Viral infections of the skin

Skin can be directly infected by viruses, which means viruses infect epithelial cells of skin layer and in this case they produce lesions that depend on the virus (type of the lesion), as we know viruses require viable cells to replicate in, but the outer most layer of the skin is dead. So it’s difficult for the viruses to infect the skin and as a consequence few viruses can penetrate intact skin or pass through breaks and cause infections.

However skin can also be involved in systematic infection acting as a mirror of the body in this case. (Systematic disease has cutaneous manifestations)

*Again there are two types of viruses that infect the skin (Causative agents):

1. Directly infect skin cells and mucus membrane --primary target—include:
   
   A. Herpes simplex virus type 1  
   B. Herpes simplex virus type 2  
   C. VZV (varicella-zoster virus)  
   D. Poxviruses  
   E. papilloma viruses

2. Viruses cause systematic infection with cutaneous manifestation (skin lesions or rash) include:
   
   A. Parvovirus B19  
   B. Measles virus  
   C. Rubella virus  
   D. Human herpes virus 6

*herpes simplex viruses:*

As you know from the last semester herpes viruses are abundant in nature and they characteristically cause skin and mucus membrane infections.
Herpes viruses are classified according to biological features. However, the inclusion in the family of herpes is based on structural (Architectural) features that are composed of an envelope decorated with numerous short glycoprotein spikes utilized for binding to the infected cells, then there is a layer that varies in length between capsid and envelope, referred to as tegument, then we have icosahedral capsid, then we have the core of double stranded DNA wrapped around fibrous protein.

So we divide herpes viruses to type 1 or 2 according to biological features as well as the functions of their glycoproteins; both infect skin and mucus membrane but characteristically herpes simplex 1 infections are limited to the orofacial region so they infect the region above the waist. On the other hand, herpes simplex virus type 2 causes genital lesions.

The lesions caused by these viruses spread across mucus membranes and the skin, and that’s why the name is herpes, which is derived from the Greek word herpein, which means, “to creep”. Herpes virus must gain access to skin or mucus membrane that are either abraded or traumatized so that they can establish infection, so infection requires lesions and as a result intact skin is largely resistant to herpes virus infection.

Skin lesion could be microscopic not seen by naked eye, so the virus gain access to epithelial cells and establish an infection. After an incubation period of few days (an average of 4 days), lesions start to erupt, spread, and then they require 2-3 weeks in their primary form to heal leaving no scares usually. During this primary infection they gain access to nerve endings and travel back as a complete virus or as a nucleocapsid (capsid with the core) by the retrograde axoplasmic transport to the sensory ganglia where they establish themselves latent for the rest of the individual’s life (forever).

The most common site for latency:

1. HSV Type1: trigeminal sensory ganglia
2. HSV Type2: sacral sensory ganglia

Depending on the individual and other factors, virus might be reactivated from time to other by a certain mechanism that is largely unknown. There are theories in this regard, which we have mentioned last semester, these theories include: LATs (Latency activation transcripts), which are mRNAs that can bind to ICP-0 preventing the replication of the virus. Others include histone deacetylase 1 and 2 that are believed to be involved in the establishment of latency. So we don’t know exactly what governs the establishment of latency and reactivation, but we know that certain factors can trigger the reactivation such as: sunburns, trauma, physical stress, menstruation and mental stress.
Reactivation of these viruses is associated with the appearance of lesions that are identical to those of the primary infection on the same area, however, the extent of pathology is less, lesions are the same but they are less in number, inflammatory response is milder and the healing time is shorter (1-2) weeks. Frequency of reactivation varies significantly (every month or few times in a year or never during the life of the individual)

So in normal healthy individuals, herpes viruses cause skin and mucus membrane lesions then become latent, then reactivated to cause lesions of the same area. But in some individuals, where we can’t limit the spread of the virus, herpes viruses may spread via blood stream and as a consequence, they involve different organs and in this case they cause different lesions.

The pathology varies: in viscera herpes simplex causes hemorrhagic necrotic lesions, whereas in skin or mucus membrane they cause vesicular eruption (vesicles ulcerate then they become pustules then they heal), but if it infects the brain, liver, heart or adrenals, they cause damage (necrotic damage).

Under normal condition herpes viruses don’t disseminate, however, they do in immune compromised individuals or in neonates because they don’t have the capacity to limit the spread of the virus. And as consequence, HSV causes disseminated infections in the form of encephalitis, meningitis, hepatitis, etc.

Primary infections in the vast majority of cases cause facial lesions ex. Lips (vermilion border of lips) and eye. In some cases it may involve buccal mucosa, gums, pharynx and tonsils. After primary infection, the virus travels to the nerve to establish it self in the ganglia, after that it may be activated to involve the branches of the trigeminal nerve that innervate part of the skin, like eye, maxillar or mandibular divisions of this nerve, and reactivation is involved with many lesions.

Regarding types of lesions caused by this virus, these lesions are identical, whether primary or secondary, they are the same. HSV replicates in the nuclei of the infected cell, so they are nuclear viruses and the first changes are observed in the nucleus like chromatin changes in the form of degeneration of nucleus, displacement of nuclei, etc.
This is seen at the cellular level as:

1- Ballooning and the appearance of condensed chromatin within nuclei of infected cells.

2- Degeneration of nuclei generally within parabasal and intermediate cells of the epithelium.

3- HSV is known to fuse to adjacent cells so they can form multinucleated giant cells and polykaryons are generated.

4- These changes appear in the form of thin-walled vesicles, that contain clear fluid and evolve between dermal and epidermal layers.

**Histopathology**

- Intraepidermal vesicle produced by profound degeneration (Ballooning) of epidermal cells --> marked acantholysis.
- Ballooning degeneration occurs mainly at the base of viral vesicles.
- This is usually associated with inflammatory response where mononuclear cell infiltration takes place.
- The characteristic change of herpes infection is intense inflammatory response surrounding lesions; it usually develops in the corium of the skin. So we have clear vesicle surrounded by a base of erythema and that is what referred to as dew drop on a rose petal.
- Eosinophilic intranuclear bodies, surrounded by a clear halo, are usually seen in balloon cells.
- Lesions are present on both, skin and mucous membranes. However, their appearance is different.
- Lesion on the mucous membranes are different because the cornified layer is very thin, so these lesions are shallow, and the vesicles cannot be seen. These vesicles erupts the skin and cause ulcerative lesions with erythema to appear on mucous membranes.
- If HSV infects viscera, it will cause hemorrhagic necrosis rather than vesicular eruption, also this is the case with the infection of other organs such as the brain.

- HSV causes many clinical syndromes depending on the infection whether it is primary or secondary, and these symptoms are:
  - gingivostomatitis: it is the most common form of primary infections with HSV, the recurrent form of it is called cold sores or fever blisters because these lesions are
associated with common cold, where they appear around the mouth.

Lesions are usually limited to small areas, it evolves at lips (vermillion border), buccal mucosa, gums, pharynx, palate of the oral cavity. In addition, it may involve some parts of the face such as the nose. They are associated with systemic manifestations in children, such as fever, difficulty in swallowing especially fluids, because these lesions ulcerate and become painful.

Lesions need an incubation period that varies from 2-10 days with an average of 4 days from the acquiring of the virus to appear, and they are associated with intense inflammatory reaction.

Lesions develops from a macule to a papule then to a vesicle which is fluid filled. The vesicle remain for a maximal period of 24 hours then it ruptures to form pustule which start to heal leaving no scars behind except in cases where secondary bacterial infections take place; scars may be present (so in normal cases they don’t form scars). These lesions require a maximal period of 2-3 weeks for complete healing from the moment of appearing in the case of primary infections.

After healing, patients may or may not witness recurrent or secondary lesions that result because of reactivation of herpes virus in the same area that has been involved in primary lesions (an area of 1 cm²). However, theses lesions are few in number (1-10) and smaller in size, in addition, inflammatory reaction is not as intense as the one in the primary form. These lesions are usually followed by complete healing.

* Secondary lesions are also called: cold sores, herpes labialis (facialis), and fever blisters.

* Regional LNs are not enlarged unless 2 infection of vesicles occurs.

* No fever or malaise.

✓ Predisposing factors for reactivation of HSV:

- Minor trauma
- UV
- Immunodeficiency
- Emotional stress
- Menstruation
- Infections (e.g. FLU, common cold), (other viruses can reactivate HSV)

- Keratoconjunctivitis: This type involves the eye, it appears in primary and reactivating infections.
HSV can infect the eye. Inoculation of the virus takes place mostly in children, where it cause lesions of the eye lids, cornea and conjunctiva, so it’s called keratoconjunctivitis, it also causes chemosis (edema) of the eye lid depending on the severity of the infection.

It is a follicular lesion that involve the eye, they are followed by healing, the virus then travels to the trigeminal nerve establishing latency there, if it is reactivated, it will involve the same eye, and repeated infection of the eye will produce damage in the cornea, which is followed by corneal opacity, causing infectious blindness. (HSV is the most common cause of infectious blindness).

*The most common cause of corneal blindness is trauma followed by infections caused by HSV, it affects 300 thousand individual annually in the USA.

Lesions start as keratitis, conjunctivitis, and edema of eyelids followed by punctate or marginal keratitis and finally dendritic ulcers, that is, Characteristic ulcer lesions that form corneal opacity. These ulcers appear in repeated not primary infections.

*Treatment of corneal opacity followed by blindness requires corneal transplantation, and this is the only way for treatment of this problem.

*Eczema herpeticum: A severe life threatening infection that appears in individuals with atopic dermatitis (Eczema). These individual have eczema then they develop herpes. Lesion associated are widely spread, they may involve viscera and in this can be fatal.

*Atopy: refers to the non typical response to commonly present antigen by the production of IgE antibodies, where in normal conditions IgG is produced

Individual with atopy, which is present in about 40% of population, do not respond by the production of IgG antibodies, the produce IgE instead.

IgE antibodies bind to mast cells, and upon reexposure to the same antigen, antigen will bind to the IgE on the mast cells which will cause mast cell degranulation with the release of vasoactive amines; pharmacologically active substances that promote inflammation. So, some individuals have atopic dermatitis and once infected with Herpes, those individuals produce what’s known as Kaposi’s varicelliform eruption.

In Herpes Simplex, all lesions develop spontaneously, so lesions of the same time –age– appear together and follow the same progression and the same developmental stages and finally the healing.
In Varicella- Zoster Virus, lesions appear as crops. So, in the same area we find lesions of different times –ages-. We find macules, papules, vesicles and pustules all in the same area. And that’s why in the case of Eczema herpeticum, lesions of different ages appear in the same area, and because of that they are given the name varicelliform because they are similar to varicella but this is not the characteristic of it, it is characteristic of varicella and that’s why the name is varicelliform eruption.

Extensive eruption of vesicles and pustules occurs mainly in the areas with dermatosis, with fever and prostration. The face is usually severely affected. Sometimes, the virus disseminates causing visceral involvement and in this case it could be fatal. So, ulcers of similar shape and size appear on different parts.

- Herpetic whitlow: Herpetic whitlow is a condition where herpetic lesions involve the fingers (base of fingers), and this is common in certain professions such as nurses, dentists, especially those who work without gloving. Small lesions are formed and the virus infects such lesions in thumb-sucking children where they develop Herpetic whitlow. They have the same cause and development of those of gengivostomatitis.

- Herpetic Gladiatorum: As the name indicates, it is a condition that can involve any part of the skin and it is the result of intimate contact during wrestling or rugby playing, where the oral secretions of one of the wrestlers who is infected contaminate others, and this viral contact produces lesions of the skin and the virus gain access to the skin through these lesion. This results in the development of vesicles surrounded by intense erythema involving any part of the skin.

- Erythema multiform: it is an autoimmune condition. 80% of this case is associated with HSV, where DNA of this virus is found.

So, primary Herpes Simplex infections usually appear in the form of gengivostomatitis. Reoccurrence can take place from time to time but lesions are usually mild. The most important forms are Keratoconjunctivitis and Eczima herpiticum.
Varicella zoster virus (VZV)

VZV is structurally and virologically similar to HSV (they are classified within the same subfamily which is alpha herpes viridae). Like HSV, VZV replicates in epithelial cells of the skin and mucous membranes establishing latency in sensory nerve ganglia. This establishment is a result of two pathways, either via the hematogenous route (i.e. through blood) causing viremia - primary viremia- and dissemination of the virus to sensory ganglia. The second pathway is through skin lesions.

Studies that have been done to demonstrate and detect VZV in the sensory ganglia showed that all ganglia have viruses (the rate is about $6^{30}$ virus / 100000 ganglial cell). VZV causes primary infection in the form of varicella or chickenpox and then establish latency at the sensory ganglia to be reactivated and cause a secondary form of the disease known as zoster, which usually involves the dermatomal distribution of one sensory nerve. (zoster is different from varicella).

The difference between varicella and HSV is that HSV establish latency then become reactivated frequently causing mild lesions. Whereas VZV is usually reactivated once in the lifetime of an individual leading to serious lesions. So frequency of reactivation and severity of lesion vary between varicella and HSV.

They gain access through the respiratory tract, the viruses usually replicate in the lymphoid tissue associated with the oral cavity then they enter the blood stream causing primary viremia which lasts for few days then they disseminate to the reticular endothelial system (spleen, liver,...) where they replicate for few days then overwhelming their sites they spread to the blood stream causing secondary viremia. So there are two phases of viremia; primary and secondary. Secondary viremia disseminates the virus to the target organs (the most important target is the skin, more specifically the epithelial layer of the skin and the mucous membrane). However other organs can be affected, the second most common target is the lung. The liver can also be affected by VZV causing hepatitis and (or) lose of function. It also can disseminate through the CNS causing encephalitis and aseptic meningitis. The secondary viremia coincides with the last 4 to 5 days of the incubation period (24-72 hours) of the acute varicella.

Cell-associated viremia continues after the initial skin lesions appear, but the infected PBMC (peripheral blood mononuclear cells) are cleared within 24-72 hours after the appearance of the rash. The virus remains within the infected blood cells until the development of lesion. So there is delay in the exposure of the immune system to the virus (i.e. no immune response during the primary viremia and even the secondary one) because the virus is largely inaccessible for the immune cells. The cells of the epidermis is a major target for varicella replication, and the first changes consists of vasculitis, then progressive “ballooning” degeneration of epithelial cells, coalescence of fluid-filled vacuoles between
cells, and increased numbers of infected cells at the base of the lesion are noted as the maculopapular lesions evolve into vesicles. These are similar to those seen in HSV, so the course of development of the lesion is similar to HSV.

The virus travels from infected vessels to the epithelium whether as free virus or associated with cells. Destruction of germinal layer of the epithelium is observed in large lesions not in small ones.

As we have mentioned, infiltration of the involved skin sites by inflammatory cells is minimal in the early vesicular phase, because tactic factors are not released to promote the inflammatory response.

After the appearance of lesions and once they ulcerate, necrosis through the whole dermis can be seen and inflammatory response is marked. Clinically, incubation period of the varicella is relatively long 10-21 days with an average of 16 days (Recall that we have 2 phases of viremia).

*Then skin rash appear on the scalp, face or trunk where crops of lesions appear progressively on the skin.

Because varicella causes prolonged viremia the lesions appear in crops (i.e. intermittent viremia is the cause of the appearance of these crops) and thus all types of lesions can be seen at the same area (lesions that are evolving and lesions that are healing) because the release of virus from the blood stream over a period of time ranging 1-7 days.

*Hypopigmentation of the skin often persists for several weeks but scarring is unusual unless a secondary bacterial infection takes place.

*Usually the first lesion appears on the forehead, this lesion may leave a scar.

The lesions vary from one case to another; for example varicella can be very mild to a degree that can be unnoticed. Lesions can be as few as 12 lesions over the whole body. But lesion can be severe reaching 2000 and more accompanied by severe inflammatory response. Lesions are itchy and they stimulate children to scratch leading to bacterial secondary infection, so we have to cover lesions by an antihistamine.

In young children, prodromal symptoms of chickenpox are uncommon, but in older children and adults, the manifestation of the rash may be preceded by two or three days of fever and chills, malaise, headache, backache, sore throat, and dry cough. Varicella in children is very benign and usually not associated with complications, whereas in adults its considered a very serious illness, it is associated with many complication like pneumonia, encephalitis, hepatitis (pneumonia in pregnant woman can be fatal with mortality of 15%). Fortunately now we have vaccines for varicella.
The rash begins on the face and scalp and spreads rapidly to the trunk, with relative sparing of the extremities.

The first sign of chickenpox is rose-colored macules that rapidly progress to papules then to vesicles, then to pustules, and finally to scabbing over with crusts.

It can be associated with thrombocytopenia leading to hemorrhagic varicella.

** Don’t forget to refer to slides for pictures and some info that is not mentioned in this sheet.

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