The Nikolsky sign

The Nikolsky sign was described originally by the Russian dermatologist Pyotr Vasilyevich Nikolsky in 1895 and refers to the dislodgement of the superficial layers of the epidermis through the application of lateral pressure to intact skin or the border of a blister (Moss and Gupta, 1998).

The accepted procedure for eliciting the Nikolsky sign is through the application of firm sliding pressure with the thumb or finger on to seemingly unaffected skin, particularly over a bony prominence (Moss and Gupta, 1998). This leads to large areas of the stratum corneum being displaced, leaving behind an erythematous, moist and denuded dermis which can be painful and at risk of developing a secondary infection.

The Nikolsky sign is a useful sign clinically that can help to differentiate an intra-epidermal blister from a sub-epidermal blister. When used clinically it can help with the diagnosis of some serious and potentially life-threatening dermatological conditions.

Causes of a positive Nikolsky sign

There are several clinical situations where damage within the epidermis can result in a positive Nikolsky sign. These may be the result of autoimmune blistering disorders, infections or immune reactions in response to drugs (*Table 1*).

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Table 1. Common causes of positive Nikolsky's sign findings

Cause	Comments
Pemphigus	Mainly seen in adults. Follows a sub-acute onset. Flaccid blisters form with extensive mucous membrane involvement
Staphylococcal scalded skin syndrome	Characteristically seen in acutely unwell children with evidence of staphylococcal skin infection. Large fluid-filled blisters typically appear in the flexural areas including axillae and groin
Stevens–Johnson syndrome/ toxic epidermal necrolysis	Acute onset of dusky rash followed by blistering and mucosal involvement. A drug is typically implicated
Epidermolysis bullosa	Inherited blistering disorder seen in infants

Pemphigus

Pemphigus is a rare, potentially life-threatening autoimmune blistering disorder. Antibodies target desmosomal proteins called desmogleins; these are cell to cell adhesion molecules found in the skin and mucous membranes. The clinical picture depends upon the type of desmoglein targeted.

The commonest variant of this condition is pemphigus vulgaris in which the target antigen is predominantly desmoglein 3. Desmoglein 3 is preferentially expressed in the mucous membranes. Patients therefore tend to present with mucosal lesions, in particular painful mouth ulcers. Skin involvement occurs later and characteristically patients develop flaccid blisters affecting the scalp, neck and upper chest (*Figure 1*). The blisters are fragile and rupture easily leaving peripherally enlarging erosion.

Pemphigus foliaceus is a less common variant in which the target antigen is desmoglein 1. This is predominantly found in the upper epidermis. Disruption of cell to cell adhesion results in fragile thin-roofed blisters which easily rupture to leave erosions with a collarette of scale and superficial crusting. The chest and face tend to be the most commonly affected areas.

Nikolsky sign is positive in active disease. This can be useful clinically when trying to differentiate pemphigus from other blistering disorders such as pemphigoid, or scaly epidermal disorders such as lupus or seborrheic dermatitis (Harman et al, 2003). Pemphigus tends to affect middle-aged adults, but is occasionally seen in children. There is a significant morbidity and mortality resulting from both the disease process and the use of immunosuppressive drugs to suppress disease activity. Oral corticosteroids are the first-line treatment, but steroid-sparing drugs, in particular azathioprine, may be required (Harman et al, 2003).

Figure 1. Pemphigus vulgaris showing areas of eroded skin with a peripheral collar of scale where the roof of the blister has peeled away from the underlying dermis.

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome is an infective cause for a positive Nikolsky sign. Around 5% of all *Staphylococcus aureus* strains produce an exfoliative toxin, which cleaves desmoglein 1 and leads to keratinocyte disassociation. This results in skin fragility, superficial blistering and consequently a positive Nikolsky sign (*Figure 2*). This condition is mainly seen in children, and starts as a localized staphylococcal infection, but haematogenous spread of the exfoliative toxin causes a generalized rash with accompanying pyrexia to develop a few days later. Importantly, the patient may complain of skin tenderness. Superficial blistering develops, particularly in the flexures, subsequently rupturing to leave painful, eroded areas of skin.

Treatment includes analgesia, antibiotics (flucloxacillin being first line) and supportive care (Griffiths et al, 2016). Skin care is vital; this comprises protection of eroded areas with emollients and non-adherent dressings and monitoring the skin for signs of secondary infection.

Drug-related reactions

Various drugs can cause idiosyncratic reactions resulting in epidermal necrosis. In its milder form this is known as Stevens–Johnson syndrome. Toxic epidermal necrolysis is a more severe mucocutaneous reaction with a significant mortality (*Figure 3*). It is now thought that these two conditions represent either end of a spectrum of disorders and hence are collectively referred to as Stevens–Johnson syndrome/toxic epidermal necrolysis. These conditions are immunologically mediated by cytotoxic T lymphocytes leading to the production of pro-apoptotic mediators, resulting in keratinocyte apoptosis and skin necrosis.

Stevens–Johnson syndrome/toxic epidermal necrolysis may present in any age group and may be caused by a variety of drugs, particularly anticonvulsants, allopurinol and sulphonamides. There is usually a latent period of between 7 and 10 days between administration of the culprit drug and onset of symptoms. The patient presents with malaise and pyrexia before developing a rash. Lesions may be target-like, or purpuric macules, and typically start on the face, upper torso and proximal limbs. The skin usually feels tender, followed by blistering and subsequent epidermal detachment and peeling (desquamation) resulting in exposed dermis.

Nikolsky sign is positive, and helpful in distinguishing Stevens–Johnson syndrome/toxic epidermal necrolysis from other acute dermatoses such as erythema multiforme or erythroderma. Mucous membranes are often involved resulting in oral, nasal and genital erosions. Conjunctival involvement can be particularly serious and may lead to long-term visual loss therefore early liaison with ophthalmology is imperative.

Extensive epidermal loss results in high fluid and protein loss, hypothermia, sepsis and may lead to multi-organ failure. Patients with more than 10% body surface area involved should be managed in an intensive care setting and those with over 30% involvement may be transferred to a burns unit.

Treatment is supportive and should be under the care of a multidisciplinary team. The culprit drug should be stopped immediately and a conservative approach adopted, paying attention to all organ systems involved. Skin care is vital, including the regular use of antimicrobial washes, emollients, appropriate dressings and topical antimicrobial treatments. Close monitoring for secondary infection is important and regular skin and oral swabs are recommended, ideally from three different areas. If active treatment is needed, this should be decided by a specialist skin failure multidisciplinary team. It is highly important that the patient is not given the offending drug again and this should be clearly documented and communicated with the patient's primary care team. Occasionally Stevens–Johnson syndrome/toxic epidermal necrolysis can have an infective cause, predominantly seen in children as a result of mycoplasma infection (Creamer et al, 2016).

A useful prognostic scoring system called the SCORTEN (*Tables 2* and *3*) can be used to try and predict the risk of mortality from Stevens–Johnson syndrome/toxic epidermal necrolysis and should be calculated within the first 24 hours (Creamer et al, 2016).

Figure 2. Staphylococcal scalded skin syndrome in a child with facial impetigo. Note the generalized rash and peeling of the skin in the neck creases.

Figure 3. Toxic epidermal necrolysis with extensive areas of epidermal loss (erosions) with a background of dark and necrotic macular lesions.

Table 2. SCORTEN calculation

Age >40 years
Presence of malignancy
Heart rate >120 beats/min
Epidermal detachment >10% body surface area at admission
Serum urea >10 mmol/litre
Serum glucose >14 mmol/litre
Bicarbonate <20 mmol/litre

KEY POINTS

- The Nikolsky sign is characterized by dislodgement of the superficial layers of the epidermis through the application of lateral pressure to intact skin, resulting in an eroded, moist, denuded dermis.
- Skin pain should be considered as an early warning sign.
- The clinical history including a thorough drug history is imperative in this situation.
- In patients with Stevens–Johnson syndrome or toxic epidermal necrolysis a multidisciplinary team approach should be adopted and a SCORTEN score calculated within the first 24 hours.
- Close monitoring for superadded infection particularly of eroded skin is vital.
- If a clinician suspects any of the conditions associated with a positive Nikolsky sign it is important to gain senior support immediately.

Histopathology

The mechanism that underlies the Nikolsky sign is dependent on the disease's respective pathophysiological process. The histopathology will vary depending on the underlying condition.

In pemphigus vulgaris there is loss of keratinocyte cell-to-cell adhesion in supra-basal epidermis, a process referred to as acantholysis. This leads to clefting of the epidermis and blister formation. There are usually inflammatory cells within the blister cavity with a predominance of eosinophils (Hameed and Khan, 1999; Stanley and Amagai, 2006). Direct immunofluorescence performed on peri-lesional skin (adjacent to a blister) will show a 'chicken wire appearance' as IgG and C3 are deposited inter-cellularly.

Table 3. SCORTEN predicted mortality

Number of parameters	Predicted mortality (%)
0	1
1	4
2	12
3	32
4	62
5	85
6	95
7	99

In staphylococcal scalded skin syndrome the blistering is a result of a superficial intra-epidermal sub-corneal splitting. This differentiates it from toxic epidermal necrolysis where the intra-epidermal level of the split is much lower (Hameed and Khan, 1999; Stanley and Amagai, 2006).

In established toxic epidermal necrolysis there is full thickness epidermal necrosis with blister formation and a seemingly unaffected dermis. The necrotic epidermis forms the blister roof (Hameed and Khan, 1999; Stanley and Amagai, 2006).

Conclusions

The Nikolsky sign is a useful clinical tool as it will help a clinician efficiently identify serious and life-threatening conditions. This allows prompt investigations and initiation of treatment and supportive care. **BJHM**

Conflict of interest: none.

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