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Histological differential diagnosis of verruca vulgaris: A systematic review

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Abstract
The diagnosis of Verruca Vulgaris is usually clinically, but, in certain situations, confirmation of the diagnosis with biopsy is needed. Several dermatological conditions share microscopic features with Verruca Vulgaris; however, the combination of history, dermatological examination, and histological description would confirm the diagnosis. The purpose of this study is to describe pathological conditions that share histological characteristics with verruca Vulgaris. A systematic review of the literature was used in this study. The histological differential diagnosis of verruca Vulgaris was divided into two categories. First, dermatological conditions that characterized by the presence of vacuolated cells; these conditions are Bowen's Disease and Epidermodysplasia Verruciformis. Second, dermatological conditions that show papillomatosis which includes Verrucous Epidermal Nevus, Hyperkeratotic Seborrheic keratosis, and Acanthosis Nigricans Verruciform xanthoma, Confluent and reticulated papillomatosis.

Keywords: verruca vulgaris, koilocytosis, papillomatosis, human papillomavirus

Introduction
Verruca Vulgaris (VV), or cutaneous wart, is a common skin lesion caused by low-risk subtype (type 1, 2, 6, 11) of human papillomavirus (HPV) as a result of expression of E6 and E7 oncoprotein [1]. It is essential to mention that E6 and E7 oncoprotein also associated with the most aggressive type of HPV (16 and 18); however, the difference is the structural variation of E6 and E7 between benign subtypes HPV versus malignant subtype HPV [1, 2]. VV represents a proliferative lesion of squamous epithelial [3]. It commonly affects the skin of the fingers, toes, soles, and dorsal surfaces of hands; however, in rare cases, it can infect the mucus membrane [4]. Grossly, VV varies in size and number; it appears as hyperkeratotic plaques or papules with clear boundaries and irregular rough surface [1, 4-6]. VV affects any age group; however, it is mostly seen in children and adolescents [7], and it is more common in males [7]. Immunodeficiency status is well known to be associated with the development of numerous and large size verruca Vulgaris [1, 7].

HPV is highly contagious, and it can survive for months on dry surfaces [8]. Acquiring the virus can be through direct contact with viral particles such as physical contact; it can also be by autoinoculation or indirect contact via fomites, such as clothes and sports equipment [9]. Body fluid does not transmit HPV; therefore, HPV is not associated with systemic infection or viremia [1, 3, 7].

Once HPV becomes in contact with the skin, the presence of microdamage to the epidermis allows the virus to enter the superficial epithelial layer of the skin, particularly the stratum basalis, where the virus binds the cellular receptor and enters the cell [10-12]. After the incubation period of HPV, which is 1 -6 months, the virus will undergo three possible scenarios, first; the virus cleared by the immune system, second; entering latency period, which can take up to three years, lastly; development of clinical symptoms [7-9].

The formation of cutaneous warts begins with stimulation of the basal epidermal cells to replicate via HPV E1 and E2 protein, other HPV proteins such as E6 and E7 are also involved in the pathogenesis of Verruca Vulgaris; as the basal epidermal cells differentiate into keratinocytes, they replicate and progress toward the outer epidermis; within these differentiating keratinocytes, the viral genome also amplified, leads to the epidermal thickening and hyperkeratinization that forms visible warts [1, 10, 13].

Histologically, VV presents with a benign feature, with the two most important characteristic features of VV under the microscope include Papillomatous epidermal hyperplasia and cytoplasmic vacuolization, producing halos of pallor surrounding infected nuclei (koilocytosis) [14]. Koilocyte is characterized by perinuclear halos, nuclear enlargement, hyperchromasia, and irregular nuclear membrane. Papillomatosis is a projection of dermal papillae above the surface of the skin, resulting in an irregular undulating configuration of the epidermis, and it is often associated with epidermal hyperplasia [15]. Other histological features which could be present are clumped keratohyalin granules where cells of the stratum spinosum and granulosum showed an increased number of proteinaceous, basophilic, granular inclusion bodies [14]. Additional histological features of VV are acanthosis, hyperkeratosis, and parakeratosis [1, 7, 14, 15].

Several pathological conditions share similar histological features with VV, in particular the koilocytosis and papillomatosis. This review aims to illustrate the histological differential diagnosis of papillomatosis and koilocytosis and identify the key features that help differentiate VV from other histological differential diagnoses.

Method and Materials

Data sources

A systematic review of the literature was used in this study. This study was conducted and prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and Centre of Reviews and Dissemination (CRD's) guidelines [16, 17]. PubMed, PubMed Central, Upto Date, Medline Plus, EMBASE, Google Scholar, and Cochrane Library searching engines were inquired for studies, literature, and case reports, published in the English Language, that focus on the histological description of dermatological conditions (other than Verruca Vulgaris) that present histologically with papillomatosis, koilocytosis (or cellular vacuolization) or both, between the period January 1980 to May 2021. Search terms were the following: "Verruca Vulgaris," "Human Papillomatous virus," "Wart," "papillomatosis," "Digitated Epidermal Hyperplasia," "koilocytes," and "bird's eye cells." There were no restrictions or limitations placed on our search strategy. Inclusion criteria include the following: Original published studies, literature review, case reports, studies that involve human subjects, studies that provide a detailed histological description including the key histological findings seen in VV; which are papillomatosis, koilocytosis, or vacuolization. All the articles are in the English Language.

The following were the exclusion criteria: animal studies, articles that lack histological details, articles with histological details other than papillomatosis, koilocytosis, or vacuolization, articles that are not available in full text, and articles in languages other than English. Also, because the purpose of this study is to explore the histological differential diagnosis of VV, studies that describe VV itself were excluded.

Data Extraction

Extraction and review of the articles, literature, and case reports were conducted by the authors**.** The study authors determined the inclusion and exclusion criteria for each article, literature, and case report with an inter-independent rater assessment indicating a high degree of agreement (Cohen kappa= 0.920). Rater disagreement was subsequently resolved by discussion between the authors. A systematic presentation of the characteristics and findings of the included studies and literature was conducted.

Results

A total of 4490 records involving differential diagnosis of Verruca Vulgaris) that presents were retrieved from PubMed and other searching engines (PubMed Central, Upto Date, Medline Plus, EMBASE, Google Scholar, and Cochrane Library), these conditions present histologically with papillomatosis, cellular vacuolization, or both. After the removal of duplicate records, 870 studies, Literature, and case reports remained. After screening the abstracts of 870 records, 824 were excluded because they were not compatible with the purpose of this study. Of 46 full-text studies, Literature, and case reports reviewed, 28 records were excluded for not meeting our inclusion criteria. A total of 18 full-text records were included in our study. The number of included and excluded records were shown in figure 1.

Dermatological Conditions involved in differential diagnosis of Verruca Vulgaris

From the total 18 included records, seven dermatological conditions were found to be the histological differential diagnosis of VV: Bowen's Disease, Epidermodysplasia Verruciformis, Verrucous Epidermal Nevus, Hyperkeratotic Seborrheic keratosis, Acanthosis Nigricans, Confluent and reticulated papillomatosis, and Verruciform xanthoma.

The included records are divided as following

- One record describes Bowen's Disease.
- Two records outline Epidermodysplasia Verruciformis.
- Two records detailed Verrucous Epidermal Nevus.
- One record explains Hyperkeratotic Seborrheic keratosis.
- Three records delineate Acanthosis Nigricans.
- Three records describe Confluent and reticulated papillomatosis.
- Six records depict Verruciform xanthoma.

Table 1 describes in detail the differential diagnosis of VV, the histological presentation of each dermatological condition, and its clinical presentation.

The dermatological conditions involved in the histological differential diagnosis of VV were divided into two categories: those conditions that show cellular vacuolization and those conditions that show papillomatosis. Figure 2 describes the categorization of the differential diagnosis of VV. Also, it is important to mention that VV has other variants, such as Myrmecia, Condyloma Acuminatum, Verruca Plana, Bowenoid Papulosis, Heck Disease, and Verrucous Cyst. Figure 2 illustrates the variants of VV; these variants were included for clarification purposes and were not counted with included records for differential diagnosis as the aim of the current study is to explore the differential diagnosis of VV.

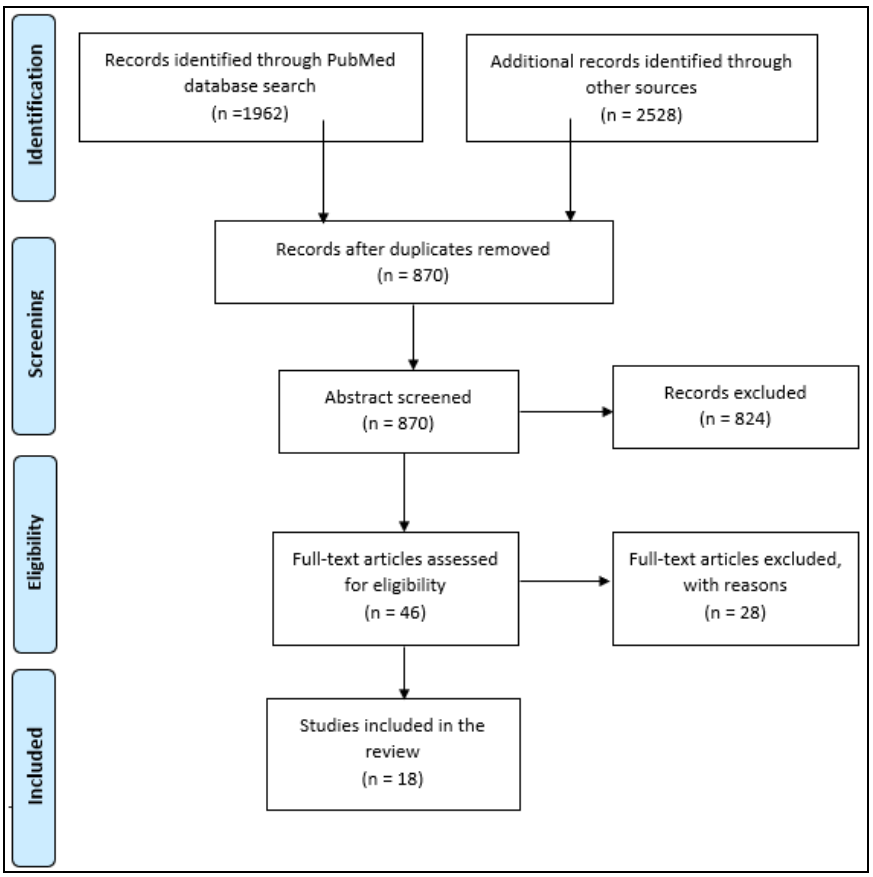

Fig 1: Study selection flow chart of the included studies, literature, and case reports involve the histological differential diagnosis of verruca vulgaris

Table 1: Histological differential diagnosis of verruca vulgaris, and clinical presentation of each condition

Dermatological Condition	Article Title	Summary of Clinical Presentation	Summary of Histologic Description
Bowen's Disease	Bowen's Disease. Lee, MM, *et al*.	Isolated, well-demarcated, scaly plaques with an erythematous base (millimeters to several centimeters).	Vacuolated cells, large pleomorphic nuclei, acanthosis, elongated and thickened rete ridges. Hyperkeratosis and parakeratosis.
Epidermodysplasia Verruciformis	1. Epidermodysplasia Verruciformis. Burger B, *et al*. 2. Epidermodysplasia Verruciformis as a Model in Studies on the Role of Papovaviruses in Oncogenesis. Jablonska s, *et al*.	Red or red brownish plaques on face, trunk, and extremities.	Hyperkeratosis, mild acanthosis, vacuolated cells, and dark blue cells
Verrucous Epidermal Nevus	1. Linear verrucous epidermal nevus with oral manifestations: report of two cases. Gomes RT, *et al*. 2. Verrucous Epidermal Nevus: Dermoscopy, Reflectance Confocal Microscopy, and Histopathological correlation. Verzi AE, *et al.*	Well-demarcated skin-colored or brown plaques following the lines of Blaschko.	Hyperkeratosis, acanthosis, Pigmented keratinocytes, and papillomatosis.
Hyperkeratotic Seborrheic keratosis	Seborrheic keratosis. Hafner C, *et al*.	Sharply demarcated, round, or oval-shaped, elevated and stuck on lesion.	Acanthosis, papillomatosis, hyperkeratosis, horn cysts and horn pseudocysts.
Acanthosis Nigricans	1. Acanthosis Nigricans: A practical approach to evaluation and management. Higgins SP, *et al*. 2. A Study Of Pathogenesis Of Acanthosis Nigricans And Its Clinical Implications. Puri N. 3. An approach to acanthosis nigricans. Phiske, MM.	Thickened, hyperpigmented plaques, typically on the intertriginous surfaces and neck.	Papillomatosis and hyperkeratosis.
Confluent and reticulated papillomatosis	1. Confluent and reticulated papillomatosis: clinical and histopathological study of 10 cases from Lebanon. Tamraz, H, *et al*. 2. Is confluent and reticulated papillomatosis without papillomatosis early or late stage of confluent and reticulated papillomatosis? Atasoy, M, *et al*. 3. Clinical and Histopathologic Study of Confluent and Reticulated Papillomatosis by Anatomic Site and Age. Cho YM, *et al*.	Brown papules and plaques that are confluent centrally and reticulated peripherally.	Papillomatosis, hyperkeratosis, minimal acanthosis, and mild perivascular infiltration in the upper dermis
Verruciform xanthoma	1. Vegas (Verruciform Genital-Associated) Xanthoma: A Comprehensive Literature Review Stiff KM, *et al*.	Papillary or cauliflower-like growth commonly seen in the	Hyperkeratosis, focal parakeratosis, acanthosis without

	2. Verruciform xanthoma: A view on the concepts of its etiopathogenesis. Hegde U, *et al*. 3. Verruciform xanthoma. Gill BJ, *et al*. 4. Genital verruciform xanthoma: lessons from a contemporary multi-institutional series. Grace W, *et al*. 5. Verruciform xanthoma accompanying a cystic growth: A case report. Hara M, *et al*. 6. Bilateral Systematized Epidermolytic Verrucous Epidermal Nevus. Onda T, *et al*.	oral mucosa. sometimes pedunculated	atypia, papillomatosis, and accumulation of the xanthoma-characteristic foamy macrophages with lipid-containing vacuoles.

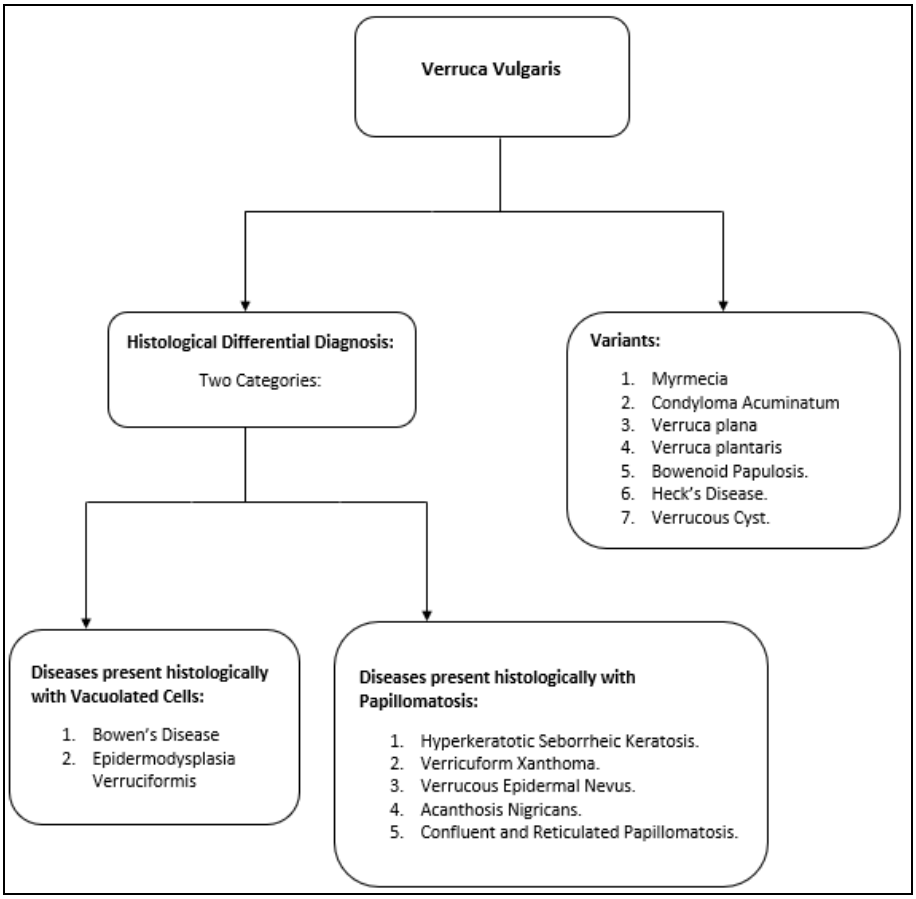

Fig 2: Categories of the histological differential diagnosis of verruca vulgaris, and the Variants of Verruca Vulgaris.

Discussion

The result from this review showed seven dermatological conditions that share histological features with VV. Cellular vacuolization and papillomatosis are the main histological features of VV. Bowen's disease and Epidermodysplasia Verruciformis are two dermatological conditions that showed cellular vacuolization (Figure 2). Bowen's Disease, also identified as squamous cell carcinoma in situ, can occur on any mucocutaneous surface, including nail bed [19]. Clinically, Bowen's Disease is distinct from VV; it is present with a well-circumscribed erythematous plaque with scaling and crust [19], however, histologically, Bowen's Disease showed pleomorphic cells, mitosis, full-thickness atypia of the epidermis, in addition to cellular vacuolization [19], in comparison, VV present histologically with more benign features. Unlike Bowen's disease, papillomatosis is very prominent with VV.

Another dermatological condition associated histologically with cellular vacuolization is Epidermodysplasia Verruciformis**.** Clinically, it is manifested as red or red-brown plaque as with verruca plana. Histologically, although present with cellular vacuolization, acanthosis, and hyperkeratosis, it can be differentiated from VV by the presence of the characteristic "blue cells," which are elongated keratinocytes with bluish cytoplasm [20, 21].

Verrucous Epidermal Nevus manifested as well-demarcated light to dark brown plaques, usually during childhood. Its clinical presentation can be easily differentiated from VV, however, histologically, Verrucous Epidermal Nevus shares a few features with VV, including papillomatosis, acanthosis, and hyperkeratosis, but its lack the presence of vacuolated cells, and there are no granular inclusion bodies. In addition, pigmented keratinocytes can be seen in Verrucous Epidermal Nevus [22, 23].

Sharply demarcated, round, or oval-shaped, elevated, and stuck on lesion is the characteristic clinical presentation of Hyperkeratotic Seborrheic Keratosis. Microscopically it shares papillomatosis with VV; however, the papillomatosis in Hyperkeratotic Seborrheic Keratosis is more pronounced, showing hills and dales pattern "Church Spire." Hyperkeratotic Seborrheic Keratosis lacks koilocytes; in addition, the presence of horn cyst or pseudocyst is distinctive for seborrheic keratosis [24].

The clinical presentation and location of Acanthosis Nigricans distinguish it from VV. Acanthosis Nigricans manifested as hyperpigmented thickened plaque in the intertriginous area and neck. Histologically, Acanthosis Nigricans showed papillomatosis, but there is no

koilocytosis. Despite the name, the acanthosis is moderate in Acanthosis Nigricans, and the hyperpigmentation is due to the hyperkeratosis rather than pigmented keratinocytes [25, 26, 27].

Confluent and Reticulated Papillomatosis (CRP) is an uncommon dermatosis, clinically manifested as hyperpigmented macules, papules, and plaques that are confluent centrally and reticulated peripherally. Histologically, CRP shares few features with VV, including papillomatosis and hyperkeratosis; However, CRP shows mild perivascular infiltration in the upper dermis and minimal acanthosis CRP lacks Koilocytosis and hypergranulosis seen in VV [28-30].

Verruciform Xanthoma (VX) is another uncommon benign mucocutaneous lesion. Clinically, VX is presented as Papillary or cauliflower-like growth commonly seen in the oral mucosa and is sometimes pedunculated. Microscopically, the lesion has a hallmark of accumulation of foamy macrophages with lipid-containing vacuoles; however, VX shares hyperkeratosis, parakeratosis, and papillomatosis with VV [31-36].

In addition to the differential diagnosis, VV has several variants [Figure 2]. Myrmecia, a cutaneous wart associated with HPV 1, usually seen in the skin of hands and feet (palmoplantar), has many histological features similar to VV; however, the presence of red cytoplasmic inclusion bodies helps to distinguish Myrmecia [37]. Condyloma Acuminatum, which is genital warts, histologically showed koilocytosis and papillomatosis [38]; however, the papillomatosis in Condyloma Acuminatum is more rounded rather than spiked papillomatosis seen in VV [39]. Bowenoid Papulosis (BP) also presents in the genital area and is clinically challenging to differentiate from condyloma acuminatum; however, histologically, BP showed atypia [40], a feature typically not seen with Condyloma Acuminatum. Verruca Plana showed acanthosis, basket weave pattern orthokeratotic hyperkeratosis, mild papillomatosis, and characteristic bird's eyes cell (centrally located basophilic nucleus with perinuclear vacuoles) [41]. Heck's Disease, which is also caused by HPV resulting in an oral lesion; histologically showed acanthosis, elongated rete ridges, koilocytosis, and parakeratosis [42]. Verrucous cyst, which is an epidermoid cyst with verrucous changes, microscopically showed cyst with papillomatosis, acanthosis, hyperkeratosis, and keratohyalin granules [43].

Our study has several limitations. First, the conduction of this study required extensive evidence from numerous databases, textbooks, and multiple peer-reviewed materials; it also required access to various databases that need permissions. The authors mitigated this by using university library resources. Second: selection bias, despite the inclusion and exclusion criteria, it is essential to acknowledge that the selection of the included studies was based on the subjective interpretation of the researchers. Third: the inclusion of multiple articles in the systematic review can result in the pooling of several limitations/biases from numerous articles into one study.

Conclusion

Verruca Vulgaris is diagnosed clinically; however, in certain scenarios, a biopsy is needed. Such scenarios include immunocompromised status, excessive verrucous lesions, or diagnosis is in doubt. The key microscopic features of Verruca Vulgaris include papillomatosis and koilocytosis and other histologic features such as acanthosis, hypergranulosis, hyperkeratosis, and keratohyalin granules. Several dermatological conditions also share some histological features with VV, but they can be differentiated with history, physical examination, and careful microscopic examination. Also, several variants of Verruca Vulgaris were identified, and they can be diagnosed based on location, morphological appearance, and histological description.

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