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Nikolsky's Sign in Autoimmune Skin Disorders

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Abstract

Soft tissues of the oral cavity are often affected by various mucocutaneous disorders of variable etiology, affecting both the skin and mucosae, with severe clinical manifestations such as blisters involving the tissues; and therefore, their appropriate management relies on their correct diagnosis. Clinical signs to elicit characteristics of blisters are a crucial part of the examination of patients with such disorders. It is therefore essential for clinicians to be familiar with, or rather be expert at eliciting these signs to frame an accurate diagnosis, since proper treatment and follow up will depend on which disease is involved. The Nikolsky's sign is one such sign that can be helpful in the clinical diagnosis of pemphigus group of disease and differentiating it from other blistering dermatoses. This review gives an overview of sign of Nikolsky and other related sign, its clinical presentation and their diagnostic implications, using PubMed and Medline databases searching for articles written in English. Peer reviewed articles were targeted using the keywords "Nikolsky's sign", "mucocutaneous disorders" and "pemphigus". Available full text articles were read, and related articles were also scrutinized and finally the search was subsequently refined to articles concerning to "Nikolsky's sign". It was concluded that early recognition of these signs is necessary to prevent delayed diagnosis and for early institution of appropriate treatment of these potentially serious mucosal and dermatological diseases.

Keywords: Dermis, epidermis, mucocutaneous disorders, Nikolsky's sign, pemphigus.

Introduction

The autoimmune mucocutaneous disorders are the group of diseases, sometimes characterized by acantholysis and in which components of the epidermis and basement membrane zone are targeted resulting in the formation of mucosal and cutaneous blisters.[1] Clinical identification of these blisters are necessary to interpret the pathology accurately. Clinical signs are the well known mechanical signs evolved by clinicians and are considered an important part of clinical examination in patient with these disorders. The Nikolsky's sign is defined as a well described clinical sign which manifest as dislodgement of intact superficial epidermis by a shearing force, indicating a plane of cleavage in the epidermis. The defect may be due to epidermal antibodies as in pemphigus or staphylococcal toxin as in staphylococcal scalded skin syndrome.[2] It is characteristically associated with pemphigus vulgaris.[3] The presence of Nikolsky's sign is a significant indicator of active acantholysis and altered structural integrity within the epidermis,[4] which allows a physician to determine the level of the split in the skin so as to distinguish between intraepidermal and subepidermal blistering diseases in the clinical settings.[5,7] Literature often covers clinical observations and individual case reports in relation to these diseases but little attention has been paid to the importance and clinical utility of Nikolsky's sign and other related sign in the diagnosis of these disorders. This clinical paper is an attempt to illustrate the usefulness of Nikolsky's sign and other related signs along with their diagnostic and prognostic significance in the clinical diagnosis of various mucocutaneous blistering diseases affecting the skin and oral cavity.

Historical Perspective

Pyotr Vasilyewich Nikolsky (1858–1940) was a Russian dermatologist who studied at the University of Kiev and published a thesis on pemphigus in 1895. He subsequently was appointed Professor and Chief of Dermatology at the University of Warsaw and authored numerous papers and books on a variety of topics, including gangrene and syphilis. [8] Nikolsky first described the sign that bears his name in 1896. He related how, after rubbing the skin of patients who had pemphigus foliaceus, there was a blistering or denudation of the epidermis with a glistening, moist surface underneath.[9] According to his explanation, the skin showed a weakening relationship and contact between the corneal (horny) and granular layers on all surfaces, even in places between lesions (e.g., blisters, excoriations) on seemingly unaffected skin.[5] Nikolsky's observations were later confirmed by Lyell in 1956,

who described a Nikolsky sign in patients with toxic epidermal necrolysis.[7]

Elicitation of Nikolsky's sign

Till today there is no absolute consensus available in the literature on a standard method to elicit the Nikolsky's sign. However, Nikolsky originally described three methods to elicit the sign: [5, 8, and 10]

1. Horny layer can be detached for a long distance, even on normal appearing skin, by pulling a remnant of the ruptured wall of the blister.
2. Horny layer can be dislodged on visibly normal skin areas at the periphery of existing lesions by lateral pressure with a finger; and
3. Normal appearing skin can be denuded leaving the moist surface of the granular layer by rubbing the epidermis.

Although the classic Nikolsky's sign is seen on the skin, there have been two case reports showing its appearance on mucous membranes of other tissues. In one instance, a Nikolsky's sign was elicited in the esophageal mucosa of a patient with pemphigus vulgar is. [12] In the other, Nikolsky's sign was elicited in the mucosa of the uterine cervix in 13 of 16 patients with pemphigus.[13] However, these occurrences are exceedingly rare.

Pathophysiology

The mechanism of Nikolsky's sign most likely reflects the underlying pathologic disease process. The primary histologic finding in patients with pemphigus is acantholysis with the occurrence of supra basal epidermal/intraepidermal splits [8, 14] these events presumably contribute to the epidermal separation characteristic of a positive Nikolsky's sign. One study corroborated these findings by demonstrating a microscopic Nikolsky's sign in patients with pemphigus in whom tangential pressure was applied to perilesional skin, resulting in the characteristic biopsy findings described above. [14]

Figure 1. Elicitation of Nikolsky's sign. Reprinted with permission from Fitzpatrick TB, Johnson RA, Polano MK, et al. Color atlas and synopsis of clinical dermatology: common and serious diseases. 2nd ed. New York: McGraw-Hill;1992:539.

Conditions associated with Nikolsky's sign

Positive Nikolsky's sign is the hallmark of pemphigus vulgar is [4] and is helpful in the clinical diagnosis of pemphigus group of diseases. [8] Uzun and Durdu [5] in their study on 123 consecutive patients with various cutaneous diseases presenting as intact blisters and/or erosions concluded that Nikolsky' s sign offers a moderately sensitive but highly specific tool for the diagnosis of pemphigus. Other blistering conditions, which are known to exhibit Nikolsky's sign include pemphigus foliaceous, paraneoplastic pemphigus, Stevens-Johnson syndrome, staphylococcal scalded skin syndrome (SSSS), toxic epidermal necrolysis (TEN), oral lichen planus, benign mucous membrane pemphigoid, and epidermolysis bullosa.[15,17]

Variants of Nikolsky's sign

Clinical Nikolsky's sign.

When the tangential pressure is applied on apparently normal skin/mucosa, or on peri-lesional skin/mucosa or on affected skin/mucosa with the thumb or finger pad result is a shearing force that dislodges the upper layers of epidermis from the lower epidermis resulting in formation of blisters, a phenomenon is known as Nikolsky's sign (Clinical Nikolsky's sign). [4, 5, 18, 17, 19].

Microscopic Nikolsky's sign

Microscopic Nikolsky's sign is the subclinical counterpart of Nikolsky's sign. [20] When tangential pressure is exerted on apparently normal skin/mucosa, same as in eliciting clinical Nikolsky's sign, result in weakening of the intercellular adhesion. This may produce minimal damage at the cellular level which can be demonstrated only microscopically. The pathological changes that are induced after applying tearing tangential pressure to skin/mucosa at the subclinical level, is defined as microscopic Nikolsky's sign.[4,20,14] It has been proposed that microscopic Nikolsky's sign may be a better and more sensitive method of rapid diagnosis and can increase the sensitivity of the histopathological studies.[19] Hameed and Khan [14] in their study demonstrated a positive microscopic Nikolsky's sign in 73.9% of pemphigus patients who were biopsied after applying tangential pressure. There were no changes in the biopsies of healthy controls. They suggested that this technique could be of value in areas where immunofluorescence is not readily available. In another study by Barzegari M et al.,[4] they suggested that microscopic Nikolsky's

sign was significantly higher in patients with generalized disease. Pemphigus vulgaris patients with mucocutaneous involvement have both desmoglein (Dsg3) and Dsg1 antibodies.[21,17] Presence of the generalized disease is probably due to much higher pemphigus antibody levels, making the development of microscopic Nikolsky's sign more frequent. Thus, they concluded that microscopic Nikolsky's sign can increase the sensitivity of histologic diagnosis microscopic Nikolsky's sign was significantly higher in patients with generalized disease. Pemphigus vulgaris patients with mucocutaneous involvement have both desmoglein (Dsg3) and Dsg1 antibodies.[21,17] Presence of the generalized disease is probably due to much higher pemphigus antibody levels, making the development of microscopic Nikolsky's sign more frequent. Thus, they concluded that microscopic Nikolsky's sign can increase the sensitivity of histologic diagnosis of pemphigus vulgar is. [4]

Marginal and Direct Nikolsky's sign

"Marginal Nikolsky's sign" can be described as the extension of the erosion on the surrounding normal-appearing skin by rubbing the skin surrounding existing lesions; while "Direct Nikolsky's sign" is the induction of an erosion on normal-appearing skin, distant from the lesions.[17] A positive direct Nikolsky's sign indicates severe activity of the disease in pemphigus. It is the first sign to disappear as the disease responds to therapy; the marginal Nikolsky's sign may persist for some time. [24] Uzun and Durdu [5] determine the usefulness of the Nikolsky's sign on the clinical diagnosis of pemphigus in 123 consecutive patients and found that the sensitivity of "direct" Nikolsky's sign (38.4%) was less than that of the "marginal" form (69.2%), but the specificity of "direct" Nikolsky's sign (100%) was higher than that of the "marginal" form (93.8%). Based on the result of the study they concluded that a positive Nikolsky's sign, when elicited especially with ''direct'' modification, is moderately sensitive but highly specific for clinical diagnosis of pemphigus, particularly for pemphigus vulgaris.

Wet and Dry Nikolsky's sign

Nikolsky's sign is further characterized as "wet" and "dry". After applying pressure on the skin or oral mucosal surface, when the eroded base is found to be moist and glistening, the Nikolsky's sign is considered as "wet"; while "dry" Nikolsky's sign can be described as those, in which the base of eroded skin or oral mucosal surface is dry. [25, 26]

Modified Nikolsky's sign

The "modified Nikolsky's" sign is described as the peripheral extension of blisters on applying pressure to their surface. This is helpful in patients in whom a new vesicle or bulla is not available for biopsy. The advantage here is that the artificially extended blister cannot show epithelial regeneration, which is sometimes seen in the floor of older subepidermal blisters making them appears as intraepidermal. [26, 27, 28]

Prognostic implication

- Nikolsky's sign may also be considered as a suggestive sign for the prognosis of pemphigus by indicating active disease or clinical exacerbation. [5] The Nikolsky's sign is positive in the active or progressive stage of pemphigus. It becomes negative when patient receives immunosuppressive therapy and it indicates the end of acute stage disease. However, its reappearance during the course of treatment signals a flare up. Such a patient would require an increase in the dosage of immunosuppressant or the introduction of new drug
- In patients with active pemphigus vulgaris, a wet sign is expected, whereas the dry sign indicates re-epithelialization beneath a pemphigus blister which would signifying healing and thus a favorable finding.[29]

Nikolsky's phenomenon

The term "Nikolsky's phenomenon" is applied when the superficial layer of the epidermis is felt to move over the deeper layer, and instead of immediately forming erosion as in Nikolsky's sign, a blister develops after some time. [30]

Mauserung phenomenon

The Nikolsky's sign may also be elicitable in the rare ichthyosis bullosa of Siemens, where it is termed the "Mauserung phenomenon". [30]

False Nikolsky's sign False

Nikolsky's sign, also known as Sheklakov's sign, is described as pulling the peripheral remnant roof of a ruptured blister, thereby extending the erosion on the surrounding normal skin. The erosions thus induced are limited in size, lack the tendency to extend spontaneously, and heal rapidly. [20, 31] It is called the "false Nikolsky's sign" because it is a subepidermal cleavage occurring in the perilesional skin.[5]

False Nikolsky's sign is positive in sub-epidermal blistering disorders that includes bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestation is, dermatitis herpetiformis, linear immunoglobulin A (IgA) bullous dermatosis, epidermolysis bullosa acquisitor, junctional and dystrophic epidermolysis bullosa, porphyry as and bullous systemic lupus erythematosus (SLE).[24]

Pseudo Nikolsky's sign

Pseudo Nikolsky's sign or epidermal peeling sign can be elicited in the same way as for true Nikolsky's sign, but this could be elicited only in the involved erythematous areas. Here, the underlying mechanism is necrosis of epidermal cells in contrast to acantholysis in true Nikolsky's sign. [20, 24] Pseudo Nikolsky's sign is positive in Stevens-Johnson syndrome, toxic epidermal necrolysis, in some cases of burns and bullous ichthyosis form erythroderma. [24]

Conclusion

Despite the numerous investigation methods that are used in the diagnosis of autoimmune blistering diseases, Nikolsky's sign, if performed correctly and interpreted properly, can still serve as a useful and rapid diagnostic tool to assist in preliminary chairside diagnosis of the pemphigus group of disease and also differentiating it from other blistering diseases. Also, in those areas where facilities for immunofluorescence are limited and appropriate lesions for obtaining meaningful results by routine histopathology are not readily available, these clinical signs could be used as an adjunctive diagnostic measure. In summary, it appears reasonable to conclude that every clinician should be aware about these clinical signs which are imperative in early diagnosis and prompt treatment of these potentially fatal mucocutaneous diseases in clinical settings. Although the lack of standardization regarding how exactly to elicit the sign has limited its usefulness, but it remains an interesting sign to observe and interpret.

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