

Current perspectives

Viral infections in atopic dermatitis: Pathogenic aspects and clinical management

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A number of different widespread and disseminated viral infections can occur in patients with atopic dermatitis. Eczema molluscum is troublesome but not dangerous. Although eczema vaccinatum is rare, it is life-threatening and of increased concern as smallpox vaccinations are reintroduced as a response to possible bioterrorism. There is little information on the course of smallpox itself in atopic dermatitis. Eczema herpeticum is the most common member of this group; recent advances in understanding its pathogenesis might contribute to a more successful management of this serious complication. (J Allergy Clin Immunol 2003;112:667-74.)

Key words: Atopic dermatitis, cowpox, smallpox, eczema herpeticum, eczema molluscum, eczema vaccinatum

Patients with atopic dermatitis (AD) tend to have widespread disseminated viral infections^{1,2} named after the causative virus eczema molluscum (EM), eczema vaccinatum (EV), or eczema herpeticum (EH). The disturbed skin barrier in AD might provide easier access for the virus. In addition, T_H2 cell predominance leads to production of IL-4, which induces IgE production and prevents differentiation of IFN- γ -producing T_H1 cells. The lower levels of IFN- γ in the skin of patients with AD may allow the viruses to overgrow.³ Other causative factors may include impaired recruitment of plasmacytoid dendritic cells (PDCs).⁴ We review the pathogenesis, clinical aspects, and therapy of these potentially dangerous complications of AD.

MOLLUSCUM CONTAGIOSUM: EM

Molluscum contagiosum virus (MCV) is a poxvirus and the sole member of the Molluscipoxvirus subfamily. It is highly distinct from variola, vaccinia, and cowpox viruses, which belong to the *Orthopoxvirinae* genus. Virus particles are brick shaped with round corners and contain a large, double-stranded DNA genome of 130 to

Abbreviations used

AD: Atopic dermatitis
CDC: Centers for Disease Control and Prevention
EH: Eczema herpeticum
EM: Eczema molluscum
EV: Eczema vaccinatum
HSV: Herpes simplex virus
MCV: Molluscum contagiosum virus
PDC: Plasmacytoid dendritic cell
VIG: Vaccinia immunoglobulin

300 kb. The key feature of the diverse poxviruses is replication in the cytoplasm mediated by distinct enzymes not present in other DNA viruses. The poxviruses are brick shaped and large enough to be seen on light microscopy. MCV has unique proteins that help it avoid antiviral defense mechanisms.⁵ MCV produces a soluble IL-18 binding protein that inhibits the IL-18-mediated induction of IFN- γ .⁶ These findings help explain the absence of T-lymphocyte and natural killer cell subsets at the base of typical MCV lesions.⁷

Umbilicated, small, skin-colored papules are the diagnostic hallmark of molluscum infection. In children the lesions usually involve the face, trunk, or limbs, whereas in adults the genital area is most commonly affected. Usually only a few lesions are present, and the infection is self-limited.

Patients with AD not only have more MCV infections than nonatopic individuals, but they also have more widespread disease, with up to several hundred lesions.⁸ This disseminated eruption is designated as EM (Fig 1). Although papules are frequently confined to the eczematous lesions, autoinoculation might produce papules in other areas. There are no systemic findings.

In most cases molluscum contagiosum can be diagnosed clinically. If the diagnosis is uncertain, it can be confirmed histologically because epidermal hyperplasia is found with an invagination loaded with molluscum or Henderson-Paterson bodies (MCV-infected keratinocytes). The MCV particles can also be seen with electron microscopy.⁹

Although EM lesions resolve spontaneously, treatment speeds healing and prevents spreading by autoinoculation and heteroinoculation. We usually destroy limited numbers of lesions with small curved forceps or remove

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FIG 1. EM. A disseminated eruption of whitish umbilicated papules on eczematous skin shows considerable variation in size.

them by means of curettage. Pretreatment for 30 minutes with EMLA cream provides local anesthesia and softens the lesion for easier removal. Other destructive treatment measures include cryotherapy or carbon dioxide laser vaporization. Topical application of imiquimod or other topical immunostimulatory drugs shows promising results.¹⁰ Topical corticosteroids or calcineurin inhibitors should be stopped to facilitate mounting of a natural immune response against the virus (Wetzel et al, unpublished data). Because the virus is easily spread by a scratching hand, the affected areas should be covered. Children can continue in daycare or school.

ORTHOPOXVIRUS INFECTION: EV

Variola virus, which causes smallpox; vaccinia virus, which is used for vaccination; and cowpox virus all belong to the *Orthopoxvirinae* genus and share many clinical similarities.

Cowpox inoculation in AD: Localized and disseminated infection

Cowpox virus infection of human subjects has been described only in Europe.¹¹ Despite its name, cowpox is rare in cattle. The reservoir hosts are rodents; secondary hosts include cats, cows, and human subjects. Transmission to human subjects occurs by means of contact with domestic cats or the infected teats of milk cows. Smallpox vaccination might provide some protection against cowpox infection.

Clinically, the infection is usually limited, with pustular lesions at the inoculation site, most often the hands. The individual lesions look similar to those caused by smallpox vaccination, although they are more inflamed. Fever, malaise, and lymphadenopathy are rare. Patients with an underlying immunodeficiency, such as AD, are at risk for generalized cowpox infections with a more severe or even fatal course.¹¹⁻¹³

Identification and isolation of animals infected with cowpox help prevent human infections, as does proper hand washing. Cowpox is treated just as vaccinia. Because single lesions tend to regress spontaneously, the administration of anti-vaccinia immunoglobulin (anti-VIG) should be restricted to disseminated or severe cases.

Vaccinia inoculation: EV

The origin of vaccinia virus is not completely clear, but most likely, it is derived from a cowpox virus strain. Since Jenner's historic experiments in 1796, vaccination with vaccinia virus has been performed to prevent or attenuate smallpox infection with the variola virus in human subjects.¹⁴ After the declaration of smallpox eradication by the World Health Organization in 1980, all countries stopped widespread vaccination. Today vaccination is restricted to military personnel, specialized laboratory workers, and, in some countries, hospital workers.³ Along with its legacy of enormous success, the live-virus smallpox vaccine has the dubious distinction of having one of the highest rates of vaccine-associated adverse events among all vaccines currently in routine use.³ Other virus strains, such as modified vaccinia virus Ankara, with a much better risk/benefit ratio could replace the vaccinia virus.¹⁵

An underlying immunologic deficiency, such as AD, might lead to a disseminated eruption of vaccinia, which is known as EV, presenting with a dense eruption of large disseminated blisters and pustules together with fever and systemic findings. Because AD is a contraindication to smallpox vaccination, EV is more frequently caused from accidental contact with vaccinated individuals (65%) than from vaccination.¹⁶ In the past, the incidence of EV in the United States was 123 per million primary vaccines, with case fatality rates of approximately 1% to 5%.^{17,18} Recent data from a cohort of Israel Defense Force recruits showed an overall complication rate of 40 per million vaccinees, with a low rate of severe compli-

TABLE I. Antiviral chemotherapy of EH

Substance	Class	Indication	Dosage	Side effects
Acyclovir	Nucleoside analog	Mild EH Severe EH Prophylaxis	400 mg po 5 times per day 5-10 mg/kg per dose iv tid 200 mg po tid	Nephrotoxicity, local inflammation
Valacyclovir	Nucleoside analog	Mild EH	500 mg po tid	Similar to acyclovir
Famciclovir	Nucleoside analog	Mild EH	500 mg po bid	Similar to acyclovir
Penciclovir (not yet licensed)	Nucleoside analog	Mild EH	5 mg/kg per dose iv bid	Similar to acyclovir
Foscarnet	Phosphonate	Acyclovir resistance	40 mg/kg per dose iv bid	Nephrotoxicity, hypokalemia, myelosuppression

po, By mouth; tid, 3 times daily; bid, twice daily.

cations similar to previously published data.¹⁹ Seemingly contradictory are published data suggesting that two thirds of patients with EV did not have active atopic disease at the time of their vaccinia virus exposure.¹⁶ If variola virus is released as a biologic weapon, ring vaccination of first and second contacts with vaccinia virus will certainly produce some cases of EV.²⁰

The main differential diagnostic consideration is smallpox infection, which might be suspected from the centripetal and less dense distribution pattern of the lesions, which show a clear predilection for wrists and face. Because most physicians have not seen patients with EV, we recommend visiting the highly useful Centers for Disease Control and Prevention (CDC) smallpox Internet training module, which includes a number of excellent clinical pictures, including EV (<http://www.bt.cdc.gov/Agent/Smallpox/Smallpox.asp>). Other potential adverse events from smallpox vaccination are discussed elsewhere in this issue.²¹

PCR is the method of choice to diagnose vaccinia virus infection and to distinguish it from variola virus. Electron microscopy can demonstrate poxvirus particles in the blister fluid. Commercial serologic or antigen detection assays are not available. In the United States federal law requires that public health authorities be informed if EV is suspected. The legal situation in Europe differs from country to country, but public health authorities should be contacted.

Therapy of EV requires prompt administration of VIG, which is stored at the CDC in Atlanta. Even if there is a delay in recognition, VIG should still be started as soon as possible. Normally, the initial dose of intramuscular VIG is 0.6 to 1.0 mL/kg body weight.²² In case of extensive lesions, as much as 5 to 10 mL/kg intramuscular VIG divided into multiple doses should be administered over several days. Most patients can be saved by VIG treatment.

Smallpox infection in AD

Smallpox is caused by variola virus, the only natural host of which is human subjects. Smallpox can be spread through aerosols or direct contact with fluids or scabs of an infected person or any contaminated objects. Smallpox is a serious and sometimes fatal infection divided into 2 subtypes: variola major and variola minor. Variola

major has an overall fatality rate of about 30%; rare variants, such as flat and hemorrhagic smallpox, are usually fatal. There is no specific treatment for smallpox, and the only proved prevention is vaccination. After the declaration of successful eradication by the World Health Organization in 1980, the variola virus should have been eliminated except for laboratory stockpiles legally preserved in laboratories in Atlanta and Moscow. Since September 11, 2001, there has been increasing concern that variola virus might be preserved in other places and used for bioterrorism. Worldwide precautions for dealing with a smallpox outbreak, including vaccination campaigns, have been undertaken.

The diagnostic clinical presentation of smallpox is a number of large firm papules transforming synchronously into vesicles, pustules, and scabs presenting in a peripheral distribution in a severely sick patient. After an incubation period from 7 to 17 days, the first symptoms include fever, malaise, and headaches. During this prodrome phase, the fever is usually high, and patients feel too sick to carry on their normal activities. After 2 to 4 days of fever, a rash occurs on the tongue and in the mouth, spreading all over the body. By the fourth day, the rash becomes papular and then vesicular; by the seventh day, pustules develop, form a crust, and then scab. As a rule, all the lesions look the same at any given time in smallpox, whereas those in varicella do not. Although there is no historical evidence for a different clinical course of smallpox infection in patients with AD,¹⁴ it is likely that smallpox does take a more severe course in patients with AD.

Therapy of manifest smallpox infection is disappointing. VIG and mithisazone (methylisatin-thiosemicarbazone) have some prophylactic but no therapeutic effects. VIG was produced in the 1960s from plasma obtained from recently vaccinated donors and is stored at the CDC in Atlanta. It contained a high titer of antivaccinia neutralizing antibody but also a high proportion of aggregated protein, so that it must be given intramuscularly. A new formulation of VIG with a low level of aggregated protein for intravenous administration is currently being produced to support larger scale emergency vaccination programs.²³

Immediate vaccination after exposure to smallpox might prevent infection or at least beneficially affect the



FIG 2. EH, vesiculopustular stage. A disseminated eruption of distinctly monomorphic dome-shaped blisters and secondary pustules on eczematous skin is suggestive of EH.



FIG 3. EH, crust stage. After a few days, the blisters are drying out and form crusts that fill eroded pits.

course. Because AD and a number of immunodeficiency syndromes are a contraindication to smallpox vaccination, these patients must be reliably identified. Clinical trials with nonreplicating viral vaccines are planned.²⁴

EH

EH is the most important disseminated viral infection because it can occur in many settings and requires immediate medical action. EH was first described by the Austrian dermatologist Moritz Kaposi in 1887, when he published data on 10 children with “eczema larvare infantum” complicated by a vesicopustular eruption.²⁵ Today, the diagnosis of Kaposi’s varicelliform eruption is used for disseminated cutaneous infection with the herpes simplex virus (HSV) of any skin disease, including not only AD and other types of dermatitis but also Darier-White disease,²⁶ pemphigus foliaceus,²⁷ mycosis fungoides,²⁸ Sézary syndrome,²⁹ ichthyosis vulgaris,³⁰ Hailey-Hailey disease,³¹ and burns.³² EH should be restricted to disseminated HSV infection in AD or other forms of dermatitis.

Clinical characteristics of EH

Clinically, patients with EH present with a disseminated, distinctly monomorphic eruption of dome-shaped vesicles (Fig 2) accompanied by fever, malaise, and lymphadenopathy. The head, neck, and trunk are most commonly affected. Within 2 weeks, the blisters usually dry out, forming crusts that fill eroded pits (Fig 3). Characteristic disseminated slits in tense erythematous plaques might also occur. Lesions generally heal within 2 to 6 weeks. Associated complications include keratoconjunctivitis and viremia, leading to multiple organ involvement with meningitis and encephalitis. The mortality of EH was about 75% before effective antiviral treatment.^{33,34}

Epidemiologic data on EH is scarce; only 2 large studies are available.^{35,36} Predisposing factors include early onset of AD and a high total serum IgE level.³⁶ Although topical corticosteroids do not seem to predispose to EH,³⁶ topical calcineurin inhibitors might increase the incidence of EH.³⁷

Pathogenesis of EH

Primary infection with HSV-1 usually occurs during childhood and is either asymptomatic or causes herpetic gingivostomatitis. Later HSV reactivation presents as recurrent herpes simplex of the perioral region (cold sore or fever blister). Patients with compromised cell-mediated immunity, as present in AD, may have recurrent and severe HSV infections, including EH, which may be caused by either primary or secondary HSV infection.³⁶

The impaired skin barrier of patients with severe AD makes it easier for the virus to invade the skin and bind to cellular receptors. A desmosomal protein has recently been identified as one of the relevant HSV receptors in human subjects.³⁸ A predisposition to T_H2-type responses might also contribute to HSV overgrowth.³

Impairment of PDCs in the skin of patients with AD may be a cofactor for the susceptibility of patients with AD to EH.⁴ PDCs are a novel dendritic cell subset that circulate in the blood and make up 0.1% of PBMCs.³⁹ PDCs produce large amounts of antiviral type I IFN- α and IFN- β on viral infection and are capable of inducing both T_H1 and T_H2 responses. Although the number of peripheral blood PDCs is increased in AD,⁴⁰ impaired recruitment of PDCs into AD skin lesions compared with other inflammatory skin diseases, such as psoriasis or contact dermatitis, is observed.⁴ Because a patient's ability to defend himself against HSV infection might critically depend on the production of antiviral type I IFNs, a lack of cutaneous PDCs can explain why patients with AD show a predisposition to viral skin infections.⁴

Defensins and cathelicidins are antimicrobiologic peptides that play a major role in innate and adaptive immunity.⁴¹ There are several human defensins but only one cathelicidin, LL-37.⁴¹ The upregulation of β -defensin in the presence of bacterial LPS and TNF- α is a key function in innate antimicrobial defense. The β -defensin HBD-2 and LL-37 are significantly decreased in skin lesions of patients with AD compared with lesions of patients with psoriasis, providing an explanation for the predisposition of patients with AD to *Staphylococcus aureus* infection.⁴² Although the antimicrobial activity of antimicrobiologic peptides is well established, there are little data on their antiviral function. Defensins show antiviral activity by binding directly to some enveloped viruses, such as recombinant adeno-associated virus and HSV,^{43,44} whereas LL-37 can kill vaccinia virus⁴⁵ and HSV (Jones and Leung, unpublished observation).

Diagnostic procedures in EH

In most cases the typical clinical features of EH distinguish it from chickenpox, widespread impetigo, other disseminated infections, or contact dermatitis. The clinical diagnosis should be confirmed by means of PCR for viral DNA, electron microscopic detection of herpes group virus from blister fluid, or commercial immunofluorescence tests to identify HSV-infected cells. The diagnosis is supported by demonstration of large multinucleated cells in the blister fluid with conventional light

microscopy (Tzanck test). Serologic assays may indicate a primary HSV infection or reactivation but are less specific than identification of the pathogen. Virus isolation is very time consuming and relatively insensitive.³⁶

Differential blood count, erythrocyte sedimentation rate, and body temperature can all reflect the severity of the infection. Serum creatinine levels should be checked before starting systemic acyclovir therapy. Bacterial superinfection can be excluded with culture.

Patients with EH should be seen by an ophthalmologist to monitor for herpetic keratitis. A neurologist should examine the patient if meningitis is suspected. Clinical features of central nervous system infection with HSV include headache and confusion. Areas of decreased attenuation in the temporal lobes in the computed tomographic scan, electroencephalographic abnormalities, and pleocytosis and increased protein levels in the cerebrospinal fluid suggest herpes encephalitis.⁴⁶

Therapy of EH

The keystone of EH therapy is prompt systemic antiviral chemotherapy to limit disease duration and prevent further complications. Oral antibiotics are frequently given to control bacterial superinfection; oral cephalosporins (eg, cefadroxil, 1 g by mouth twice daily) are our treatment of choice. Topical antiseptic lotions may help by drying out the vesicles and preventing bacterial superinfection.

The administration of anti-inflammatory therapy, including glucocorticosteroids, in acute EH is controversial because the desired anti-inflammatory activity will be inevitably associated with an unwanted attenuation of the overall immune defense. In spite of convincing evidence, most clinicians avoid topical and systemic glucocorticosteroids in the acute phase of EH. Topical calcineurin inhibitors are contraindicated in acute EH.

Systemic antiviral chemotherapy of EH. Currently, the most potent drugs used for HSV therapy are nucleoside analogues, such as acyclovir, which interfere with viral DNA replication. Before the introduction of acyclovir, the mortality rate of EH was approximately 75%.^{33,34} Shortening of disease duration by oral acyclovir has been demonstrated in a multicenter, double-blind, placebo-controlled study involving patients with EH.⁴⁷ The currently recommended regimen for EH is a 7-day course of intravenous acyclovir (5-10 mg/kg per dose administered intravenously 3 times daily), which may be prolonged according to the clinical course of the disease. For children less than 12 years old, the recommended dose is 750 mg/m² per dose administered intravenously 3 times daily for 7 days. Oral acyclovir has a lower bioavailability (15%-30%) than intravenously administered acyclovir and should therefore be restricted to the treatment of mild EH (400 mg by mouth 5 times per day). Acyclovir resistance, which appears in 4.7%⁴⁸ to 17%⁴⁹ of patients with HIV is rarely seen in patients with EH. Although there are no studies about acyclovir prophylaxis in patients with recurrent EH, oral acyclovir in a dosage of 200 mg by mouth 3 times daily might be a therapeutic option in patients with severe recurrent EH.

Acyclovir has few side effects because it is only active after modification by the viral enzyme thymidine kinase, which is only present in HSV-infected cells. There is no evidence for a teratogenic effect of acyclovir, but its administration during pregnancy is still a matter of controversy because no large well-controlled studies have been performed.⁵⁰ Most women are treated with intravenous acyclovir (5–10 mg/kg per dose administered intravenously 3 times daily) for at least 7 days⁵⁰ because EH during pregnancy can lead to intrauterine infection in about 50% of fetuses, usually during the first 20 weeks, with an increased rate of spontaneous abortions and birth defects.⁵¹

The prodrug valacyclovir is almost completely converted to acyclovir during first-pass metabolism in the liver but has a better oral bioavailability than acyclovir. There are no studies about the efficacy of valacyclovir in the treatment of EH. We recommend a 7-day course of oral valacyclovir (500 mg by mouth 3 times daily) for EH treatment; treatment can be prolonged according to the clinical course.⁴⁹

Penciclovir and its prodrug famciclovir are nucleoside deoxyguanosine analogs that exhibit an antiviral activity spectrum largely identical to that of acyclovir. Intravenous penciclovir is not currently licensed as treatment for HSV infections, but doses of 5 mg/kg per dose administered intravenously twice daily were as effective as acyclovir in clinical trials.⁵² Famciclovir has also not been studied in EH, but a treatment regimen of famciclovir, 500 mg by mouth twice daily, for at least 7 days has been recommended for mild clinical courses of EH.⁵³

The phosphonate foscarnet inhibits the viral DNA polymerase independently of thymidine kinases and is thus the treatment of choice for patients with acyclovir resistance, including those with EH. The recommended dosage in HSV infections is 40 mg/kg per dose intravenous foscarnet twice daily for at least 10 days.⁵⁴

Topical antiviral chemotherapy of EH. Topical antiviral agents carry a risk for contact sensitization and drug reactions⁵⁵ and are usually not required for cutaneous EH lesions but offer many advantages for prophylaxis and treatment of ocular complications. Patients with EH and lid lesions and reduced corneal sensitivity should be treated prophylactically, whereas patients with keratitis almost always receive combined systemic and topical therapy. Although the efficacy of acyclovir ointment for the treatment of mucocutaneous HSV lesions is in dispute, topical penciclovir and foscarnet are both effective.⁵⁶ Study results of topical IFN in mucocutaneous lesions or HSV-keratitis are promising, but its topical formulation is not licensed yet.⁵⁷ Trifluorothymidine 1% eye drops 7 to 9 times per day, as well as 3% acyclovir ointment 3 to 5 times per day, are typically instituted prophylactically, as well as in patients with established epithelial keratitis.^{58,59} Topical idoxuridine and brivudin, which is not licensed yet, also demonstrate good activity in the treatment of herpetic keratitis.^{60,61}

Future treatment techniques for HSV infection. New therapeutic approaches are currently being developed to enhance the immune response against HSV. Human vacci-

nation studies with or without immune response modifiers, such as imiquimod or resiquimod, or trials with immune response modifiers alone showed promising results for genital HSV infections.^{62,63} Further investigations are necessary to evaluate whether vaccination or immunostimulation can become an effective method to prevent HSV infections and EH recurrences in patients with AD.

In clinical trials IFN- α and IFN- γ were found to control HSV-1 spread and shedding in recurrent herpetic lesions and inhibited HSV replication, as was high-dose acyclovir.⁶⁴ Topical administration of a plasmid DNA encoding IFN- α 1 onto mouse corneas before HSV infection suggests a possible beneficial effect of IFN- α in HSV infection.⁵⁷

OUTLOOK

The number of immunocompromised individuals has clearly increased in the past 3 decades because of HIV/AIDS, more extensive use of immunosuppressive therapy, and an apparent increase in AD.⁶⁵ Consequently, the number of patients with EH, EV, and EM is likely to increase. Unfortunately, only a few studies with larger numbers of patients give hints on epidemiologic data.

At present, EH is the clinically most important disseminated cutaneous viral infection in patients with AD. EM is less dangerous. Only a few cases of life-threatening or even fatal cowpox infections in patients with AD have been described. Because these cowpox infections were probably transmitted by domestic cats, this is another reason why patients with AD should be careful about handling cats.

An enigmatic multistate outbreak of monkeypox, which is the first in the United States and has been reported this summer from Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, is under current investigation by the CDC and state and local health departments.⁶⁶ As a reaction, the federal government has banned the sale and distribution of prairie dogs in the United States and prohibited the import of all rodents from Africa. The smallpox vaccine discussed above is about 85% effective in preventing monkeypox.⁶⁶

As we face possible bioterrorism, smallpox infection and side effects of vaccination, such as EV, have become important issues again. In case of a widespread vaccination campaign, all patients at risk for EV or other cutaneous side effects of vaccination need to be identified properly.

Although it has been known for a long time that patients with AD have an impaired cellular immunity and are more susceptible to viral infections, insights into the mechanisms for this defect have only recently been acquired. These include a decreased recruitment of PDCs to the skin, as well as the potential role of defensins and cathelicidins.^{4,42} Further studies will shed additional light on the pathophysiology of AD and its imminent cellular immunodeficiency.

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