

## Nikolsky's Sign: A Diagnostic Blessing?

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Nikolsky's sign, a term coined in honour of a renowned Russian dermatologist, is a well-known clinical manifestation that is primarily elicited in the pemphigus group of disorders. Although it is seen in other dermatological conditions like Staphylococcal Scalded Skin Syndrome (SSSS), Epidermolysis Bullosa (EB), Stevens-Johnson syndrome (SJS), Oral Lichen Planus (OLP) and Toxic Epidermal Necrolysis (TEN), it is characteristically associated with and seen in the pemphigus group of diseases, most notably pemphigus vulgaris (PV). A characteristic clinical feature seen in PV is the separation of the epidermis from the dermis on application of pressure on the skin with a sliding/pressing motion. The etio-pathogenesis, histopathology, clinical variants and their significance are briefly discussed in this short communication.

**Keywords:** Pemphigus; Nikolsky's Sign; Acantholysis; Intraepidermal Cleft**Introduction**

Nikolsky's sign is a well-known clinico-pathological manifestation that is primarily evident in a rare group of blister-causing mucocutaneous, auto-immune diseases, known as the pemphigus group of disorders. Although Nikolsky's sign has been evident in other dermatological conditions like Staphylococcal Scalded Skin Syndrome (SSSS), Epidermolysis Bullosa (EB), Stevens-Johnson syndrome (SJS), Oral Lichen Planus (OLP) and Toxic Epidermal Necrolysis (TEN), it is characteristically seen in, and associated with the pemphigus group of diseases, most notably pemphigus vulgaris (PV) [1]. A characteristic clinical feature seen in PV is the disentanglement and detachment of the epidermis from the dermis on application of pressure on the skin with a sliding/pressing motion [2].

The term was coined in honour of the renowned Russian dermatologist, Dr Pyotr Vasilyevich Nikolsky (1858-1940). Dr. Nikolsky

first observed this clinical finding in 1884 on a patient suffering from pemphigus foliaceus<sup>4</sup>. On rubbing the skin of the affected individual, he noticed that there was a blistering or breaking of the epidermis with a glistening, moist surface underneath. The probability of blister formation lies with the machinations of the immune system which may be provoked to attack the intracellular adhesion that is normally present in the epidermal/epithelial cells, rendering them defective [3,4]. The immune cells attack the cell-cell attachment zone (cadherins) or extracellular matrix (basement membrane zone proteins) adhesion structures, causing the attachment defect. Applying pressure on the affected tissue causes the superficial layers to separate from one another, culminating in the formation of a blister or slough. Histopathologically, PV presents with the detachment of suprabasal keratinocytes, with a "tombstone-like" appearance of the remaining row of cells on the basal membrane [3]. Thus, even a seemingly non serious or trivial trauma may elicit blister formation when the cells are manually separated by the application of mild pressure on the mucosal surface.

### Clinical Presentation

The commonly accepted procedure for eliciting Nikolsky's sign is to exert firm, sliding or tangential pressure with the thumb on the patient's skin/mucosa. However, the resulting dislodgement of the epidermis was a deeply distressing and painful experience for the patient. Hence, a better, alternative technique was suggested whereby a medium-sized, round-ended paper clip is to be held at an angle and firmly slid with moderate pressure along the skin in the direction of the clip's narrow axis [5]. The advantages of this method were palpably evident as it required less pressure and hence consequently less painful to the patient. It also affected a smaller surface area because of the clip's narrow axis and therefore aesthetically less damaging to the patient. Typically, the classic Nikolsky's sign occurs on the skin in an overwhelming majority of cases [6]. However, in rare instances, it has reportedly been elicited in the mucous membrane of other tissues [7,8].

### Clinical Significance

When a patient tests positive for Nikolsky's sign, epithelial cells are detached either from one another or from the basement membrane, insinuating the fragility of epithelial attachment mechanisms. Therefore, its presence almost always hints at the presence of autoimmune mucocutaneous blistering diseases (AMBDs), such as PV, bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), and bullous lichenoid lesions. If a patient tests positive for Nikolsky's sign, a new blister will form, or a superficial layer of the epithelium will become separated and peel off very easily. The positive presence of this sign indicates active acantholysis and loss of coherence of epidermal cells, which enables the clinician to discern between epidermal/intra-epidermal and sub-epidermal blisters which is the single most significant diagnostic and prognostic implication of the classic or conventional Nikolsky's sign [9].

### Variants of Nikolsky's sign

Clinically, there are different variants of the Nikolsky's sign and these variants have different clinical implications. The most commonly described is the 'conventional' or 'classical' Nikolsky's sign where the application of tangential pressure on the skin of an affected individual results in dislodgement of the upper epidermis from the lower epidermis due to the acantholysis phenomenon resulting in blisters [10-13]. This is evident clinically and hence the name. The next most common variant is the 'microscopic' Nikolsky's sign where the tenuous intercellular adhesion of the affected cells are evident microscopically and confirmed by taking a biopsy

of the affected part [14]. The presence of microscopic Nikolsky's sign is especially significant because studies have documented the fact that the microscopic variant often plays a vital role in the histological diagnosis of PV as it has been documented to be a better, more effective method for rapid diagnosis. When Nikolsky's sign is elicited in normal looking skin around the margins of the lesion (vicinity of the blister), it is called 'marginal' Nikolsky's sign and if it is elicited on the skin away from the location of the lesion or the blister, it is referred to as 'direct' Nikolsky's sign. If the base of the eroded lesional area is dry, then it is referred to as the 'dry' variant and if the base of the eroded lesional area is glistening or moist, it is termed as the 'wet' variant. Finally, the 'modified' Nikolsky's sign is described as the extension of blisters peripherally surrounding the lesion which is seen when pressure is applied on the skin of the affected individual [10-13]. This is particularly useful diagnostically as some patients may not exhibit the presence of a recent vesicle or bulla for biopsy.

Another significant prognostic implication in this regard that is similar to the conventional Nikolsky's sign is the false Nikolsky's sign that is also commonly referred to as Sheklakov's Sign. This is positively elicited in sub-epidermal blistering disorders such as cicatricial pemphigoid, dermatitis herpetiformis, BP, EB, bullous systemic lupus erythematosus (SLE) etc. This 'sign' can be induced when the lesional area is 'extended' on the abutting normal skin by pulling at the roof of a blister that has already undergone rupture. Thus, this results in the form are limited in size, lack the tendency to extend spontaneously, and heal rapidly. It is called the False Nikolsky's sign because it is a split that occurs at the subepidermal level unlike the conventional Nikolsky's sign where the 'split' occurs at the suprabasal epidermal/interepidermal level. It is elicited in the normal skin surrounding the primary lesion where the blister has ruptured.

An interesting 'sign' that closely resembles the conventional Nikolsky's sign is the 'pseudo' Nikolsky's sign that is elicited positively in SJS (a rare but serious disorder affecting the skin and mucous membranes), TEN (a more serious variant of SJS), bullous ichthyosiform erythroderma and in some cases of moderate to severe skin burns. As the lesions which exhibit this sign may indicate, the underlying pathophysiology of the 'pseudo' Nikolsky's sign is the necrosis of epidermal cells whereas in the classical Nikolsky's sign, the affected cells undergo acantholysis. Hence, the prognosis is more severe in the former.

### Pathophysiology

The chief pathophysiology behind this sign is called as acantholysis. Auspitz first described this term in 1881 referring to the loss of intracellular epidermal cell coherence. The term 'acantholysis' is derived from the Greek words "akantha", meaning a thorn and lysis is loosening. This dearth of coherence between the epidermal cells develops due to the breakdown of intercellular bridges [15]. A distinctive feature of the classic or conventional Nikolsky's sign is that the acantholysis phenomenon is often evident on both the affected and surrounding intact areas. Acantholysis is an important pathogenetic mechanism underlying various bullous disorders, particularly the pemphigus group, as well as many non-blistering disorders. Syndecan-1, a heparan sulfate proteoglycan on the keratinocyte membrane functions in intercellular adhesion. It is the primary pathological change occurring in pemphigus. A number of triggering factors commence the cascade of acantholysis which is initially characterized by separation of the inter-desmosomal regions and is then followed by splitting and disappearance of desmosomes, forming intercellular gaps. These intercellular gaps result in fluid influx from the dermis. The acantholytic cells remain metabolically active for some time and retain their capacity for DNA synthesis. Degeneration and cell death represent secondary phenomena. Absent or markedly decreased syndecan-1 expression by acantholytic keratinocytes has been reported in biopsies of pemphigus. Some factors that can induce acantholysis include extreme heat, autoimmunity, drugs, infections, physical friction, trauma, contact dermatitis, ultraviolet radiation, etc. Recent studies on acantholysis revealed an interesting finding when apoptosis was proposed as an important precedent that triggers acantholysis. Analysis has revealed that blisters occurring in PV exhibited discrete, isolated cells and cellular debris with fragmented, irregularly shaped nuclei and apoptotic bodies, that is a characteristic feature of apoptosis. There were marked indications of acantholytic cells mirroring apoptotic cells and apoptosis preceding the phenomenon of acantholysis. More studies and analysis is required in this regard as understanding acantholysis is the key to understanding the phenomenon of Nikolsky's sign [12,14,15].

Primary acantholysis is of prime pathogenic relevance in diseases of the pemphigus group. Dissociation and disintegration of desmosomes lead to the separation of keratinocytes. It can be either due to direct or hereditary defects. Thus, in these diseases, acantholysis is the primary event leading to the formation of intra-epidermal cavities and hence the manifestations of the disease.

### Conclusion

Ever since Vasilyevich Nikolsky famously published his doctoral thesis in 1896 reporting this phenomenon, Nikolsky's sign is considered to be one of the most clinically reliable and frequent signs to be elicited for the diagnosis of the pemphigus group of disorders, most notably PV. As mentioned previously, the clinical significance of this sign cannot be overstated. Multiple studies and analyses have been carried out to test the sensitivity and specificity of the Nikolsky's test for diagnosing mucocutaneous, auto immune, blistering disorders. It has been educed that Nikolsky's sign has proven to be effective in the initial diagnosis of oral blistering diseases, and an invaluable asset as a simple clinical diagnostic tool in detecting lesions. It has been instrumental in reducing a number of undiagnosed or misdiagnosed cases of these mucocutaneous blistering diseases which have an adverse effect on the health of the patient while also considerably reducing their quality of life that arises as a result of grappling with these disorders. Thus, it is incumbent on the part of the general dental practitioner as well as a practising dental specialist to have a sound theoretical and clinical knowledge of Nikolsky's sign as the right, rapid and effective diagnosis of the 'sign' can have a profoundly positive impact on the patient's physical and mental health. The specificity of the test is generally very high as an effective clinician is very often proved to be right if he/she picks up the right clinical cues as regards suspicion and diagnosis.

Despite the advent of manifold innovations and highly specific and successful diagnostic methods for detecting auto-immune blistering diseases, Nikolsky's sign is still the gold standard for clinicians to diagnose the pemphigus group of diseases economically and rapidly. Since the method to elicit the 'sign' is still considered to be arbitrary and left to the individual devices of the clinician, the lack of universal standardization has limited the effectiveness of using the Nikolsky's sign as a diagnostic tool. Nevertheless, many clinicians and practitioners have demonstrated alternative, simpler and efficient techniques to elicit the sign. As briefed previously, there is a need to delve deeper into studying the pathophysiology of acantholysis and despite the fact that for more advanced cases, tests like biopsy and immunofluorescence may be required for confirmatory diagnosis, Nikolsky's sign is still a reliable method to a large extent for busy general and specialist dental practitioners for the preliminary diagnosis of the pemphigus group of diseases.

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