

Herpes viruses and the microbiome

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The focus of this article will be to examine the role of common herpesviruses as a component of the microbiome of atopic patients and to review clinical observations suggesting that atopic patients might be predisposed to more severe and atypical herpes-related illness because their immune response is biased toward a T_H2 cytokine profile. Human populations are infected with 8 herpesviruses, including herpes simplex virus HSV1 and HSV2 (also termed HHV1 and HHV2), varicella zoster virus (VZV or HHV3), EBV (HHV4), cytomegalovirus (HHV5), HHV6, HHV7, and Kaposi sarcoma-associated herpesvirus (termed KSV or HHV8). Herpesviruses are highly adapted to lifelong infection of their human hosts and thus can be considered a component of the human “microbiome” in addition to their role in illness triggered by primary infection. HSV1 and HSV2 infection and reactivation can present with more severe cutaneous symptoms termed eczema herpeticum in the atopic population, similar to the more severe eczema vaccinatum, and drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is associated with reactivation of HSV6 and possibly other herpesviruses in both atopic and nonatopic patients. In this review evidence is reviewed that primary infection with herpesviruses may have an atypical presentation in the atopic patient and conversely that childhood infection might alter the atopic phenotype. Reactivation of latent herpesviruses can directly alter host cytokine profiles through viral expression of cytokine-like proteins, such as IL-10 (EBV) or IL-6 (cytomegalovirus and HHV8), viral encoded and secreted siRNA and microRNAs, and modulation of expression of host transcription pathways, such as nuclear factor κ B. Physicians caring for allergic and atopic populations should be aware of common and uncommon presentations of herpes-related disease in atopic patients to provide accurate diagnosis and avoid unnecessary laboratory testing or incorrect diagnosis of other conditions, such as drug allergy or autoimmune disease. Antiviral therapy and vaccines should be administered promptly when indicated clinically. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

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Increasing evidence suggests that the human genome is only one component of allergic and atopic disease and that the complex

Abbreviations used

CMV:	Cytomegalovirus
DRESS:	Drug reaction with eosinophilia and systemic symptoms
EBNA:	Epstein-Barr nuclear antigen
HSV:	Herpes simplex virus
HSV1:	Herpes simplex virus type 1, also known as HHV1 (human herpes virus type 1)
HSV2:	Herpes simplex virus type 2, also known as HHV2 (human herpes virus type 2)
KSV:	Kaposi sarcoma virus
vIL-10:	Viral IL-10-like protein encoded by EBV
VZV (or HHV3):	Varicella zoster virus

“human biome,” including bacteria and fungi, interacts with the genome in complex pathways influencing allergic and atopic disease.^{1,2} The human microbiome can also include herpesviruses because these infectious agents establish lifelong infection of the human host, although unlike bacteria and fungi, this persistent state is maintained through latent genomic persistence within the host cell nucleus. Herpesviruses are ubiquitous, large, double-stranded DNA viruses categorized into 3 families. α Herpesviruses, such as human herpes simplex virus (HSV) 1 and HSV and varicella zoster virus (VZV or HHV3), establish latency in neurons; β herpesviruses, such as cytomegalovirus (CMV or HHV5) and human herpesvirus (HHV) 6 and HHV7, establish latency in macrophages and lymphocytes; and γ herpesviruses, such as EBV (HHV4) and HHV8, establish latency only in lymphocytes. The ability of herpesviruses to establish a latent state of infection with low levels of viral gene expression for the life of the host is a defining feature of these pathogens and requires that the virus establish means of evading or neutralizing the host’s immune system.

Soon after the discovery of human cytokines and the differentiation of these cytokines into type 1 and type 2 cytokines, which direct responses against intracellular and extracellular pathogens, respectively, it was observed that EBV (HHV4) encodes a protein resembling human IL-10, a cytokine with actions in the T_H2 family.³⁻⁵ The ability of a virus to encode a copy of a human cytokine supported the hypothesis that EBV and related herpesviruses might in some way exploit the host immune system for their own purposes.⁶⁻⁸ Clinical observations had also previously suggested that patients with atopic disease, such as severe eczema, reflecting a T_H2 cytokine bias, were at risk for more severe reactions (termed eczema herpeticum or eczema vaccinatum) to other non-herpes DNA viruses, such as smallpox.⁹⁻¹¹

Epidemiologic studies suggest that age of infection with EBV and related herpesviruses can affect the subsequent development of atopic disease, possibly related to viral modulation of T_H2 cytokines.¹²⁻¹⁷ Subsequent study of EBV suggested herpesviruses can encode or trigger the expression of superantigens that nonspecifically activate T-lymphocyte

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subsets, possibility resulting in increased allergic cytokine expression and inflammation.^{18,19} Because of the possibility that atopic patients might be at increased risk of atypical or severe presentations of herpesvirus-related disease both during primary infection and viral reactivation, common and uncommon presentations of herpesvirus infection, as well as therapy options, should be familiar to physicians caring for the atopic patient, and therapy, such as antiviral drugs and vaccines, should be administered promptly when indicated. This review will examine evidence that human herpesviruses are a component of the human microbiome and important in modulating allergic and atopic disease and summarize existing evidence that atopic patients are at increased risk of severe and atypical responses to herpes pathogens.

EBV AS A PROTOTYPE OF IMMUNOMODULATION BY HUMAN HERPESVIRUSES

As noted above, the discovery that a human herpesvirus EBV encodes a copy of a cytokine related to IL-10 (encoded by the BCRF1 open reading frame) was a seminal observation, suggesting that common and ubiquitous herpesvirus pathogens could have immunomodulatory properties.⁶⁻⁸ Remarkably, the viral IL-10–like protein encoded by EBV (vIL-10) is different than cellular IL-10. vIL-10 has effects primarily on B lymphocytes; this is in contrast to the human cytokine, which targets both B and T lymphocytes.²⁰ In several experimental systems, an inflammatory effect of vIL-10 is evident because the inflammatory and proliferative effects of IL-10 on B lymphocytes are not opposed by the suppressive effects of IL-10 on T lymphocytes.^{3,20} In addition, EBV infection also triggers expression of cellular IL-10 and other host cytokines because EBV activates host transcription factors.²¹⁻²⁴

A virus-encoded protein (termed BZLF-1 or ZEBRA) activates the EBV replication cycle and is also a homolog of proteins in the activator protein 1 Fos/Jun family and nuclear factor κ B transcription proteins, potentially activating multiple host inflammatory proteins regulated by these pathways.²⁵ EBV and other herpesviruses encode microRNAs that can be released into the cytoplasm in endosomes causing immunomodulation of distant cells.²⁶⁻²⁹ Although many EBV-encoded proteins, noncoding RNAs, and cellular transcription factors are required for the viral lifecycle *in vitro*, it has been more challenging to demonstrate that EBV infection modulates the human immune system *in vivo*³⁰ because response to the virus might be an effect rather than a cause of T_H2 bias in patients with common autoimmune disease³¹ and cancer.^{32,33}

EARLY (INFANCY OR EARLY CHILDHOOD) VERSUS LATE (ADOLESCENCE OR ADULTHOOD) INFECTION WITH EBV AND OTHER HERPESVIRUSES AS A MODULATING FACTOR IN PATIENTS WITH ATOPIC DISEASE

Because of the immunomodulatory properties of EBV, population-based studies of EBV as a prototypical and ubiquitous herpesvirus suggest that early infection (infancy or early childhood) might have protective effects while later infection predisposes to atopic disease.¹²⁻¹⁷ These studies do not distinguish between effects of primary infection versus effects of subsequent viral persistence with episodes of reactivation. In infancy maternal antibodies against EBV might limit the severity of primary infection and modulate the immune response, whereas in early childhood the immune

system can respond differently to viral infections relative to the response in later childhood, adolescence, or adulthood.

These studies must all be controlled for the fact that patients with early childhood EBV infection might have other environmental exposures differing from those of patients with late infection. Thus it is difficult to prove with observational studies that increasing atopy and allergy with increasing age of EBV infection are causally related rather than common effects of different childhood hygiene, such as exposure to other components of the microbiome through exchange of body fluids or exposure to environmental antigens. Prospective studies of herpesvirus seroconversion in healthy infants followed through childhood would be required to determine to what extent age of infection with EBV and related viruses is correlated with allergy and atopy independent of other variables.

CLINICAL EVALUATION OF EBV AND RELATED CUTANEOUS SYNDROMES

Patients with nonspecific maculopapular rashes can be referred to allergists for evaluation of allergy, urticaria, immune deficiency, or autoimmune disease, often after extensive and unnecessary laboratory evaluation. EBV and related herpes pathogens often present with a maculopapular or urticarial rash that can persist for prolonged periods after primary infection (Fig 1). Maculopapular rashes are not specific for EBV and can also be associated with other herpesviruses, as well as acute infection with HIV, which should be considered depending on the clinical setting. Concurrent use of antibiotics during suspected primary infection with EBV or related viruses should be avoided because drug rash might be more common and lead to misdiagnosis of drug allergy.

If recent EBV infection is suspected, focused testing for virus-specific antigens, such as IgG and IgM to the viral capsid antigen, IgG to early antigen, and Epstein-Barr nuclear antigen (EBNA), can determine the presence or absence of primary infection, whereas the monospot test is less sensitive and specific for acute EBV infection but also less expensive. During viral latency, the virus expresses a very limited set of proteins, primarily EBNA-1, and thus past but not current or recent viral infection with EBV can be confirmed by expression of IgG against EBNA to distinguish between recent and past infection with viral reactivation. Because of the potential for atypical or prolonged primary infection or viral reactivation, clinicians caring for atopic patients should have a high index of suspicion to avoid misdiagnosis of EBV for other infectious diseases or allergic conditions (Figs 1 and 2).

Primary infection with other herpesviruses, such as CMV, can also present with a nonspecific rash. Serologic tests for IgG and IgM to virus-specific antigens for EBV and CMV are available from most clinical laboratories, with virus-specific IgM confirming recent primary infection and virus-specific IgG confirming past infection. After acute infection, virus-specific IgM values should gradually decrease to undetectable levels after infection, whereas virus-specific IgG levels will remain positive for the life of the host. PCR for EBV or CMV is also available at most academic centers but is rarely required to make a diagnosis. In general, a focused history including evidence of recent symptoms, such as fever and pharyngitis, is sufficient to make a clinical diagnosis of a postviral rash or syndrome without any required laboratory testing, although laboratory testing can be very useful in confirming the clinical diagnosis and excluding other incorrect diagnoses.



FIG 1. A teenage boy with a history of seasonal allergic rhinitis was referred for evaluation of suspected antibiotic allergy and possible Rocky Mountain spotted fever. The previous week, amoxicillin had been administered for pharyngitis and a flu-like illness. On examination, he was afebrile and well appearing, with a diffuse maculopapular rash on his torso (*right panel*) and the palms of his hands (*left panel*). Subsequent laboratory testing showed no evidence of Rocky Mountain spotted fever or related rickettsial pathogens but conclusive evidence of recent EBV infection, increased viral capsid antigen IgG and IgM and early antigen levels, and negative EBNA results. Photographs were provided by the author with the patient's consent.



FIG 2. A teenage boy with a history of allergy, eczema, and asthma was referred for evaluation of urticaria or drug allergy because his hands and feet were “turning blue and itching.” He was taking amoxicillin for sinusitis and had a low-grade fever and flu-like symptoms over the past several weeks, but seasonal allergy and asthma were stable. Examination showed swollen extremities with purpura (*left panel*). One week later, desquamation of the palms and soles was evident (*right panel*). An ultrasound for Kawasaki cardiovascular disease was normal. Subsequent serology showed evidence of recent EBV infection, increased viral capsid antigen IgG and IgM and early antigen levels, and negative EBNA results. After a short course of oral corticosteroids, he resumed his normal state of health. Photographs were provided by the author with the patient's consent.



FIG 3. A woman with previous allergy and eczema was referred for possible contact allergy to her necklace. She had no previous history of contact allergy and had worn the necklace previously without problems. Examination showed erythematous vesicular lesions confined to a single hemi-dermatome region consistent with shingles rather than contact allergy. The rash resolved with topical acyclovir antiviral therapy, and subsequent testing showed no evidence of contact allergy to metal or other contact allergens. Photographs were provided by the author with the patient's consent.

THERAPY OF ACUTE INFECTION WITH EBV AND RELATED β AND γ HERPESVIRUSES

In most cases acute infection with EBV and other herpesviruses is a self-limiting condition. Therefore in cases of prolonged or severe acute illness, a hereditary or acquired immunodeficiency should be considered (eg, rare conditions, such as X-linked immunoproliferative syndrome). However, more commonly, prolonged or atypical syndromes are not associated with any identified acquired or hereditary immune deficiency (Fig 2). Therapy options for acute EBV infection and related syndromes resulting from primary herpesvirus infections currently include oral corticosteroids for upper airway obstruction, vasculitis, or prolonged or atypical symptoms, such as hepatitis. Other immunomodulatory agents, such as intravenous immunoglobulin or rituximab, might be indicated for immunomodulation or depletion of abnormal B-lymphocyte proliferation in patients with X-linked immunoproliferative syndrome or similarly severe or atypical cases.¹⁸

Antiviral therapy with nucleoside inhibitors, such as acyclovir, administered to patients with acute mononucleosis decreases viral shedding but seems to have no effect on the course of the primary illness or viral latency, suggesting a clinical need for more effective antiviral therapy.³⁴ Unusual EBV-related conditions, such as oral hairy leukoplakia or B-cell lymphoma, should also be considered as possible presenting conditions of hereditary immune deficiency or AIDS. Vaccines targeting the viral glycoprotein GP350/220, a potential neutralizing antibody for prophylaxis of EBV primary infection, have been studied in phase I and II human clinical trials and appear to be safe, but no approved prophylactic or therapeutic vaccine is currently available.

SHINGLES, VZV VACCINE, CORTICOSTEROID USE, AND OTHER ISSUES RELATED TO α HHV3 IN ATOPIC PATIENTS

Clinicians caring for atopic patients will often encounter cutaneous reactivation of VZV (or HSV3). Reactivation of VZV, termed shingles, can be mistaken for contact or drug allergy; however, the characteristic distribution of a vesicular rash confined to a single hemi-dermatome is usually sufficient to make the diagnosis without additional testing (Fig 3). Unfortunately, the effectiveness of available therapies, such as oral corticosteroids and acyclovir or related antiviral drugs, after onset of shingles lesions is limited,³⁵ although as with EBV, additional antiviral drugs might be available in the future.³⁴ The immunobiology of VZV has been intensively studied in the past several decades because in contrast to other chronic herpesvirus pathogens, a live attenuated vaccine has been in widespread clinical use for the past decade.³⁶ Because VZV live attenuated vaccine is the first successful vaccine for a herpes pathogen, it might provide a model for understanding issues related to vaccines for other chronic viral pathogens that could be available in the future.³⁷⁻⁴⁴

Concerns that have been raised regarding the attenuated VZV vaccine include the possibility that VZV-vaccinated children might have increased incidence of atopic dermatitis versus wild-type VZV-infected children, suggesting that wild-type virus zoster might be protective against some forms of atopic disease.⁴⁵ In the elderly increased incidence of shingles is associated with decreased cellular immunity to VZV, and thus elderly subjects, particularly those with atopic disease, should receive the shingles vaccine because they are at increased risk of viral reactivation.⁴⁶ Additional studies are in progress to determine the effect of large-scale VZV vaccination, particularly with respect to later viral illness, such as shingles, and as with all live vaccines, VZV vaccine



FIG 4. Cutaneous HSV1 or HSV2 infection presenting with skin lesions, including oral (*left panel*) and periorbital (*right panel*) lesions termed “eczema herpeticum” can be mistaken for exacerbations of atopic dermatitis or contact allergy. Ocular disease can require prompt therapy with antiviral drugs to prevent subsequent corneal scarring, vision loss, and blindness. Photographs are from www.CDC.gov.

should be administered with caution to patients with known or suspected defects in cellular immunity.⁴⁷ Concerns that the VZV vaccine and future vaccines in development for other herpesviruses in clinical trials might contribute to some increase in atopy versus wild-type viral infection must be balanced against the largely positive overall efficacy of the VZV vaccine, which has conclusively reduced VZV-related mortality and morbidity since its introduction (see the Conclusions section).

Oral corticosteroid, but not inhaled corticosteroid, use in atopic or asthmatic patients can contribute to vaccine failure.⁴⁸ Some data suggest that complications, including shingles, can occur from the vaccine and might be more common in patients with atopy, asthma, or both.^{49–51} Before the clinical approval of the VZV vaccine, clinical reports suggested that patients receiving both inhaled and oral corticosteroids were at increased risk of severe or atypical VZV, but subsequent studies have not confirmed an increased risk of VZV-related illness related to standard doses of inhaled corticosteroids.^{52–54} Atopic patients receiving long-term oral corticosteroids for asthma or eczema, as well as immunodeficient patients, are at increased risk for severe or atypical VZV infection, and appropriate therapy, such as VZV immune globulin, or antiviral drugs, such as acyclovir, should be considered if these patients are suspected of exposure to wild-type virus.⁵⁵

ECZEMA HERPETICUM AND RELATED CUTANEOUS, PULMONARY, AND NEUROLOGIC SYNDROMES RELATED TO THE α HERPESVIRUSES HSV1 AND HSV2

Herpesviruses infect and replicate in cutaneous and pulmonary epithelial cells during primary infection and during episodes of viral reactivation before establishing latency in neuronal cells, and pulmonary epithelial cells are also a primary route of viral spread. Therefore both atopic patients and neonates and young infants with immature immune systems are at higher risk of pulmonary syndromes, such as bronchitis and pneumonia, and neurologic syndromes, such as encephalitis, which are encountered in immunodeficient populations. The most common presentation of atypical herpesvirus infection in the atopic population is a severe or disseminated skin rash termed eczema herpeticum.^{56,57} As shown in Fig 4, a high index of suspicion should be present for eczema herpeticum in patients with pre-existing atopic dermatitis because antiviral therapy is indicated

in addition to standard anti-inflammatory therapy for atopic eczema when symptoms involve the eye.

A clinical concern has been that patients with atopic dermatitis can have more severe eczema herpeticum if they are simultaneously using topical corticosteroids, and whether topical corticosteroid therapy should be discontinued when herpes-related skin rashes are present.⁵⁸ Fortunately, topical corticosteroids do not seem to be associated with worse outcomes in patients with eczema herpeticum, although prior use of oral corticosteroids can be associated with more severe disease.⁵⁸ Prophylactic use of antibacterial antibiotics for patients with eczema herpeticum does not seem to improve outcomes, except in patients with documented bacterial bloodstream infection.⁵⁹ Notably, use of antiviral therapy for prophylaxis in patients at high risk of disease from HSV or VZV because of bone marrow transplantation may be interfere with protective immune responses to VZV and onset of shingles if prophylaxis is discontinued prematurely.³⁵

Atopic patients may have a hereditary predisposition toward decreased expression of T_H1 cytokines, such as interferon, in addition to or related to increased T_H2 cytokine expression.⁶⁰ Increasing knowledge of specific defects in the innate and acquired immune system demonstrates that healthy-appearing patients of any age can have catastrophic illnesses, such as herpes encephalitis caused by HSV1, HSV2, or HHV3 (VZV), as a result of single mutations in T_H1 -related host immune response proteins.^{33,61–66} Because these molecular defects are apparently specific for innate immune receptors required for response to α herpesviruses, they cannot be identified by using standard methods. Instead, if a family or personal history is suggestive of a hereditary innate immune defect specific for recurrent or severe herpes infection or eczema herpeticum, patients and their families should be referred for specialized testing to centers offering these services.⁶⁰

HSV conjunctivitis might be more severe in the atopic patient and require immediate recognition and appropriate therapy with antiviral agents.^{67,68} Interestingly, survival of corneal grafts appears to be related inversely to atopy, which is consistent with suppression of T_H1 cytokine-mediated graft rejection by T_H2 cytokines, which can also affect T_H1 -mediated viral immunity.⁶⁹ In summary, clinical and epidemiologic observations confirm that acute HSV1, HSV2, and HHV3 (VZV) infections are more severe in the atopic population,^{12,13,17,70–73} although the consequences of herpesvirus latent

infection on progression of atopic disease are less well established because of complex environmental interactions.⁷⁴

CMV AND RELATED β HERPESVIRUSES HHV6 AND HHV7 ARE ASSOCIATED WITH CARDIOVASCULAR SYNDROMES AND DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS SYNDROME

CMV (HHV5) can cause cutaneous syndromes similar to those associated with EBV (Figs 1 and 2). CMV, like HSV, is also associated with ocular diseases, causing diagnostic uncertainty.⁷⁵ CMV causes chronic inflammation and cardiovascular disease because it exists in a latent form in macrophages associated with vascular inflammation and can infect the vascular endothelium. *In vitro* and *in vivo* evidence confirms that CMV directly induces host T_H2 cytokines, such as IL-6.⁷⁶ In patients with HIV and other immunodeficiencies, cardiovascular and other CMV-related pathologies are more pronounced.⁷⁷ Remarkably, cardiovascular disease is also more common in atopic patients, and thus a connection between CMV, atopic disease, and cardiovascular disease might exist.^{78,79}

HHV6 and the less common but similar HHV7 are the cause of roseola, a febrile illness in infancy or early childhood followed by a nonspecific maculopapular rash (Fig 1) that can be mistaken for allergic urticaria or vaccine or drug allergy.⁸⁰⁻⁸⁵ Although 2 forms of HHV6 termed “alpha” and “beta” are currently circulating in human populations, functionally these 2 viral strains are considered similar.⁸⁰⁻⁸⁴ Typically, no laboratory evaluation is required for primary infection with HHV6 or HHV7, which is a self-limiting condition unless associated with neurologic symptoms or immunodeficiency syndromes, in which case PCR might be useful to differentiate past from recent infection. Primary infection with HHV6 occurs in virtually 100% of the pediatric population, and therefore the results of laboratory evaluation in any patient after early childhood will almost invariably be positive for past infection. Approximately 1% of the population carries a stable integrated copy of the virus in the germline transmitted to all progeny, and thus even if universal vaccination were available, the virus could not be eliminated.^{86,87}

Recently, a role for herpesvirus reactivation has been found in severe drug allergy termed drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.⁸⁸⁻⁹¹ DRESS syndrome with HHV6 or HHV7 viral reactivation is detected through a combination of increased IgG levels to viral proteins and PCR and is more common in the setting of organ transplantation or other syndromes of immune deficiency. Antiviral therapy directed at HHV6 and HHV7 can thus be indicated for DRESS syndrome or another cutaneous disease in the setting of drug allergy or immunosuppression, although this has not been confirmed in placebo-controlled studies. Complicating the diagnosis of DRESS syndrome because of herpes reactivation, germline-integrated genomes of HHV6 can be detected by means of PCR as highly increased levels of circulating viral DNA that might be confused with acute infection or viral reactivation. In addition, the clinical significance of integrated germline HHV6 for carriers seems to be unknown.^{86,87} Therefore additional studies are urgently needed to clarify the risks and benefits of antiviral therapy for DRESS syndrome and related severe drug allergy syndromes, but such therapy can be considered on a case-by-case basis, despite the absence of placebo-controlled studies.

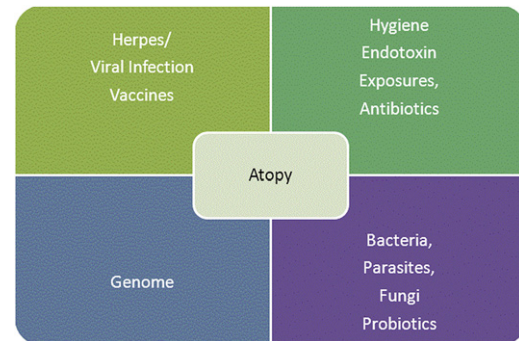


FIG 5. Atopy (center) represents complex interactions between herpes and other viral infections and vaccines (top left); hygiene, such as exposure to endotoxin and other probiotic agents (top right); colonization with other infectious agents, such as bacteria, parasites, and fungi (bottom right); and the host genome (bottom left). Because each of these factors interact with each other, it might be difficult or impossible in a particular patient to predict the effects of one factor on other factors and atopy; however, trends might be evident in large populations.

KAPOSI SARCOMA VIRUS AND OTHER HERPESVIRUSES IN PATIENTS WITH AIDS

Kaposi sarcoma virus (KSV or HHV8) infects a smaller percentage of the human population than other herpesviruses and presents with symptoms mostly in patients with immunodeficiency diseases, such as AIDS. Thus AIDS or hereditary immunodeficiency should be considered in all cases of HHV8-related Kaposi sarcoma or Castleman disease.⁹²⁻⁹⁵ KSV can also present as eczema herpeticum similar to HSV and should be considered in the appropriate populations.⁹⁶ A protein termed vIL-6 closely related to human IL-6, a T_H2 cytokine, is encoded by HHV8, although the effects of this cytokine on the host immune system have been less well studied than the EBV-encoded vIL-10 reviewed previously.⁹⁷ In patients with HIV/AIDS, KSV-related diseases might respond to antiviral therapy of both HIV and HHV8. As noted above, prolonged or unusually severe EBV or CMV infection, chronic shingles caused by HHV3, or recurrent HSV lesions might also be signs of other chronic viral illnesses, such as HIV or hereditary immunodeficiency, requiring additional evaluation in addition to related atopic or allergic disease.

CONCLUSIONS

The atopic phenotype reflects complex interactions between the host, the herpes microbiome, other environmental factors and hygiene, other infectious agents (eg, bacteria, parasites, and fungi), and the host genome (Fig 5). These factors interact with the host, but they also interact with each other, making predictions in an individual patient difficult or impossible. Nonetheless, certain general conclusions seem plausible. For example, it is likely that as the incidence of atopic disease increases in a population, the incidence of herpes-related pathology caused by both primary infection and viral reactivation will increase. Conversely, increased use of an attenuated herpes vaccine, such as the vaccine currently available for VZV, might be associated with increased atopy in the population versus infection with wild-type virus. Nonetheless, it is neither practical nor advisable to limit vaccination against VZV and other herpes vaccines that might be available in the future to the nonatopic population because the atopic population might also be at increased risk of severe or fatal

complications from the wild-type virus, which the VZV vaccine, for example, has largely eliminated.

Therefore physicians caring for patients with atopic diseases should advocate the use of vaccines, such as the current VZV and shingles vaccines, and also be aware of common and uncommon presentations of herpesvirus-related illness, which might be more severe in atopic patients, to provide correct diagnosis and to institute effective antiviral therapy promptly. Because of the replication cycle of herpesviruses in epithelial tissues, acute viral infection and reactivation can be associated with skin rashes and neurologic and pulmonary symptoms in both immunocompetent atopic populations and immunodeficient populations. Antiviral therapy should be provided on either a treatment or prophylactic basis depending on the clinical setting, and antiviral therapy does not appear to prevent generation of subsequent viral immunity.⁹⁸ Severe or recurrent symptoms can also be a presenting sign of immunodeficiency, either acquired or hereditary, requiring additional evaluation.

Molecular evidence suggests that the herpesviruses as a group have been coevolving with the immune system since before the origins of acquired immunity. The recombination-activating gene 1 recombinase protein required for B- and T-lymphocyte recombination and the acquired immune system is closely related to a herpes-encoded recombinase apparently has resulted from insertion of a herpes-like virus into the genome before the origins of the acquired immune system more than 500 million years ago.⁹⁹ Toll receptor polymorphisms and defects in other innate immune proteins are now known to account for significant human pathology, such as viral encephalitis,^{33,61-66} and herpes pathology can also be more severe in the atopic population because of functional changes in innate immune signaling. In experimental models, vaccines or antiviral therapy can have therapeutic benefits, as in the case of the current VZV vaccine, but also potentially alter the immunomodulatory effects of lifelong chronic infection with EBV and related herpesviruses, with unknown consequences on atopy and allergy.¹⁰⁰

The hygiene hypothesis broadly stated suggests that exposures to differing components of the environment caused by improved hygiene can alter the prevalence and severity of atopic diseases in the population (Fig 5). Changes in hygiene are apparently linked to changes in the herpes microbiome, as well as exposures to other viral pathogens, such as respiratory tract viruses and hepatitis A. Changes in the herpes and viral microbiome in turn influence subsequent atopic diseases through multiple mechanisms involving inflammation and tolerance mediated not only by T_H1 and T_H2 cytokines but also by so-called suppressor or T_H3 and inflammatory T_H17 cytokines.^{101,102} The regulation of virus-encoded and host-encoded cytokines in patients with DRESS syndrome and other atopic diseases and other aspects of interaction between viral gene expression and innate immune and regulatory genes should be an important area for further study, along with other components of the human microbiome.^{103,104}

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