS3/4A protease inhibitors Simeprevir Paritaprevir Grazoprevir Glecaprevir Voxilaprevir NS5A inhibitors Daclatasvir Ombitasvir Ledipasvir Elbasvir Velpatasvir Pibrentasvir NS5B nucleoside polymerase inhibitors Sofosbuvir NS5B non-nucleoside polymerase inhibitors Dasabuvir	Block proteolytic cleavage of proteins necessary for replication; inhibit viral RNA replication and virion assembly; inhibit viral RNA synthesis	Higher sustained virologic response; combination therapies can target different viral proteins; shorten duration of treatment	Risk of resistance; potential hepatotoxicity and drug interactions; expensive

mutations.[30,31] HCV downregulates the enzyme hepcidin, causing hepatic iron overload and subsequent UROD dysfunction.[30] Early clinical manifestations include bullae, vesicles, erosions, crusting, or milia in sun-exposed areas, most commonly on the dorsal surfaces of the hands. Chronic changes in these areas include hyper- and hypopigmentation, scarring, alopecia, sclerodermoid plaques, and dystrophic calcifications. Additional features include photosensitivity and facial hypertrichosis.[26,32,33] PCT is treated with avoidance of UV exposure and exogenous risk factors, phlebotomy (iron reduction), and chloroquine or hydroxychloroquine (porphyrin reduction).[32] Historically, PCT treatment was administered before HCV treatment because IFN-based regimens are more effective after PCT therapy, and because IFN and ribavirin may worsen PCT if given first.[34] Therapy in HCV-infected patients may soon be simplified, because multiple PCT cases have resolved in response to DAA therapy without PCT-directed treatment.[35,36]

NAE is a rare and nearly pathognomonic manifestation of HCV infection (prevalence of 1.7% in HCV carriers). NAE presents as well-defined dusky, erythematous plaques occurring in an acral distribution. Burning and pruritus are common.[37,38] Although several cases have been reported in patients without HCV, NAE is considered a cutaneous marker for HCV infection.[39-41] NAE is often misdiagnosed as psoriasis, eczematous dermatitis, or other conditions that are commonly treated with topical corticosteroids. However, NAE characteristically responds poorly to corticosteroids.[42] Patients with NAE should be treated for their underlying HCV infection.[43,44] Oral zinc therapy or amino acid replacement can be useful supplemental treatment.[44,45]

Lichen planus (LP) is an inflammatory disorder affecting the skin and orogenital mucosa.[26,30] LP presents as purplish, flat-topped papules on the skin and white lace—like Wickham striae in the mucosa.[26,30] The prevalence of chronic HCV infection varies from 4% to 24% in patients with LP, with oral LP having the strongest association.[26,30] However, routine HCV testing of all LP patients is not indicated.[26]

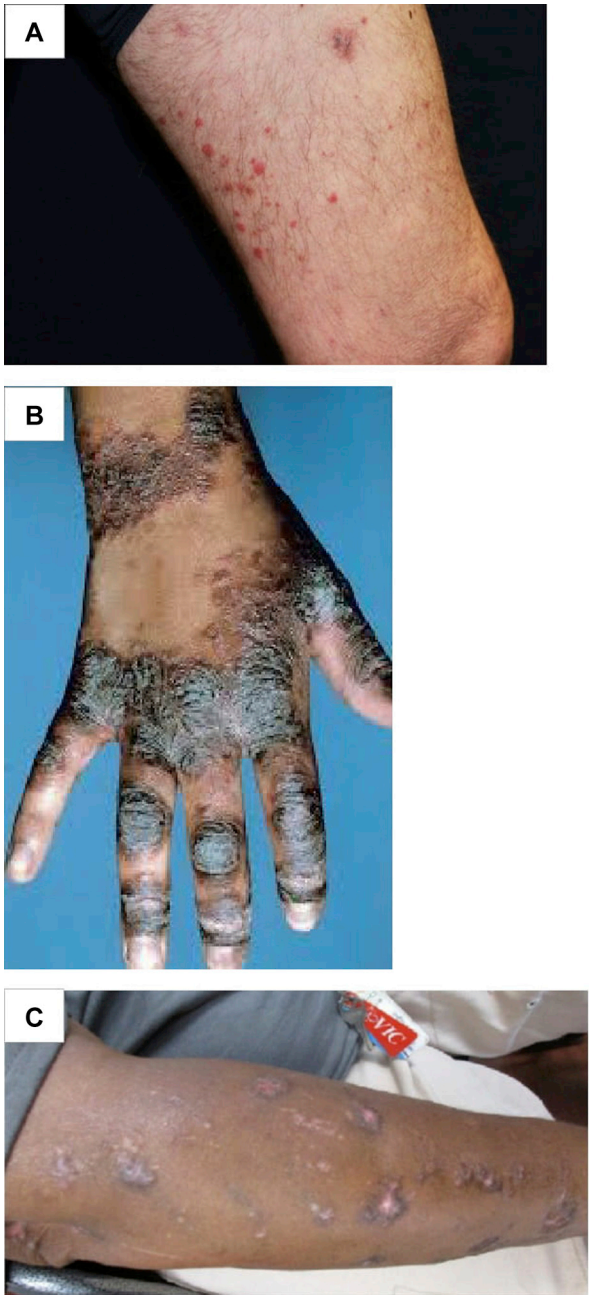


Fig 2. Cutaneous manifestations associated with hepatitis C infection. **A**, Mixed cryoglobulinemia. Reprinted with permission from Kartha et al.[131] **B**, Necrolytic acral erythema. Reprinted with permission from Hivnor et al.[132] **C**, Lichen planus. Reprinted with permission from Ansari et al.[133]

HUMAN T-LYMPHOTROPIC VIRUS 1

Key points

- **Human T-lymphotropic virus 1 infection occurs most frequently in patients of Caribbean, Japanese, African, and South American heritage**
- **Cutaneous manifestations are common in patients with adult T-cell leukemia/lymphoma and vary widely in presentation**
- **A diagnosis of infective dermatitis should be considered in patients living in human T-lymphotropic virus 1–endemic regions who present with early childhood eczema**

Human T-lymphotrophic virus 1 (HTLV-1) is an RNA retrovirus associated with adult T-cell leukemia/lymphoma (ATLL), infective dermatitis, HTLV-1–associated myelopathy/tropical spastic paraparesis, and other nonmalignant conditions.[46-51] Approximately 5 million to 10 million HTLV-1 carriers exist globally, but only 5% develop clinical disease.[52-54] HTLV-1 is most prevalent in Japan, Africa, the Caribbean islands, Central America, and South America,[52,55-57] and is becoming more prevalent in the United States.[58,59] The virus is transmitted by blood, semen, and breast milk and infects CD4, dendritic, and CD8 cells.[50,55,60-63] Transmission is prevented by elective Caesarean section and limiting the duration of breastfeeding (seropositive mothers only), barrier protection during sexual intercourse, and blood donor screening.[64] No HTLV-1 antiviral treatments or vaccines are currently available.

Dermatologic manifestations

HTLV-1 carriers have an increased risk for developing dermatologic conditions, including acquired ichthyosis, xerosis, seborrheic dermatitis, crusted scabies, and strongyloidiasis.[65-67] HTLV-1–induced ATLL and infective dermatitis (IDH) also have significant cutaneous findings (Table VI).

ATLL is an aggressive peripheral T-cell ($CD4^+CD25^+$) neoplasm that develops 20 to 60 years after HTLV-1 infection. HTLV-1 oncoproteins Tax and HTLV-1bZIP factor are essential for ATLL transformation and propagation, respectively.[50,55,68-74] Common clinical findings include generalized lymphadenopathy, hepatosplenomegaly, skin lesions, and hypercalcemia.[59,72,74,75] Opportunistic infections from *Pneumocystis jirovecci*, *Candida*, *Aspergillus*, *Cytomegalovirus*, *Strongyloides stercoralis*, and *Cryptococcus* frequently occur.[72,76] Cutaneous involvement is the first sign of disease in one third of patients with ATLL and portends a worse prognosis.[77-82] Skin findings include rashes, papules, plaques, erythrodermic and purpuric lesions, and more rarely ulcerated nodules and bullous lesions (Fig 3).[59,74,80,83,84] Histologic findings include Pautrier-like microabscesses of large atypical lymphocytes, angiocentrism, large cell morphology, epidermal infiltration of atypical lymphocytes, a CD4:CD8 ratio >20:1, and folliculotropism

Table V. Hepatitis C virus–associated dermatologic manifestations, skin findings, diagnosis, and therapy

Manifestation	Skin findings	Diagnosis	Therapy
Mixed cryoglobulinemia	Orthostatic palpable purpura and ulcers with or without livedo[26]	Diagnosis is based on clinical, histologic, and laboratory findings; histopathologic features: leukocytoclastic vasculitis involving small- and medium-sized blood vessels is the hallmark finding[26]; laboratory findings: presence of serum mixed cryoglobulins, low C4 levels, and typically positive rheumatoid factor[26]	First-line treatment is eradication of HCV with antiviral agents; corticosteroids, low-antigen-content diet, plasma exchange, and immunosuppressants should be considered in severe cases[26]
Lichen planus	Polygonal, pruritic, purple, flat-topped papules and plaques, white lace-like Wickham striae may be present in the oral mucosa[124]	Diagnosis is frequently based on clinical findings; obtaining a biopsy specimen can be used to rule out lesions that resemble lichen planus; histopathologic features: parakeratosis, orthokeratosis, and acanthosis with development of a "saw-tooth" appearance of the rete pegs[124]	High-potency topical corticosteroids and removal of any triggers; topical calcineurin inhibitors are second-line treatments for genital and oral lichen planus; oral prednisone for widespread lichen planus; most untreated cutaneous lesions will resolve within 6-9 months[124]
Porphyria cutanea tarda	Fragility of sun-exposed skin leading to erosions, vesicles, bullae, milia, hyper- or hypopigmented scar, dystrophic calcifications, alopecia, and sclerodermoid plaques; facial hypertrichosis also common[125]	Diagnosis is based on clinical, histologic, and laboratory findings; histologic features: subepidermal vesicle, thickening of papillary dermal capillary walls, no/minimal inflammation; laboratory findings: elevated levels of plasma porphyrin, urinary uroporphyrin and heptacarboxyl porphyrin, and fecal isocoproporphyrin[125]	Reduce elevated iron stores by phlebotomy, remove excess porphyrins with low-dose chloroquine or hydroxychloroquine, avoid excessive alcohol and iron consumption and sunlight exposure[125]; DAAs alone have been effective in patients infected with HCV[35,36]
Necrolytic acral erythema	Chronic, lichenified plaques that appear well-defined, dusky, erythematous, and pruritic or tender and affect the acral surfaces[42]	Diagnosis is based on clinicopathologic correlation; histologic features: acanthosis, epidermal spongiosis and superficial perivascular infiltrate initially; psoriasiform hyperplasia and prominent papillomatosis with parakeratosis and epidermal pallor can be seen in the late phase; subcorneal pustule and necrotic keratinocytes may be found in chronic lesions[42]	Treatment of the underlying HCV infection and oral zinc supplementation alone or in combination with antiviral therapy[43]; intralesional and high potency topical steroids and oral amino acids as adjunctive therapy in resistant cases[43]

DAA, Direct-acting antiviral; *HCV*, hepatitis C virus.

(Fig 4).[59] First-line ATLL treatments include chemotherapy and clinical trials.[85,86] ATLL does not respond well to treatment, but can potentially be cured by allogeneic stem cell transplantation.[87] Treatment for opportunistic infections, hypercalcemia, and tumor lysis is also essential.[88,89]

IDH is a severe, chronic, and relapsing exudative childhood dermatitis with an average onset age of 2 years.[90] Cases usually resolve by adulthood, but persistent cases and adult-onset IDH have been described.[54,64,91] IDH lesions are crusty and scaly and most commonly involve the scalp (Fig 5), forehead, paranasal area, retroauricular areas, eyelids, ears, axillae, and groin. A fine papular rash can also occur.[64] Superinfection with *Staphylococcus aureus* or beta-hemolytic streptococci is nearly

Table VI. Human T-lymphotrophic virus 1—associated dermatologic manifestations, skin findings, diagnosis, and therapy

Manifestation	Skin findings	Diagnosis	Therapy
Adult T-cell leukemia/ lymphoma	Rashes, papules, plaques, erythrodermic and purpuric lesions, and more rarely ulcerated nodules and bullous lesions	Diagnosed by demonstrating human T-lymphotrophic virus 1 seropositivity and hematologic or lesional presence of abnormal peripheral T-cells[65]; histologic features: Pautrier-like microabscesses of large atypical lymphocytes, angiocentrism, large cell morphology, epidermal infiltration of atypical lymphocytes, CD4:CD8 of >20:1, and folliculotropism	Conventional chemotherapy (eg, CHOP) has partial efficacy and a high relapse rate; zidovudine-interferon based-regimens are effective for certain subtypes[75]; mogamulizumab (monoclonal antibody against CCR4) is approved in Japan for refractory ATLL[126]; treatment for opportunistic infections, hypercalcemia, and tumor lysis is essential[89,90]
Infective dermatitis	Relapsing erythematous, scaly, and crusted lesions, with desquamation, exudation, and purulent skin infections	Diagnosed using La Grenade et al[127] criteria; histologic features: acanthosis, spongiosis, and occasional conglomerates of neutrophils in the stratum corneum; immunohistochemistry: profoundly positive for CD8 and CD57[53]	Long-term oral antibiotics until puberty (trimethoprim-sulfamethoxazole is the drug of choice); topical antibiotics, emollients, and antiseptics may be useful; topical corticosteroids and oral antihistamines for associated pruritus[65,91]

CCR4, CC chemokine receptor 4; *CHOP*, cyclophosphamide, doxorubicin, vincristine, and prednisone.

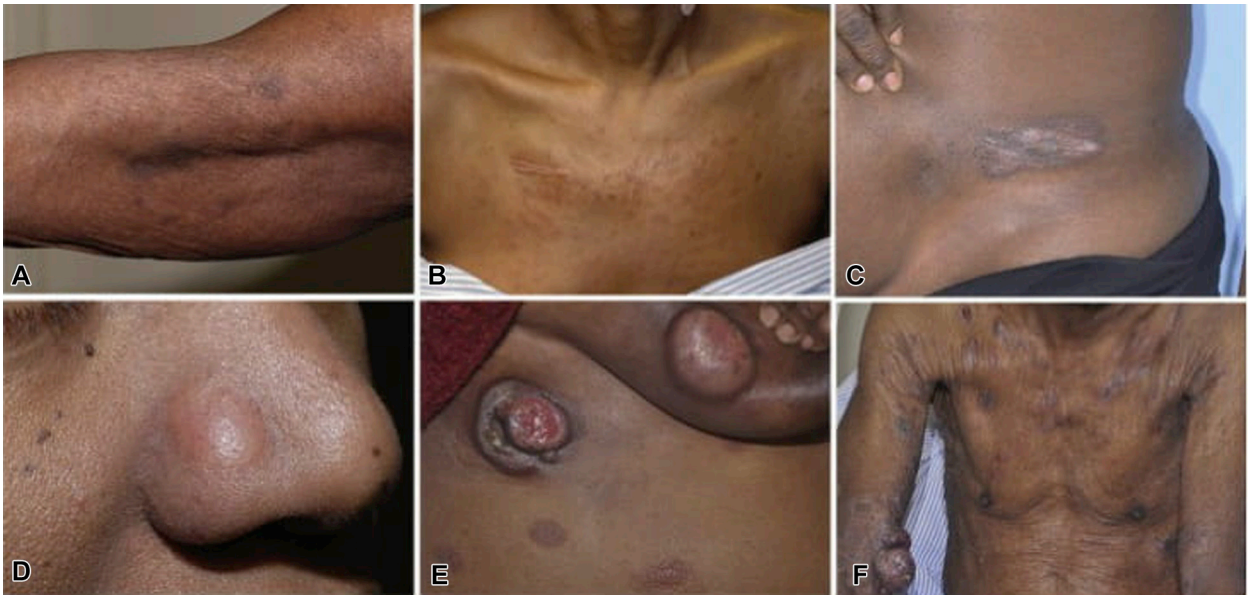


Fig 3. Clinical images of adult T-cell leukemia/lymphoma skin manifestations at diagnosis. **A**, Subtle patches on the inner aspect of right arm. **B**, Multiple papules across the chest. **C**, Solitary plaque on the left hip. **D**, Solitary nodule on the right side of nose. **E**, Rapidly proliferating ulcerated nodules on the right breast and abdomen with nearby patches and plaques. **F**, Diffuse involvement of patches, papules, plaques, and nodules on the chest, abdomen, and bilateral upper extremities. Reprinted with permission from Marchetti et al.[59]

always present.[92] Rhinorrhea and crusting of the anterior nares usually occur and are often the presenting complaints (Fig 6).[92] The pathogenesis of IDH remains unclear, but several proinflammatory cytokines, including tumor necrosis factor—alfa and IFN gamma, appear to play a role.[64,67]

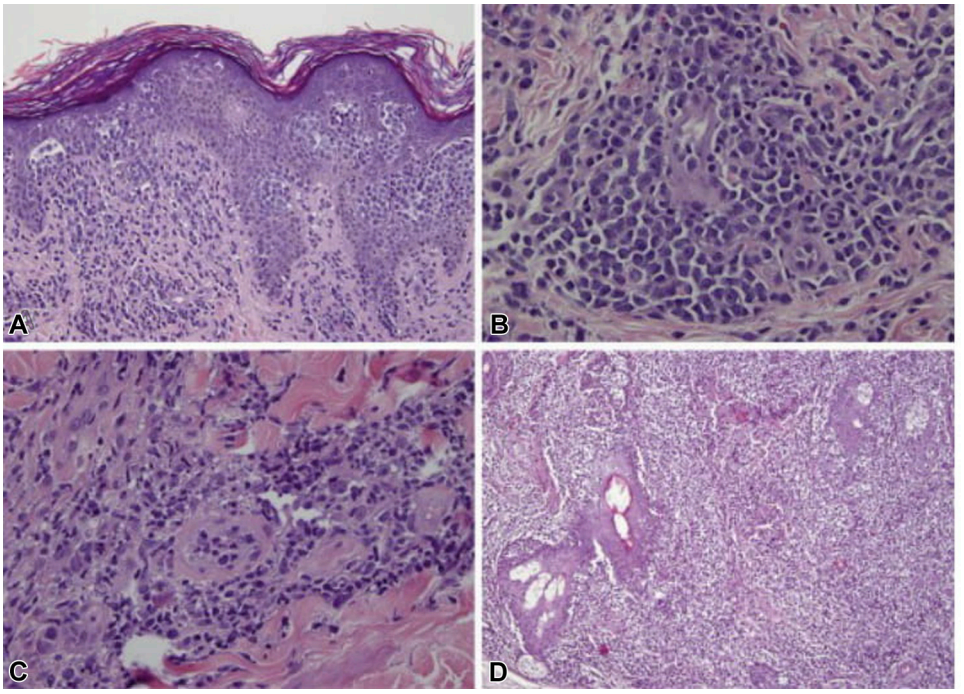


Fig 4. Histopathologic features of adult T-cell leukemia/lymphoma skin involvement. **A**, Epidermal infiltration by atypical lymphocytes forming large Pautrier-like microabscesses. **B**, Atypical lymphocytes of characteristic large size. Dense lymphocytic infiltrates showing angiocentrism/angiodestruction (**C**) and folliculotropism (**D**). Reprinted with permission from Marchetti et al.[59] (**A**-**D**, Hematoxylin–eosin stain; original magnifications: **A**, ×200; **B** and **C**, ×400; **D**, ×100.)

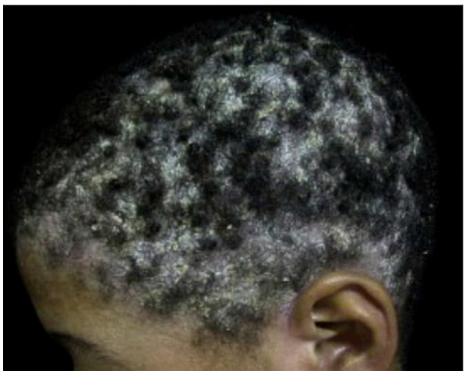


Fig 5. Infective dermatitis involving the scalp with scaling, crusting, and erythema. Reprinted with permission from Lee et al.[64] Courtesy of Maria de Fatima S. P. de Oliveira, Federal University of Bahia, Brazil.

IDH can be diagnosed by criteria proposed by La Grenade et al[46] (Table VII), which include HTLV-1 serum testing. Several characteristics such as pruritic intensity, age of onset, and crusting of anterior nares distinguish IDH from seborrheic dermatitis and atopic dermatitis (Table VIII). The treatment for IDH is long-term antibiotics, and trimethoprim-sulfamethoxazole is most-effective.[92] If antibiotics are discontinued, IDH characteristically recurs.[64,92]

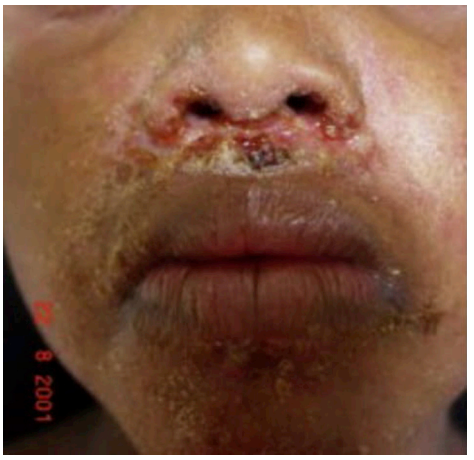


Fig 6. Infective dermatitis with facial involvement. Reprinted with permission from Lee et al.[64] Courtesy of Maria de Fatima S. P. de Oliveira, Federal University of Bahia, Brazil.

HUMAN HERPESVIRUS-8

Key points

- **Human herpesvirus-8–associated diseases primarily affect immunocompromised patients**

Table VII. Diagnostic criteria for infective dermatitis*

Major criteria
1. Eczema of scalp, axillae, groin, external ear and retroauricular areas, eyelid margins, paranasal skin, or neck
2. Chronic watery nasal discharge without other signs of rhinitis or crusting of the anterior nares
3. Chronic relapsing dermatitis with prompt response to antibiotics but prompt recurrence after withdrawal
4. Onset during early childhood
5. Human T-lymphotrophic virus 1 antibody seropositivity

Minor criteria
1. Positive cultures for *Staphylococcus aureus* or beta-hemolytic Streptococci from the skin or anterior nares
2. Generalized fine papular rash (in most severe cases)
3. Generalized lymphadenopathy with dermatopathic lymphadenitis
4. Anemia
5. Elevated erythrocyte sedimentation rate
6. Hyperimmunoglobulinemia (immunoglobulins E and D)
7. Elevated CD4 count, CD8 count, and CD4:CD8 ratio

Note: Four major criteria are required for infective dermatitis diagnosis, with inclusion of numbers 1, 3, and 5 being mandatory.
*Adapted from La Grenade et al.[127]

Table VIII. Different clinical characteristics of infective dermatitis associated with human T-lymphotrophic virus 1, atopic dermatitis, and seborrheic dermatitis*

Clinical characteristic	Infective dermatitis	Atopic dermatitis	Seborrheic dermatitis
Age at onset	From 18-24 months onward	From 18-24 months onward	All ages
Atopy	Absent	Present	Absent
Skin lesions	Erythematous scaly lesions with yellow crusts, papules, retroauricular fissures, and generalized fine papular rash	Erythematous and edematous papules and plaques, sometimes with vesiculation, generally replaced by lichenification	Erythematous greasy scaly lesions
Distribution	Scalp, retroauricular areas, external ear, eyelid margins, perinasal skin, neck, axillae, and groin	Elbow and knee flexures, sides of the neck, wrists, ankles, and hands	Scalp, retroauricular areas, external ear, glabella, eyebrows, nasolabial folds, neck, axillae, groin, umbilicus; presternal, interscapular, and submammary regions
Crusting on anterior nares	Present	Absent	Absent

*Modified with permission from Hlela and Bittencourt.[67]

- **Kaposi sarcoma is the most common cutaneous manifestation of human herpesvirus-8 infection**
- **The treatment of Kaposi sarcoma depends on the associated comorbidities and degree of involvement**

Human herpesvirus-8 (HHV-8) is a DNA virus that is transmitted via saliva, blood, and sexual contact and primarily causes disease in immunocompromised patients.[74,93,94] The HHV-8 life cycle consists of latent and lytic replication. Latent proteins contribute to oncogenesis by activating various cytokine-mediated cell proliferation and protumorigenic pathways, whereas lytic replication disseminates the virus and is reactivated when the host is immunocompromised.[94,95] No HHV-8 antiviral treatments or vaccines are currently available.

Dermatologic manifestations

HHV-8 most notably causes Kaposi sarcoma (KS), an angioproliferative spindle cell tumor arising from HHV-8–infected endothelial cells. KS is the most frequent AIDS-defining malignancy in patients who are HIV-positive.[96] The characteristic clinical features are painless, purple nodules and plaques, most commonly found on the oral mucosa, face, and lower extremities. KS clinical subtypes include classic, endemic/African, immunosuppression-

Table IX. Epstein–Barr virus–associated dermatologic manifestations, skin findings, diagnosis, and therapy

Manifestation	Skin findings	Diagnosis	Therapy
B-cell lymphoproliferative disorders			
Burkitt lymphoma	Indurated nodules and plaques	Histologic features: sheets of monotonous medium-sized lymphoid cells with nuclei the size of histocyte nuclei and "starry sky" appearance under low power due to scattered tingible body macrophages (histiocytes containing apoptotic tumor cells)[109]; immunohistochemistry: strongly positive for B-cell markers (CD19, CD20, CD22), CD10, CD43, and Bcl-6[109]	Chemotherapy
Cutaneous Hodgkin lymphoma	Painless, ulcerating papules and nodules	Histologic features: Reed–Sternberg cell–containing prominent nucleoli resembling an owl's eye[110]; immunohistochemistry: positive CD15 and CD30	Chemotherapy
Posttransplant lymphoproliferative disorder	Varies from scaly patches to erythematous nodules to mycosis fungoides	Histologic features: heterogeneous findings, such as plasmacytoid tumor, infectious mononucleosis–like lesion, monomorphic lesion resembling another lymphoma, and polymorphic lesion[111]; immunohistochemistry: positive Epstein–Barr virus, MUM-1, and IRF4[111]	Reduction in immunosuppressive agents to the lowest tolerated level is recommended as the initial therapy in patients without rapidly progressive disease; preemptive strategy with reduction in immunosuppression may prevent development of PTLD[111]
T-cell lymphoproliferative disorders			
Angioimmunoblastic T-cell lymphoma	Most frequently reported manifestation is a morbilliform eruption	Histologic features: loss of normal lymph node architecture, neoplastic T-cell population often obscured by reactive infiltrate, many cases show accompanying B cell proliferation[112]; immunohistochemistry: positive Epstein–Barr virus, CD10, and follicular helper T-cell markers (PD1, CXCL13, and ICOS)[112]	Anthracycline containing regimens are first-line treatments[112]

Continued

Table IX. Cont'd

Manifestation	Skin findings	Diagnosis	Therapy
Extranodal NK/T-cell lymphoma	Most frequently observed lesions are erythematous or violaceous plaques and nodules with or without ulceration; other manifestations include papules, cysts, patches, and cellulitis[113]	Histologic features: angiocentric and angioinvasive distribution of atypical lymphoid cells with necrosis and ulceration of the involved tissues[113]; immunohistochemistry: positive Epstein–Barr virus and CD56; negative T-cell markers[113]	Chemotherapy, radiotherapy, and hemopoietic stem cell transplantation
Hydroa vacciniforme–like lymphoma	Papulovesicular rash followed by crusting, ulceration, scarring, and disfigurement[114]	Histologic features: angiocentric and periadnexal lymphoid infiltrate with variable atypia and subcutaneous involvement; panniculitis and vasculitis are predominant features[114,120]; immunohistochemistry: positive Epstein–Barr virus, CD3, CD8 and cytotoxic marker TIA-1; negative CD4 and CD56[114]	No established treatment guideline; chemotherapy, radiotherapy, thalidomide, interferon, corticosteroids, and immunomodulators have shown variable benefits[114,120]

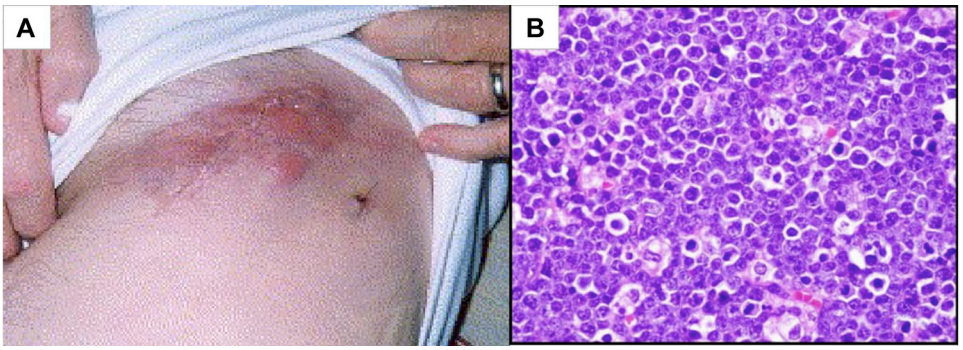


Fig 7. Burkitt lymphoma with cutaneous involvement. **A**, Indurated and nodular plaque in the left inguinal region. Reprinted with permission from Jacobson et al.[128] **B**, Mitotically active large tumor cells and macrophages engulfing apoptotic cellular debris as seen in the classic "starry-sky" pattern. Courtesy of PathologyOutlines.com chapter Lymphoma and plasma cell neoplasms.

related, and AIDS-associated. These variants share similar clinical features but occur in different patient populations: classic KS in elderly men of Mediterranean or Eastern European descent, endemic KS in young African people, immunosuppression-related KS in patients who are taking immunosuppressive drugs, and AIDS-associated KS in HIV-infected individuals.[94] Of these, AIDS-associated KS has the most aggressive clinical course and often progresses to visceral involvement, organ dysfunction, and death.[94,97] There has been an increasing number of KS cases in HIV-seronegative men who have sex with men, leading to the proposal of a new subtype to characterize these patients.[94,97] HHV-8 immunohistochemistry can be useful in confirming the diagnosis of KS in formalin-fixed tissue and may be present in 80% to 90% of cases.[98]

Observation is reasonable in patients with limited involvement and no immune dysfunction or post-transplant history. Cryotherapy, laser surgery, photodynamic therapy, intralesional chemotherapy, topical alitretinoin, and topical imiquimod are used to treat limited superficial lesions.[99] Systemic therapies are required for patients with widespread or

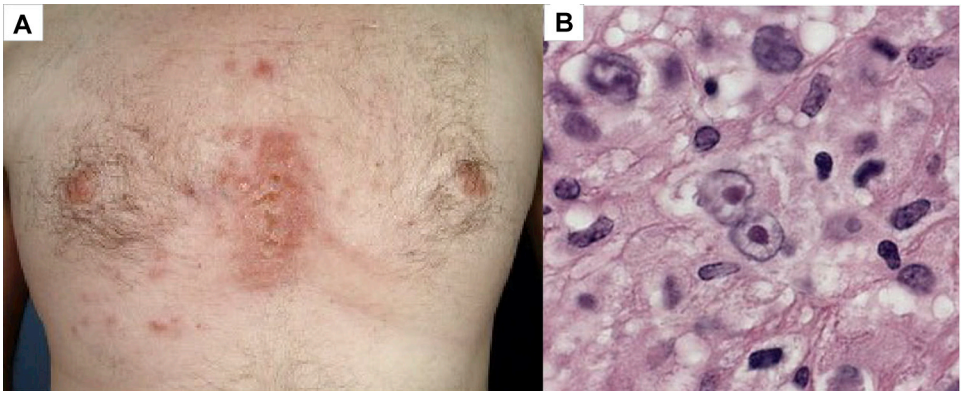


Fig 8. Cutaneous Hodgkin lymphoma. **A**, Multiple discrete erythematous papules and nodules with central area of coalescing nodules with central ulceration. Reprinted with permission from Introcaso et al.[129] **B**, A Reed–Sternberg cell with prominent nucleoli resembling an owl's eye characteristic of Hodgkin lymphoma. Courtesy of PathologyOutlines.com chapter Lymphoma and plasma cell neoplasms.

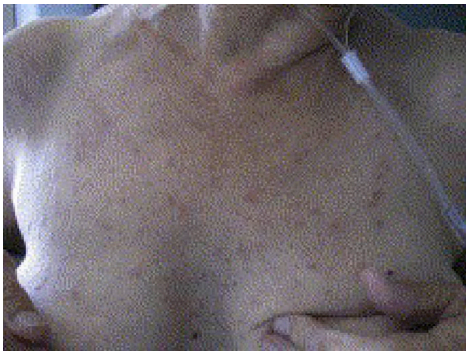


Fig 9. Angioimmunoblastic T-cell lymphoma. Multiple, ill-defined, scattered pink-red papules on upper chest. Reprinted with permission from Jacobson et al.[134]

rapidly progressive lesions, moderate to severe symptomatic edema or visceral organ involvement. Liposomal anthracyclines and paclitaxel are FDA approved as first-line and second-line monotherapy, respectively; localized radiotherapy is another option.[99] In AIDS-associated KS, antiretroviral therapy is the initial treatment choice.[100]

EPSTEIN–BARR VIRUS

Key points

- **Epstein–Barr virus–associated oncogenesis is primarily attributable to the actions of latent membrane protein 1**
- **Cutaneous manifestations of Epstein–Barr virus–associated malignancies can be difficult to recognize and require a high degree of clinical suspicion**
- **Optimal treatment of Epstein–Barr virus–associated cutaneous lesions is to treat the underlying malignancy**

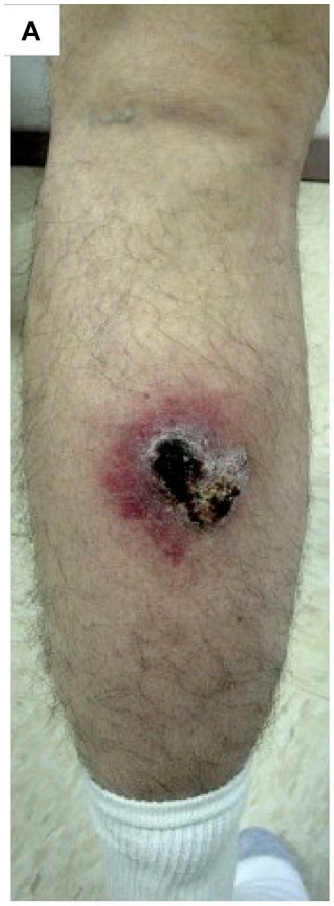
EBV is a DNA virus that infects >90% of the world's population, typically during childhood via salivary transmission.[101] EBV infection is a risk factor for the development of B- and T-cell lymphoproliferative disorders (LPDs). EBV oncogenesis is primarily driven by latent membrane protein 1, which acts as a constitutively activated CD40 receptor and is responsible for the transformation of B lymphocytes into proliferating lymphoblastoid cells.[102-104] Latent membrane protein 2A and EBV nuclear antigens also contribute to tumorigenesis by modulating key cellular processes.[102,103,105-107]

No effective treatment currently exists for EBV. EBV uses host replication machinery in latency, making it difficult to target the virus without affecting the host cell.[108] Cellular therapies, immunotherapies, and antibody therapies are novel approaches that are being investigated.[106]

Dermatologic manifestations

EBV-associated B-cell LPDs are reviewed in Table IX and include Burkitt lymphoma (Fig 7), Hodgkin lymphoma (Fig 8), and posttransplant lymphoproliferative disorders, while EBV-associated T-cell LPDs include angioimmunoblastic T-cell lymphoma (Fig 9), extranodal natural killer/T-cell lymphoma (Fig 10), and hydroa vacciniforme–like lymphoma (Fig 11).[108] Cutaneous manifestations of LPDs are rare and often lack defining clinical features,[109-114] making histology and immunohistochemistry necessary for diagnosis (Table IX).

Posttransplant LPDs (PTLD) are a group of clinically and histologically heterogenous range of diseases that occur after solid organ transplantation and hematopoietic stem cell transplantation in the setting of compromised T cell surveillance.[115] The majority



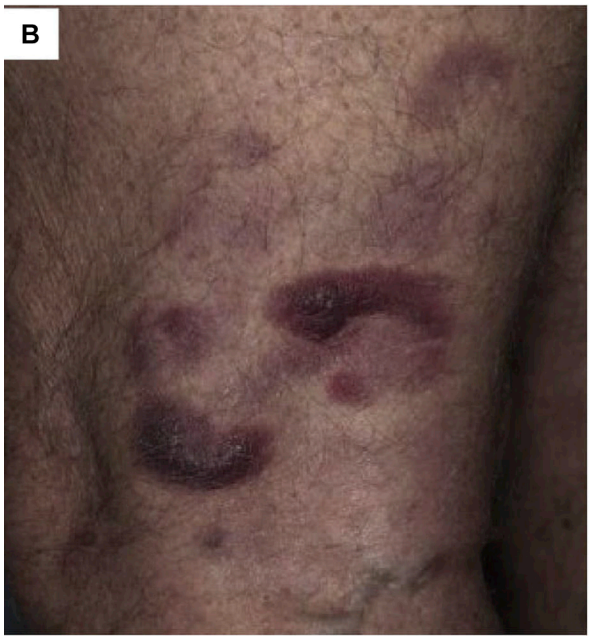


Fig 10. Cutaneous manifestations of extranodal natural killer/T-cell lymphoma. **A**, Extranodal natural killer—T cell presenting with rapidly expanding cutaneous ulcers in a previously healthy man. Reprinted with permission from Vainder et al.[135] **B**, Recurrent cutaneous T-cell lymphoma presenting as indurated violaceous plaques with arcuate morphology. Reprinted with permission from Wang et al.[136]

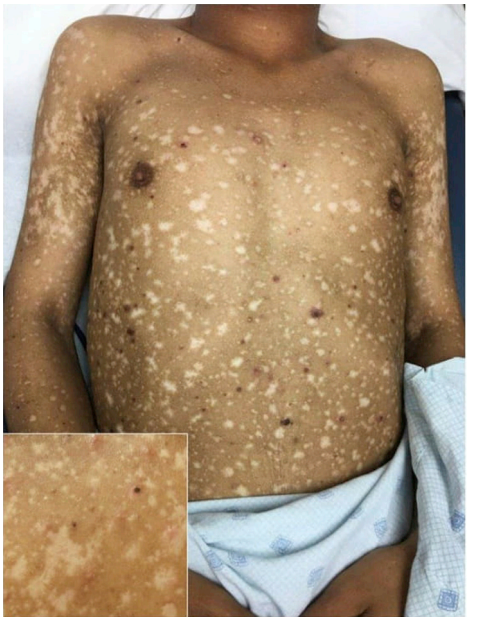


Fig 11. Cutaneous manifestations of hydroa vacciniforme—like lymphoma. Erythematous to brown papules with central necrosis and hemorrhagic crust distributed on a background of white, stellate scars. Inset shows a close-up view of the characteristic hemorrhagic-crusted, erythematous, edematous papules, and white stellate scars. Reprinted with permission from Yu et al.[137]

of PTLDs are of B-cell origin and are etiologically linked with EBV infection.[116] An increase in EBV DNA viremia can be an early sign of PTLD.[115] T-cell lymphomas occur less frequently and are typically EBV-negative.[116] The World Health Organization classifies PTLD into 4 subgroups: early lesions, monomorphic PTLD, polymorphic PTLD, and classical Hodgkin lymphoma. Early lesions are characterized by polyclonal lymphoid hyperplasia in the tonsils, adenoids, or other nodal lymphoid tissue.[115] Monomorphic and polymorphic PTLD encompass both B- and T-cell malignancies, including diffuse large B-cell lymphoma, Burkitt lymphoma, peripheral T-cell lymphoma, and natural killer/T-cell lymphoma. Posttransplant primary cutaneous lymphomas are extremely rare, and reports vary regarding whether B- or T-cell cutaneous lymphomas occur more commonly.[116-118] Cutaneous T-cell lymphoma has a worse prognosis in posttransplant patients than in the general population.[116,117] Treatment of solid organ transplantation-PTLD includes reduced immunosuppression, chemotherapy, and rituximab.[115] There is a general paucity of data to guide management of hematopoietic stem cell transplantation—associated PTLD. Enrollment in a clinical trial should be considered for all patients.[115]

Hydroa vacciniforme–like lymphoma (HVLL) is a chronic lymphoproliferative disorder of childhood that mainly affects Asian and Latin American children.[119,120] HVLL presents with a vesiculopapular eruption followed by crusting, ulceration, scarring, and disfigurement in predominantly sun-exposed skin, which clinically resembles hydroa vacciniforme (HV).[119,121] HVLL is often misdiagnosed as HV, skin infections, and allergy, leading to a delay in diagnosis.[119-121] Clinical features that distinguish HVLL include the presence of systemic symptoms and lesions in both sun-exposed and non–sun-exposed skin.[119,121] The prognosis is poor because HVLL is often refractory to chemotherapy and no effective treatment currently exists.[119,120]

In conclusion, the oncovirus-associated internal malignancies and mucocutaneous diseases described in the article can present with a wide range of dermatologic findings. While some cutaneous findings are pathognomonic for viral infection or internal malignancy, others are less specific. A high degree of clinical suspicion is required for diagnosis and early treatment. This is particularly important in HBV and HCV infections in which effective treatments or vaccines are available and can significantly decrease the risk of HCC. While there is no curative or evidence-based treatment for ATLL, KS, and B- and T-cell LPDs, recognition of their cutaneous manifestations may slow progression of the disease or guide palliative treatment.

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Answers to CME examination

Identification No. JB0719

July 2019 issue of the Journal of the American Academy of Dermatology.

Mui UN, Haley CT, Vangipuram R, Tyring SK. J Am Acad Dermatol 2019;81:23-41.

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