Chapter V

Dermatological Manifestations of Varicella

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Introduction

The Varicella Zoster virus (VZV) belongs to the alpha-herpesviridae family and shares several biological properties with the Herpes Simplex viruses (HSV) types -I and -II (Weller 1965, Weller 1983). The alpha-herpesviridae also present highly similar elementary skin lesions that are histologically indistinguishable (Nikkels et al. 1995).

This chapter describes the pathomechanisms of the typical varicella skin lesions and the dermatological features according to the age of the patient. Furthermore a whole array of atypical and uncommon VZV manifestations is presented to increase awareness of these difficult to recognize patterns. These peculiar presentations may be associated with increased morbidity, especially in the immunocompromised subject.

Pathomechanisms

The pathogenesis of the varicella skin lesions differs from that of HZ cutaneous lesions, although the dermatological semiology is very similar (Weller 1965, Weller 1983, Nikkels 2011). In fact, the varicella skin lesions originate during the secondary VZV viremia that is associated with a high viral load. VZV then infects numerous endothelial cells from small cutaneous capillaries through capture of the virus from the blood circulation via specific adhesion molecules expressed on endothelial cells. After internalization of the virus, the endothelial cells permit some viral replication during which these cells exhibit a more swollen

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appearance. Subsequently, newly formed viral particles probably migrate to and into perivascular dermal dendritic FXIII+ cells exhibiting antigen-presenting properties (Nikkels et al. 1995). It is probably this cell lineage that transports the virus further to the keratinocytes of the basal layer of the epidermis. Once arrived in the basal keratinocytes, active viral replication is taken place with secondary dissemination to surrounding, overlying keratinocytes. These keratinocytes in the suprabasal layer then become swollen, their nuclei present intranuclear inclusion bodies and their cytoplasm becomes more eosinophilic and sometimes present giant syncytial cell formation, that finally leads to the formation of small intraepidermal blisters. This is called the cytopathic effect (CPE) of epithelial infection by VZV. HSV and VZV CPE are undistinguishable. The small blisters soon coalesce to larger blisters that become clinically visible as vesicles. The innate and adaptive cutaneous immune systems finally limit the extension of the infection. Subsequently, there is a neutrophil infiltration of the blisters, clinically recognizable as pustules, followed by the formation of a crusted lesion that will finally disappear after about 5-7 days, leaving a small scar or not. The scar formation is probably related to the VZV infection in dermal FXIII+ dendrocytes that also play a role in healing and cicatrivial processes. In contrast, during HZ, the virus is transported via the axonal microtubular system to a predetermined dermatome where the intra-epidermal free nerve endings and those surrounding the pilosebaceous structures nurture the keratinocytes with infecting virus (Nikkels 2011). After the release of the virus in the basal layer epidermal and/or follicular keratinocytes the pathogenic process is identical for that described for the varicella skin lesions.

**Predilective Sites for VZV Lesion Localization**

Any factor intervening with the superficial cutaneous vasculation and/or preexisting endothelial cell damage may favor the development of VZV skin lesions, as observed in patients wearing a cast (Wilkin 1981). Furthermore, disruption of the integrity of epidermal keratinocytes favors the development of VZV skin lesions. Hence, VZV skin lesions may be more severe at certain skin areas or remain restricted to certain predilection sites. Patients with sunburn and photolocalized varicella are a well-known clinical example (Weller 1965, Castrow 1973, Cupoli 1977, Findlay 1979, Muckle 1978, Feder 1988, Boyd 1992, Boyd 1991, Serrano 1986, Belhorn 1994, Gilchrest 1974). The VZV eruption may also be restricted to the sites of previous skin test (Martner 1927). Atopic dermatitis, recent surgical or traumatic scars, postinflammatory areas and diaper dermatitis in toddlers also constitute predilection sites. In addition, acantholytic skin diseases such as Darier's and Grover's disease, pemphigus vulgaris or foliaceous, Staphylococcal scalded skin syndrome, focal acantholytic dyskeratosis and bullous pemphigoids, as well as burns, cutaneous T-cell lymphoma and Sézary syndrome are also more prone to VZV infection. The virus can easily spread over large areas of the tegument and even internal dissemination may be observed (el Hayderi 2012, Nikkels 2008). In adult patients, facial laser resurfacing, nonablative fractional photothermolysis (Nelson 2011, Graber 2008), deep chemical peelings (trichloracetic acid, hydroxy acids) and dermabrasion (Bestue 2000) may significantly increase the risk of VZV reactivation as well as the spreading of infection as these procedures are associated with severe epidermal injury (Gilbert 2001). Furthermore, topical medications such as
corticosteroids (Nikkel 2011), calcineurin inhibitors including pimecrolimus (Werfel 2009, Tatlican 2010) and tacrolimus (Reynolds 2002, Lubbe 2000) and retinoids (Yazici 2006) may also favor VZV skin infection.

**Diagnosis of Varicella Skin Lesions**

In the vast majority of cases, the diagnosis of varicella is based on the clinical recognition of the typical skin lesions. Sometimes, a Tzanck smear is required to proof or to exclude other vesiculobulbous disorders. The histaehological periodic acid Schieff (PAS) staining allows the identification of plurinuclear giant syncytial cells, suggestive of an alpha-herpesviridae infection. The advantage of the Tzanck smear is that it can be easily performed and analyzed in a few minutes. Immunohistochemistry adequately distinguishes VZV from HSV-I and HSV-II. This test has a very high sensitivity and specificity and is performed in about 20 minutes (Nikkel and Piérard 2009), is easy to perform and cost-effective. The viral culture is still considered as golden diagnostic standard. After some days CPE may be identified in infected cell lines, such as Vero cells. Specific VZV immunofluorescence of the viral culture often allows precise viral identification before CPE appears. Atypical skin lesions may rather benefit from a punch biopsy for histological examination. Again, haematoxilin/eosin (H/E) staining easily identifies intranuclear inclusions in infected keratinocytes and giant syncytial cells, but does not differentiate VZV from HSV. Immunohistochemistry, in situ hybridization or (in situ) PCR are mandatory for the final identification of the causative virus (Nikkel et al. 2005). Electron microscopy is a slow morphologic method and does not differentiate the alpha-herpesviridae. Although a valuable diagnostic tool for chickenpox, serology is not recommended as rapid diagnostic test as seroconversion takes some days to operate.

**Varicella during Pregnancy, Congenital and Neonatal Varicella, Neonatal Herpes Zoster**

When chickenpox is contracted during pregnancy, the fetus may present a congenital varicella infection through transplacental passage during the primary or, probably more often, during the secondary viremia. Neonatal chickenpox describes the newborn that develops chickenpox within the first 2 weeks of life. The skin lesions in the mother are frequently more severe and numerous and there is a significantly increased risk for internal complications, in particular VZV interstitial pneumopathy. The overall absolute risk of embryopathy is about 2% during pregnancy varicella. The fetal risks are variable according to the developmental age, the most dangerous period being the one associated with the development of neural structures during the second trimester (Nikkel et al. 2005). Before the 20th week of pregnancy, fetal infection is responsible for rare cases of ocular, skeletal or neurological malformations. The skin of the newborn may present typical varicella scars after in utero chickenpox. Some neurological deficiencies may sometimes not be noticed at birth and develop only later in infancy (Blume et al. 2003, Pastuszak 1994).
At term, the highest risk is when varicella occurs between 4-8 days before delivery and 2 days after delivery, as the mother has not yet developed protective IgM and IgG antibodies that are transmitted to the baby. In this instance, neonatal varicella may present with a profuse ulceronecrotic or hemorrhagic eruption and is frequently accompanied by visceral complications such as interstitial pneumonopathy (Beylot-Barry 2008). In the absence of treatment there is a mortality rate of 30% for neonatal chickenpox (Essex-Carter 1983, Meyers 1974, Miller et al. 1989).

Specific VZV serology should be tested when pregnancy starts, as anamnesis of a previous history of varicella is unreliable. Indeed, about 85% of adults who report that they have not had chickenpox are VZV seropositive (Pastuszak 1994). Specific varicella vaccination may be considered.

Neonatal HZ is another exceptional consequence of intrauterine infection with VZV. The neonate may present a zosteriform rash at birth (Jayawardene 1999). In contrast with the thoracic localization of HZ in adults, HZ in infancy has a predilection for the cervical and lumbosacral ganglia, which innervate the extremities (Nikkels et al. 2004).

**Childhood Varicella**

**Typical Skin Lesions**

A progressive cephalo-caudal spreading vesicular rash emerging in successive crops over a 3-6 day period is usual for chickenpox. Furthermore, the exanthema has in general a centripetal distribution, with more trunkal and proximal lesions than vesicles on the distal extremities.

The mechanisms of this typical progression are not known. Probably, the successive viremic waves are progressively overwhelming the innate immune system, explaining the extension of the lesions. Seldom, in immunocompetent children, chickenpox may start on the face and hands and then spread centripetally to the trunk. Conjunctival and mucous lesions, for instance on the palate, the tongue (Figure 1) or on the anal mucosa, are not uncommon. Their vesicles are larger and umbilicated or varioloid in appearance. These mucous vesicles rapidly turn into painful ulcers (Sterling 1998).

The average duration from the onset to complete clinical healing of the cutaneous lesions averages 8-10 days. Each vesicle is formed after the progression of a small macular lesion becoming papular over 1-2 days with a final diameter of 2-3 mm. The first 2 days the vesicle fluid is rather clear and the lesion often resembles a dewdrop (Figure 2). Then the vesicle may become slightly umbilicated and the fluid turns pustular. Subsequently a small dark crust forms after 4 to 5 days.

This scab may remain for 1 to 3 weeks (Glaser 1994). It is typical of varicella that all lesion stages are simultaneously present (Glaser 1994, Salles-Gomes 1963). The chickenpox eruption may occasionally be limited to a single crop of vesicular lesions that rapidly disappear, in young infants still having maternal VZV antibody. In children, the total number of lesions increases with increasing age. Hence, young children present an amount of vesicles between 200-250. In older children, varicella tends to be more severe and the number of lesions may largely exceed 500 (Glaser 1994).
In the immunocompetent child varicella occurs only once in a lifetime and stimulates a very long lasting immunity. Clinical reinfection is reported with a mild varicella-like illness but it is very uncommon in immunologically healthy children (Gershon 1984).

![Clustered small ulcerated varicella lesions in a young child.](image1)

Figure 1. Clustered small ulcerated varicella lesions in a young child.

![A typical elementary varicella “dewdrop” lesion.](image2)

Figure 2. A typical elementary varicella “dewdrop” lesion.

**Differential Diagnosis**

Although full-blown varicella is highly suggestive on the sole clinical presentation, sometimes a differential diagnosis has to be considered, among others, HZ, disseminated HZ, HSV-I and HSV-II infections, vesicular viral exanthemas including ECHO or Coxsackie virus, molluscum contagiosum, pityriasis lichenoides et varioliformis acuta (PLEVA), rickettsial pox, drug eruption, allergic or irritant contact dermatitis and insect bites or even scabies (Blume et al. 2003).

**Cutaneous Complications**

Secondary bacterial infection of varicella skin lesions is rare in temperate climates, but, under tropical conditions, may be severe and may be complicated by septicemia (Marettic 1963). Among children, about 50% of the main varicella complications are bacterial skin infections like cellulitis, abscesses, necrotizing fasciitis and sepsis (Lukesic et al. 2012).
Cutaneous gangrene \textit{(varicella gangrenosa)} may follow secondary bacterial infection. On occasion, extensive local gangrene may occur in the absence of bacterial involvement and is probably a direct consequence of the VZV infection (Illichworth 1955). Necrotizing fasciitis is an exceptional but life-threatening condition with devastating sequelae following chickenpox and an early diagnosis followed by surgical treatment is required.

The rapid progression associated with blistering necrosis, cyanosis, extreme local tenderness, high fever and altered consciousness with inadequate therapeutic responses should suggest necrotizing fasciitis (Shirler et al. 2011, de Benedictis 2009). Rare cases of Fournier’s gangrene have been described, especially in children, associated with very high mortality and morbidity rates. Following a history of varicella infection, a swelling of the perineal region and a scrotal pain should warn the practitioner (Jeffries et al. 2010). Other rare skin complications may occur such as chickenpox triggered guttate psoriasis (Veraldi et al. 2009, Fuilla et al. 2012) or erythema multiforme and Stevens-Johnson syndrome in association or following varicella (Choy et al. 1995). Acquired partial lipodystrophy (Barraquer Simons syndrome) (Kurugöl et al. 2009) has been described following varicella. Varicella may also trigger pityriasis rubra pilaris, probably by the same mechanisms chickenpox-triggered psoriasis (Ertam et al. 2009).

Cutaneous scars are often observed. The number can be highly variable. They can be hyperpigmented (Figure 3) or hypopigmented (Figure 4). Hair loss due to scarring alopecia and permanent loss of eyebrows (Figure 5) has been described. A recent report describes onychomadesis of the hands in two sister following varicella (Kocak 2012).

Figure 3. Hyperpigmented varicella scars in an adult patient.

Figure 4. Hypopigmented varicella scars in a young boy.
Paucilesionnal Varicella

Children may occasionally develop paucilesionnel varicella. They present only few clinical lesions disseminated over the tegument without the typical cephalo-caudal progression and without a typical distribution pattern. These lesions are similar to those observed during classic chickenpox are usually very mild and the typical accompanying signs and symptoms are absent. Scarring has never been reported so posterior diagnosis cannot be suggested on this basis.

In some instances, occult varicella may occur and the typical varicella lesions only occur in injured or inflamed skin, such as recent traumatic scars (Figure 6) or diaper dermatitis, without presenting other varicella cutaneous lesions (Nikkels 2009). Serology demonstrates positive specific VZV IgM and IgG levels. The diagnosis may also be made by immunohistochemical identification on a Tzanck smear of a vesicular lesion (Nikkels 2009).

As the immune response is probably less important than during classic varicella, these children are at risk for childhood HZ (Nikkels et al. 2004).
Infraclinal Varicella

Unexpectedly, positive specific anti-VZV IgG may be found in patients without recalling a precise clinical history of previous chickenpox. Infraclinal varicella may be defined as the presence of specific anti-VZV IgG's without a history of clinical varicella and an absence of typical chickenpox cutaneous scars. Approximately 85% of patients who report not having experienced varicella turn out to be VZV seropositive (Pastuszak 1994).

Recurrent Varicella

Recurrent varicella is exceptional and is defined as a recurring VZV infection appearing within the weeks after the primary infection. The recurrences can present as chickenpox, localized HZ or disseminated HZ. It seems to be more frequent in immunosuppressed children but immunocompetent children may also be affected (Junker 1991). The number of recurrent episodes varies between 2 and 5. The clinical course is not different from primary varicella but the clinical manifestations are usually milder and the number of lesions lower (Junker 1991, Crowther et al. 2009).

Breakthrough Varicella

Breakthrough varicella may be observed in a small percentage of children after receiving the OKA-strain varicella vaccine (LAVV type) (Weinmann et al. 2008, Daskalaki et al. 2012). The skin lesions are similar to wild-type varicella but are usually fewer in number and the accompanying general signs are mild. The duration is the same as classic chickenpox and scarring is rare.

Adulthood Varicella

Chickenpox in the adult patient is usually much more severe than in the healthy child. The prodromal illness is accompanied by malaise and fever 1-3 days prior to the appearance of the skin lesions. A scarlatiniform-like macular rash may precede the vesicular eruption. Furthermore, the dermatologic course, the duration and progression of the skin lesions is quite similar to that or childhood varicella. The cutaneous complications are similar to those of childhood varicella but curiously scarring is less frequent in the adult patient. In contrast, the systemic complications are more frequent and more severe. In particular VZV pneumonitis and hepatitis are common whereas CNS complications are rather exceptional in adults (Chiner 2010, Abro 2009, Triebwasser 1967, Sterling 1998). VZV pneumopathy is seen in about 14-25% of otherwise healthy individuals over the age of 19-25 years old who contract chickenpox (Triebwasser 1967). Ocular VZV complications comprise necrotizing retinitis and vascular VZV complications leading to varicella vasculitis as a complication causing giant
basilar artery aneurysm. It can be lethal in some cases, mostly in adults or HIV-afflicted subjects, causing aneuritis and hemorrhage (Gilden et al. 2009).

**Senior Varicella**

In elderly patients, it is rare when primary VZV infection has not occurred in one’s lifetime, as supported by an overall seroconversion rate reaching about 90%. Varicella skin lesions in elderly patients are more specific and fewer in number. They appear to be larger, more isolated and less clustered (Figure 7).

![Figure 7. Large lesion with central crusting typical of senior varicella.](image)

In addition, the cutaneous eruption is usually not accompanied by malaise or fever. Serology with negative VZV specific IgG and positive VZV specific IgM and an immunohistochemical identification of a vesicular lesion are keys to diagnosis of primary varicella in the elderly patient. Scarring is almost never observed. No specific data are available on systemic complications.

**Varicella in Immunosuppressed Patients**

**Risk Factors**

Varicella can be particularly dangerous and even lethal in immunosuppressed patients, especially in those presenting a deficiency of cell-mediated immunity (CMI). Classically, in these patients the duration of chickenpox is longer than usual, the severity increased and new vesicles continue to develop beyond the usual 8-10 days, called **progressive chickenpox** (Hoyer et al. 1968). Children with B-lymphocyte impairment usually tolerate varicella without difficulty, although some severe cases are reported (Good 1956). Children with absent or deficient adenosine deaminase or nucleoside phosphorylase activity, complement abnormalities or cyclic neutropenia are also at increased risk for severe varicella. Immunosuppression due to malignancy and antineoplastic therapy also favor progressive varicella. In these patients, a persistent VZV viremia and replication has been demonstrated.
(Feldman et al. 1975). There is no particular duration of therapy or specific anticancer treatment before exposure to chickenpox that is associated with an increased risk for unfavorable outcome (Feldman et al. 1975). Corticosteroid receiving children for asthma (prednisone 2 mg/kg/day or higher) may also be at a greater risk for severe varicella (Falliers 1965). Acute graft-versus-host-disease following bone marrow transplantation increases also the risk for severe varicella. Severe VZV-induced illness ranges from 7.4% to 29% after kidney transplantation (Naraqi et al. 1978, Gourishankar et al. 2004, Hwang et al. 2004) and is related to a lower number of VZV-specific CD8+ T-cells in transplant recipients compared to healthy individuals (Halloran 1999, Van Besouw et al. 2012).

The severity of varicella in HIV-infected children depends mainly on the hematological and immunological status. Chickenpox may be the typical mild to moderately severe disease in an HIV-seropositive child with relatively normal title and CD4+ lymphocyte counts (Jura et al. 1989). On the other hand, children with severely diminished CD4+ counts may present more severe and prolonged chickenpox with viral pneumonitis and bacterial superinfection as frequent complications. Severe varicella infections may also occur with VZV vaccine strains in the case of deficiency of the iNKT/CD1d pathway (Banovic et al. 2011).

Cutaneous Manifestations

In the majority of cases varicella in immunocompromised children and adults present an identical type of cutaneous lesion, lesion progression, distribution and evolution as observed in the immunocompetent subject. However, the duration is usually longer depending on the degree of immunosuppression, the severity more important, the accompanying signs more significant, the morbidity higher and a higher rate of mortality of 7-30% from a multisystemic involvement, especially affecting the lungs, liver, pancreas and occasionally the CNS. A quarter of these patients develop severe viral pneumonitis during the first week with a mortality rate of 30%. Hepatitis and pancreatitis are diagnosed mainly on the basis of abnormal elevations in serum transaminase and amylase, respectively (Feldman et al. 1975).

In immunocompromised patients varicella may present as hemorrhagic or necrotic described as malignant varicella with frequent visceral involvement and general signs. Patients receiving systemic corticosteroids and anticoagulants voluntarily present a hemorrhagic form of varicella, probably by fragilization of dermal capillaries. It is more common in some tropical regions but in temperate regions an immunosuppression is the usual risk factor (Sterling 1998).

Cases of recurrent varicella have also been observed (Sterling 1998). During a HIV infection, a « second » varicella due to endogenous reactivation may occur with fewer lesions and rather appearing as necrotic, ulcerative and varioliform-like lesions (Perrone et al. 1990).

Furthermore, there is an ever-expanding range of atypical cutaneous VZV manifestations (Whitley 1995). In these instances the clinical diagnosis may be difficult and may require complementary investigations.

Chronic hyperkeratotic, wart-like, sometimes ulcerating VZV skin lesions are most often encountered in HIV-infected patient and sometimes during other immunodeficiencies (Wauters et al. 2012). These lesions usually occur in patients already having had previous varicella, but cases presenting as primary manifestation of VZV infection have been reported (Wauters et al. 2012).
More exceptional atypical VZV skin manifestations are the lichenoid reactions, resembling inflammatory clustered lichen planus-like lesions that evolve significantly longer than classic varicella skin lesions (Baselga et al. 1996, Nikkels et al. 1998).

Follicular VZV infections are also described but are more commonly linked to HZ. They present as inflammatory folliculitis when the most of the VZV replication takes place in the bulge region of the pilosebaceous structure and as pustular folliculitis when the viral replication is located more superficially (Nikkels et al. 1995, Muraki et al. 1996, Weinberg et al. 1997). Granulomatous reactions to VZV persistent antigenic structures may follow VZV cutaneous (Nikkels et al. 1994).

Elderly patients are prone to recurrences of varicella in immunosuppressed states. The clinical lesions resemble large vesicular VZV skin lesions with central necrosis and a more profuse and diffuse erythema. The lesions heal more slowly after a period of 10-15 days (Nikkels et al. 2003).

Conclusion

The spectrum of the dermatological manifestations of varicella is highly polymorphous and ever expanding. Although the elementary skin lesion is created by intracellular viral replication leading to a CPE with secondary acatholysis, variations in the number, size, duration, evolution, distribution and progression of the cutaneous lesions may complicate the clinical diagnosis. Clinical awareness of these variations and of the atypical VZV manifestations is important for recognition and adequate treatment.

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