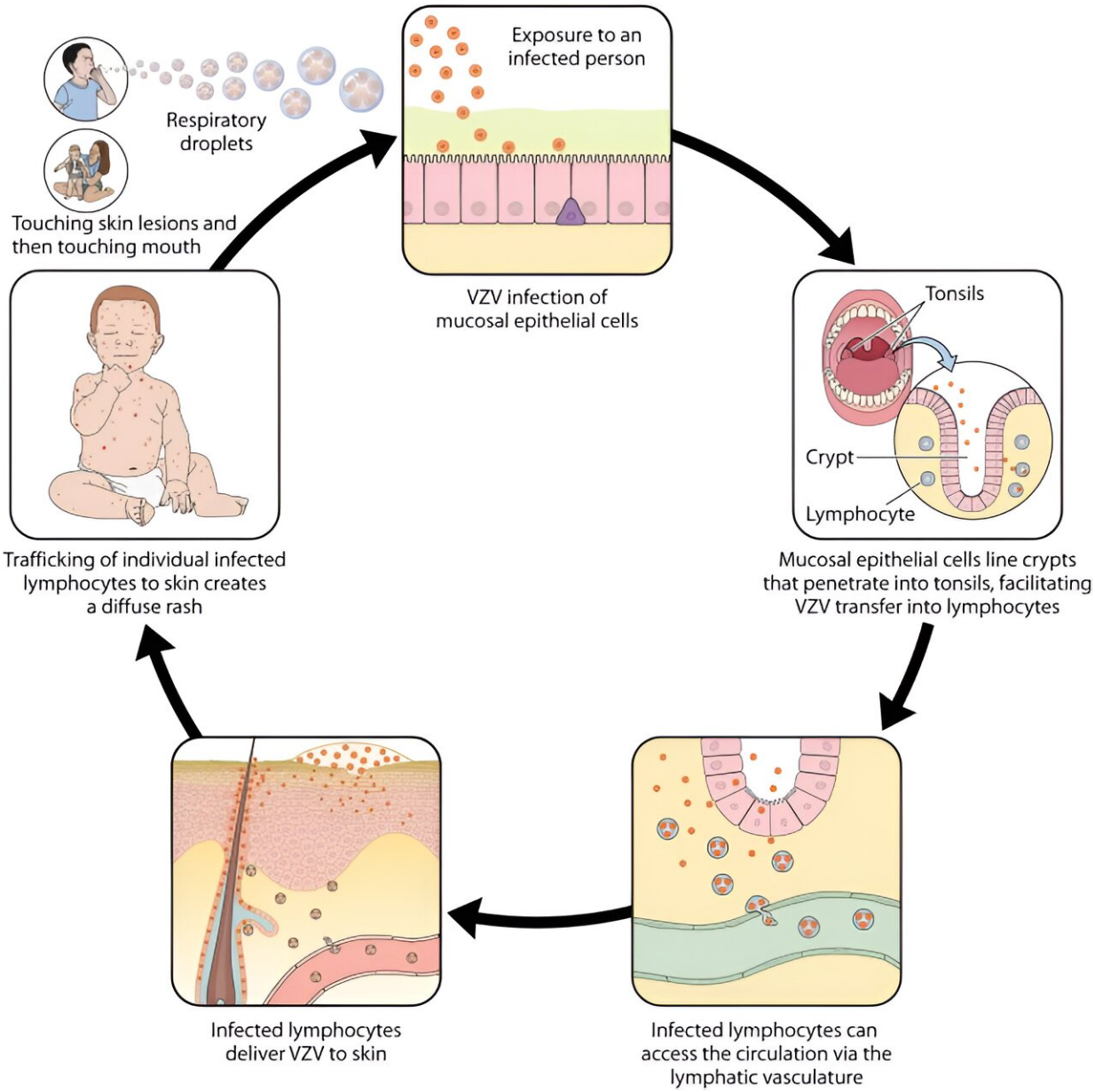
Exploring why viruses cause lesions and rashes

April 1 2024



Credit: American Society for Microbiology

Early in 2024, reports of a fatal case of Alaskapox were circulating in the news. A little-known virus with few cases to its name, Alaskapox virus triggers the eruption of 1 or more skin lesions on the body, among other symptoms. The virus is just 1 of many orthopoxviruses—some, like smallpox and mpox, with much higher disease burdens—whose modus operandi is the formation of skin lesions.

But it's not just poxviruses that cause lesions. Other viruses, like measles and herpesviruses, spark everything from pimply papules to raging rashes. There is simply a remarkable number of ways in which viruses make skin weird. While these signs of infection are easy to see, why and how they develop is less obvious.

Why do viruses cause lesions?

Lesions are any area of the skin that is altered in some way; rashes consist of a widespread eruption of lesions on 1 or more areas of the body. Viruses can induce lesions by infecting and damaging skin cells. Skin symptoms of viral infection are also literal red flags that the host is responding to the virus.

Whether lesions are part of the pathogenesis of the virus or are simply signs that the host's immune cells are hard at work (or both) depends on the virus itself.

Lesions promote viral transmission

The development of virus-induced skin lesions is often tied to

transmission. Skin is a primary way in which people interface with the world, and each other. Hanging out in—and bursting forth from—lesions is an excellent way for viruses to spread between hosts.

Sometimes the skin is the target organ for a virus. For example, mollusca contagiosum virus, a poxvirus that causes a highly contagious (but benign) skin infection, only infects keratinocytes (cells that form the outermost layer of the skin). It triggers lesions in the epidermis and does not spread beyond that. Thus, contact with the pearly papules associated with the infection spread the pathogen from 1 person to another, or to different parts of the body.

Other times, the formation of lesions on the skin is part of a larger infectious journey. Varicella-zoster virus (VZV), the cause of chickenpox and shingles, infects mucosal epithelial cells in the upper respiratory tract before being transported to lymphoid tissues (e.g., the tonsils).

There, it hijacks T cells to promote their migration to the skin. VZV then "moves out of the T cells and infects skin cells, and then spreads from cell to cell," explained Ann Arvin, Ph.D., emeritus faculty in the Pediatrics Department at Stanford University who studies VZV. "So, you have a cluster of infected skin cells, [and] every one of those cells is going to die."

As they die, the cluster of cells releases fluid that accumulates in a blister-like lesion that resembles a "dew drop on a rose petal." Each lesion (which was seeded by a single infected T cell) contains loads of viruses; if a new host touches the lesion, then their mouth, eyes or other mucosal sites, they can become infected.

Lesions are evidence of an immune response

However, not all virus-induced rashes are a means of transmission, meaning people cannot become infected if they touch lesions of this sort. Measles is a key example.

"Measles [virus'] main site of replication is lymphoid tissue, but it has the ability to infect several other kinds of cells, including epithelial cells, and skin is made up of a lot of epithelial cells," explained Diane Griffin, M.D., Ph.D., University Distinguished Professor of Molecular Microbiology and Immunology at Johns Hopkins University.

Griffin, who studies measles, highlighted that lymphocytes essentially carry the virus to new body regions to initiate infection, similar to what happens during VZV infection (poxviruses, like mpox, also exploit immune cells and the lymphatic system for bodily dissemination).

The rash associated with measles indicates that T cells that recognize the measles virus are infiltrating the skin and mounting a defense against the virus. It is purely evidence of inflammation as the virus circulates within the body; touching a measles rash will not transmit the virus (which spreads via respiratory secretions) to a new host.

Griffin noted that the battle between the immune system and the measles virus is happening in other organs, presumably leading to lesions there as well; we just can't see them like we can on the skin. And the rash is actually a welcome sight—if people have a mild rash or no rash at all (as is often the case in people who are immunocompromised), it may indicate there is less clearance of the measles virus.

Notably, lesions can be both signs of inflammation and a route for viral transmission—these traits are not mutually exclusive but are often interrelated.

What determines the appearance of a lesion or rash?

The descriptions of how a lesion or rash can look and feel read like characters in a fairy tale (there's blistery, scaly, and bumpy, oh my!), and their appearance varies depending on the viral infection or the stage of infection. They generally fall somewhere on a spectrum between macules (flat, red lesions) and pustules (large blisters).

Mpox lesions start as macules before progressing to papules (raised, red lesions), vesicles (small blisters), pustules, and ultimately, ulcers. The measles rash, on the other hand, manifests as macules and papules (i.e., a maculopapular rash). But what determines the appearance and progression of a rash?

"The cells that are in a rash are immune cells. It may just be the type of immune cell, or maybe even what the original infected cell [is and] how it responds to infection, that influence the different kinds of rash that you see," Griffin speculated.

Indeed, for VZV, fluid accumulation accounts for the blistery appearance of chickenpox lesions. Moreover, "when the virus gets to the skin, the surrounding skin cells upregulate interferon [a pro-inflammatory immune molecule] to control the virus," Arvin said. "Otherwise, you would get 1 chickenpox lesion, and it would just spread to your whole body. The ability of skin cells to protect themselves from spread is why the lesions stay small."

She noted that this ultimately demonstrates the equilibrium of infection—the virus breaks down barriers to establish infection, while the host keeps things from getting entirely out of hand. This, in the end, also benefits the virus (i.e., a dead host can't interact with and spread the virus to new hosts).

Lesion appearance may also depend on the differentiation state of the target cell. Take warts—rough lesions caused by certain types of human

papillomavirus (HPV). The HPV life cycle is linked to the differentiation of keratinocytes as they migrate from the basal layer to the epidermal layer of the skin. Throughout this process, HPV stimulates keratinocyte division and inhibits apoptosis, giving rise to keratinized, coarse-textured lesions. Viral particles can then be released from the wart to infect other body sites or hosts.

Regardless of how they show up, rashes caused by different viruses may appear similarly, which can make diagnosis a challenge. Clinicians must consider not only how a lesion or rash looks but also the presence of additional symptoms timing of lesion development (e.g., lesions from pox viruses advance through each stage at the same time, whereas new lesions caused by VZV can form as other lesions are ulcerating) and where a rash erupts on the body.

What determines lesion or rash distribution on the body?

The constellations of lesions resulting from infection depend on the virus causing the infection. Mpox lesions tend to follow a more centrifugal distribution, with lesions occurring mostly on the extremities and face. In contrast, chickenpox lesions show up on the chest, back, and face before spreading, with most remaining concentrated on the torso. Measles rash follows a still different pattern, beginning at the hairline before spreading downward to the neck, trunk, legs and feet.

While curious, the reason for such variation remains elusive. "I don't think people have any idea of why that is," Griffin stated. "It's a clinical observation that is useful, [but] I think the mechanism is completely unclear."

Rash distribution may have something to do with the behavior of the

infected host. Cowpox virus, which causes a rare skin infection in humans, spreads through direct contact with infected animals (e.g., cows, cats). Lesions develop at the site of inoculation (often the hand), and infection may spread to places like the face and neck as the person touches those areas. Given adults touch their faces every 3-5 minutes, and kids do it roughly 80 times/hour, this distribution makes logical sense.

There could also be the spatiotemporal aspect to rash location. Measles infection starts in the lungs—Griffin acknowledged that it's possible there is early spread of virus-infected lymphocytes toward the face prior to full-body circulation. In such a scenario, the immune cells in the facial region would presumably get a "head start" on combating the virus, leading to the development of lesions before they crop up elsewhere. However, this postulation is entirely speculative and has not been tested.

For certain viruses, though, there are more substantial clues. While it may be that people first notice chickenpox lesions on their chest, Arvin noted they usually get their very first pock along the hairline or eyebrow. Why?

"The cells that are most easily infected by [VZV] are the [stem cells] at the base of hair follicles," she said.

In these cells, "all the growth factors that the virus needs are already turned on, so [the virus] has a real advantage." Early chickenpox lesions are not well-controlled by the immune system. When T cells surveilling the skin pass by and check out the infected cells, they can become infected themselves and spread the virus to the rest of the body. This may be why chickenpox lesions come in waves—a new batch shows up as new T cells become infected.

And then there's the matter of latency: not all viruses are cleared from

the body after acute infection. Some, like herpes simplex virus types 1 and 2 and VZV, establish lifelong latent infections in neurons (i.e., their genomes are deposited into neurons). Reactivation of viral replication can cause viral particles to travel down neuronal axons to the skin and spark lesions, the distribution of which reflects the virus' neuronal residency. Indeed, the shingles rash—caused by reactivation of VZV—exhibits a dermatomal distribution. It appears on swaths of skin enervated by the sensory neurons (dermatomes) the virus was latent in, usually on the trunk or face.

Got a rash? See a clinician

Evidently, there is no single reason why viruses cause the skin to bubble and boil, and for the most part, the reasons are unknown. What is known is that skin issues associated with viral infections can be uncomfortable, if not painful, and are indicators that something is not right.

There are situations where a rash isn't caused by an infection at all but may be a result of some other irritation. In any case, if your skin starts looking weird, touching base with a clinician is a good idea.

Provided by American Society for Microbiology