

DOI: 10.21802/artm.2022.1.21.23
UDC 616-071+616.5+616-006.52**THE ROLE OF DERMOSCOPY IN THE DIFFERENTIAL DIAGNOSIS OF SKIN DISEASES CAUSED BY HUMAN PAPILLOMA VIRUS**M.S. Voloshynovych¹, G.Ye. Girnyk¹, V.G. Chmut¹, V.Ye. Tkach¹, N.V. Kozak¹*Ivano-Frankivsk National Medical University, Department of Dermatology and Venereology, Ivano-Frankivsk, Ukraine,*

ORCID ID: 0000-0001-7619-2289, e-mail: mvoloshynovych@gmail.com;

ORCID ID: 0000-0002-9353-6490, e-mail: galingir@ukr.net;

ORCID ID: 0000-0003-3259-4643, e-mail: chmut.valery@gmail.com;

ORCID ID: 0000-0001-5560-3923 e-mail: tkach_vasyl@ukr.net;

ORCID ID: 0000-0002-3190-5238, e-mail: nkozak@ifnmu.edu.ua

Abstract. Human papillomavirus (HPV) is a highly contagious viral infection that is spread between people through direct contact or contaminated objects. According to Centers for Disease Control and Prevention, HPV is the most common sexually transmitted infection. There are over 350 genotypically different types of HPV; most of them cause different types of warts. Many of known genotypes are harmless or are considered "low-risk" types, but 12 genotypes have a high carcinogenic effect. This situation is one of the main reasons for improving the prevention, early diagnostic and timely treatment of papilloma virus infection of different localizations. Doctors of different specialties have a common goal to unite in order to prevent this disease. The term "wart" includes all morphological types of warts and is sometimes used to describe wart-like growths, such as seborrheic keratomas, epidermal and intradermal nevi, sebaceous gland hyperplasia, and other benign and sometimes malignant tumors. Dermoscopy can provide additional information on the structural elements of small wart-like growths. Due to the clinical variability of warts and similar skin growths, they can be represented by different dermoscopic features. Common warts on dermoscopy usually appear in the form of grouped papillae with dotted or loop-like vessels, hemorrhagic points, and lines in various combinations, often centrally located and surrounded by a whitish halo. Plantar warts on dermoscopy are represented by small punctate hemorrhagic structures corresponding to thrombosed vessels and are visualized inside whitish or yellowish papillae, which destroy the skin pattern. Flat warts do not contain specific dermoscopic signs or may be represented by single dotted vascular or hemorrhagic inclusions. Filamentous warts have the same features as normal warts, but due to the elongated papillae, long loop-like vessels they are usually better visualized. The most common dermoscopic finding of genital warts is the so-called mosaic pattern, namely the presence of grouped centrally located dotted or glomerular vessels surrounded by a whitish reticular line, as well as a finger-shaped pattern associated with looped vessels. Sometimes, papilloma can be pigmented by mimicking the clinical aspect of seborrheic keratosis, but keratosis is characterized by a pattern of centrally located vessels, which looks like "frog caviar" (frogspawn-like) but formed by other types of vessels. Differential diagnosis of intradermal nevi is usually not difficult. However, when the elements have a pronounced papillomatous pattern, it may be necessary to assess the structural features of the growth. Most often, the vascular pattern is represented by curved vessels in the middle of clots of body or weakly pigmented colour. Dermatoscopic signs of keratoacanthoma are the detection of a centrally located crater filled with yellow keratin masses and surrounded by a whitish border. It can be relatively homogeneous and little transparent, or polymorphic vessels can be found in it. Dermoscopy may also be helpful in the differential diagnosis of molluscum contagiosum. In contrast to warts, there is a domed protrusion with umbilical indentation, which is filled with white, yellow, or combined amorphous structures. The peripheral zone is more often represented by so-called corona-like vessels. Knowledge of these features can be useful for choosing the right treatment.

Keywords: papillomavirus, nevus, squamous cell carcinoma.

Introduction. Human papillomavirus (HPV) is a highly contagious pathogen. According to the WHO, about 70% of the world population are infected with HPV. In the United States, the prevalence of anogenital papillomavirus lesions reaches 70 million cases with an incidence of 14 million cases per year. There are more than 350 genotypically different types of HPV. Their classification is based on the determination of viral DNA variation. Most known HPV genotypes are harmless or are considered "low-risk" types. Genotypes 1, 2, 4, 27, 57 cause normal warts. Genotypes 3, 10 cause plantar warts. Genotypes 6, 11 cause anogenital warts. These genotypes are rarely associated with malignant degeneration [1]. However, 12 genotypes have a high carcinogenic effect. Among them, subtypes

16, 18, 31, 33 have the highest absolute risks, slightly lower – 35, 39, 45, 51, 52, 56, 58, 59; genotype 68 is carcinogenic either like genotype 66 [2]. The situation is very serious, that's why prevention, early diagnostic, and timely treatment of papilloma virus infection are very important measures in the fight against the incidence of malignant neoplasms of different localization. Medical doctors of different specialties (family medicine, oncology, dermatology, gynecology, and urology) have a common goal to unite in order to prevent this disease.

HPV can be transmitted from one person to another through direct contact or contaminated objects. The infection is more typical for children. Studies show that 5 to 30% of young respondents have warts which can persist

for many years with minor signs of inflammation. At any time of life, a spontaneous gradual reduction in wart size may begin, and then its complete disappearance occurs. However, in adults this process is much slower, its disappearance can take 5-10 years or more [3].

The aim: to acquaint general practitioners with the peculiarities of the use of dermoscopy in the diagnosis and differential diagnosis of warts, and visually similar skin formations.

Results and discussion. The term "wart" includes all morphological types of warts and is sometimes used to describe wart-like growths, such as seborrheic keratomas, epidermal and intradermal nevi, sebaceous gland hyperplasia, and other benign and sometimes malignant tumors. As a rule, the diagnosis is not difficult and is based on the visual picture of the disease. According to anatomical and morphological features, warts are divided into common warts, plantar warts, flat warts, filamentous warts, and genital warts, which are often considered as a separate nosological unit.

Common warts are non-inflammatory dermal papules of various sizes of body color with a rough surface. Cracks may appear on their surface. Most often they are localized on hands and feet. Sometimes, they are prone to forming groups. Plantar warts are flat yellow or brown keratinized growths with clear borders, up to 1-2 cm in size; they can be single or multiple. The surface is speckled, sometimes with a depth in the centre. Such warts are painful when walking and on palpation. Small warts can merge to form the so-called "mosaic" warts. Flat warts mainly affect children. Their typical localization is on the face, neck, back of the hands, chest, etc. These are papules of flesh, yellow, pink, or light brown colour; they can be flat, round, or polygonal; the surface is smooth, from 1 to 3 mm in diameter, slightly rising above the skin; they are multiple, sometimes grouped or grow linearly along the scratches (isomorphic reaction), can cause itching. Filamentous warts are thin, pointed, sometimes with keratinization on the tip of the formation, flesh-coloured, localized on the face in the chin, eyelids, nostrils and mouth, neck, rarely on the torso and limbs [4].

Dermoscopy can provide additional information on the structural elements of small wart-like growths. A dermoscope is more than a ten-fold magnifying lens with a built-in light source. The main purpose of dermoscopy is to evaluate pigmented skin neoplasms for their differential diagnosis with melanocyte degeneration, but in general dermatology you can get additional information about the features of the studied elements of the rash for their subsequent differential diagnosis [5].

Due to the clinical variability of warts and similar skin growths, they can be represented by different dermoscopic features. However, there is a high probability of dotted vessels or hemorrhagic points, or a combination of both [6].

Common warts on dermoscopy usually appear in the form of grouped papillae with dotted or loop-like vessels, hemorrhagic points, and lines in various combinations, often centrally located and surrounded by a whitish halo (Fig. 1). The pattern of "frog caviar" can also be observed [7].

Plantar warts on dermoscopy are represented by small punctate hemorrhagic structures corresponding to

thrombosed vessels and are visualized inside whitish or yellowish papillae, which destroy the skin pattern [8] (Fig. 2).



Fig. 1. Dermoscopy. A common wart is localized on the index finger of the right hand. Size 1x2 mm. Dotted vessels and hemorrhagic points are surrounded by a whitish halo. The formation disrupts the normal skin pattern.

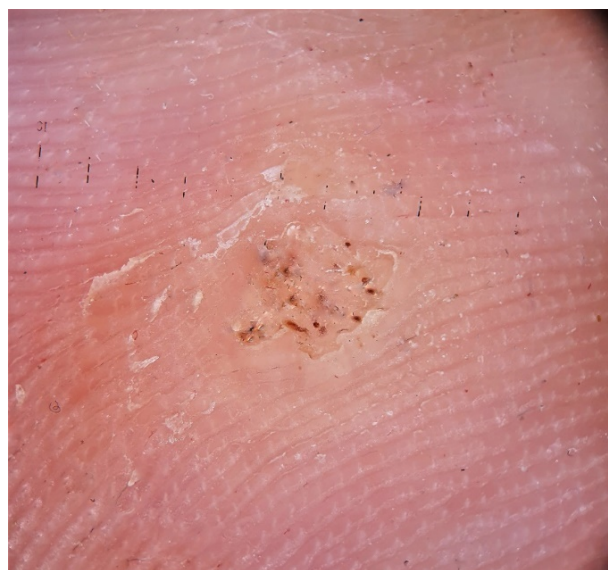


Fig. 2. Dermoscopy. Plantar wart. Size 3x3.5 mm. Multiple dotted thrombosed vessels inside the pinkish-yellow papilla, which disrupts the skin pattern.

Flat warts do not contain specific dermoscopic signs or may be represented by single dotted vascular or hemorrhagic inclusions (Fig. 3).

Filamentous warts have the same features as normal warts, but due to the elongated papillae, long loop-like vessels they are usually better visualized (Fig. 4).



Fig. 3. Dermoscopy. Flat wart on the face. Size 2x3 mm. Single dotted and hemorrhagic inclusions.



Fig. 4. Dermoscopy. Filamentous wart on the trunk. Size 3x4 mm. Looped vessels and keratinization on the tips of elongated papillae are clearly visible.

The most common dermoscopic finding of genital warts is the so-called mosaic pattern (sometimes referred to as "buttons"), namely the presence of grouped centrally located dotted or glomerular vessels surrounded by a whitish reticular lines, as well as a finger-shaped pattern associated with looped vessels [9] (Fig. 5).

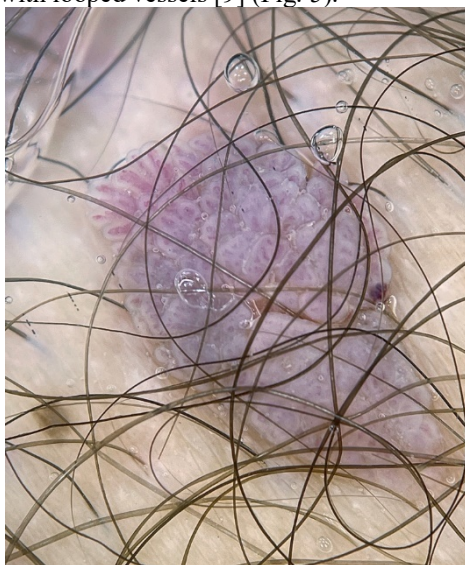


Fig. 5. Dermoscopy. Genital warts. Mosaic pattern.

Sometimes, papilloma can be pigmented by mimicking the clinical aspect of seborrheic keratosis, but keratosis is characterized by a pattern of centrally located vessels, which looks like "frog caviar" (frogspawn-like) but formed by other types of vessels (Fig. 6). In addition, milium-like cysts (white clots), comedone-like holes (from brown to black), the inclusion of yellowish keratin, as well as fissures and ridges that form a cerebral pattern are found [10, 11].

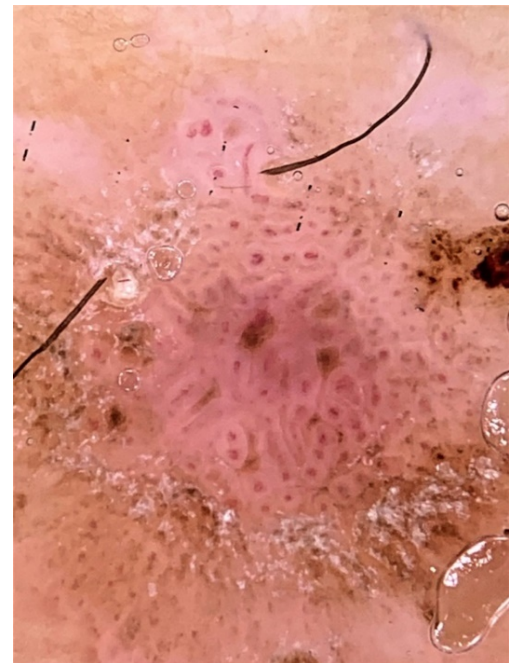


Fig. 6. Dermoscopy using light-conducting fluid. Fragment of seborrheic keratoma on the outer surface of the thigh. The focus is on the pattern of centrally located glomerular vessels with single loop vessels. Some keratin inclusions are between them. Peripherally expressed hyperkeratosis is present.

Differential diagnosis of intradermal nevi is usually not difficult. However, when the elements have a pronounced papillomatous pattern, it may be necessary to assess the structural features of the growth. Most often, the vascular pattern is represented by curved vessels in the middle of clots of body or weakly pigmented colour. Keratotic masses also often accumulate in the folds of the wart (Fig. 7).

Keratoacanthoma has many common features with warts. It is a skin tumour characterized by two stages of growth – rapid and involutive. It typically occurs on sun-damaged skin. There are many possible contributing factors including some medications. There is an ongoing debate as to whether keratoacanthoma is a type of squamous cell carcinoma or a separate nosological unit. The morphological criteria of these growths overlap. At the same time, genetic studies have shown some differences between these pathologies, while pointing to the possible role of HPV 6 in the pathogenesis of at least some keratoacanthomas [12].



Fig. 7. Dermoscopy. A fragment of an intra-dermal nevus. Curved vessels inside the body-colored particles predominate.

Dermatoscopic signs of keratoacanthoma are the detection of a centrally located crater filled with yellow keratin masses and surrounded by a whitish border. It can be relatively homogeneous and little transparent, or polymorphic vessels (dotted, linear with irregular distribution, looped and curved) can be found in it. Single hemorrhages are usually associated with the central keratin portion [13] (Fig. 8).

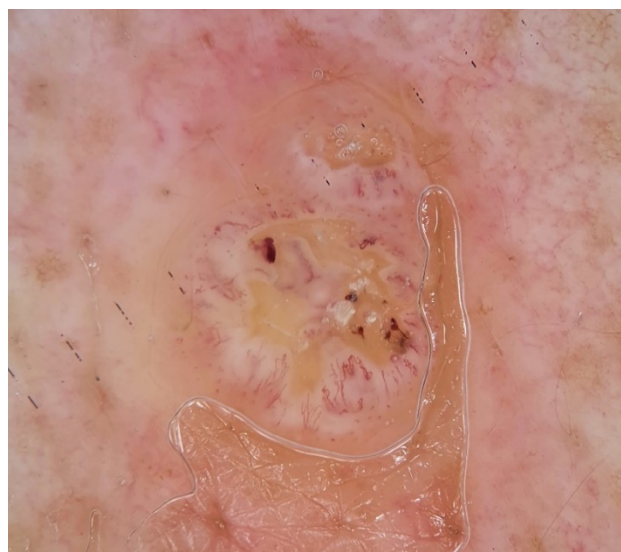


Fig. 8. Dermoscopy using light-conducting fluid. Keratoacanthoma. Size 5x5 mm. Centrally located yellow keratin masses surrounded by halo with multiple looped and curved vessels. Multiple dotted and linear vessels with uneven distribution.

Dermoscopy may also be helpful in the differential diagnosis of molluscum contagiosum. It is especially useful in detecting single growths. In contrast to warts, there is a domed protrusion with umbilical indentation, which is filled with white, yellow, or combined amorphous structures. The peripheral zone is more often represented by so-called corona-like vessels (curved vessels with minimal branching). However, this symptom sometimes is

absent. There are also radial, point vessels, or growths without visible peripheral vessels [14] (Fig. 9).

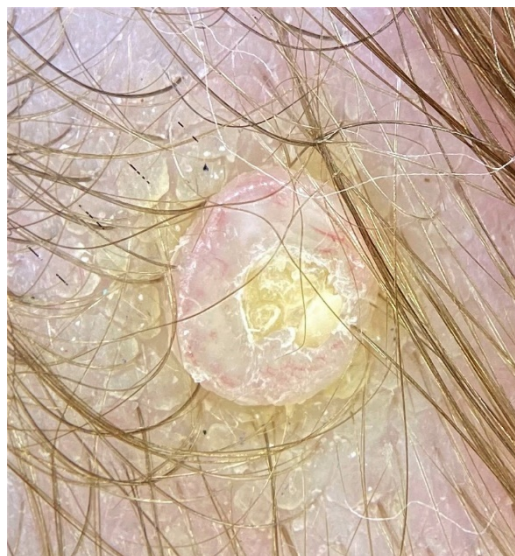


Fig. 9. Dermoscopy. Contagious mollusk on the scalp. Size 3x3 mm. Central zone with umbilical indentation filled with yellow amorphous masses. At the periphery, single curved and radial vessels.

This is a list of the most common diseases that may require differential diagnosis of warts of different localization. After establishing a clinical and dermoscopic diagnosis, the next step is to choose proper treatment. Most of the current recommendations are aimed at destroying the infected epithelium by chemical destruction (salicylic acid at a concentration of 15-26%, silver nitrate 10%, phenol (80%), formic acid, etc.), freezing with liquid nitrogen (15-30 seconds, followed by repeat procedures after 2-4 weeks for at least 3 months or 6 procedures), surgical removal (curettage, cauter, CO2 laser, pulsed dye laser). Photodynamic therapy, hyperthermia (use of heat on the rash area 40-44 ° C for 30 min for three consecutive days), administration of antitumor drugs (introduction of bleomycin into the affected area after previous anesthesia, 5-fluorouracil 5% are also used for therapeutic purposes daily + occlusion 4-12 weeks), topical antiviral therapy (Imiquimod 5% cream 2 times a day for 6 months), synthetic vitamin D analogues (Maxacalcitol three times a day for 2-6 months), systemic retinoids (Acetritin from 0.5 to 1 mg per kg for 3 months) [3].

We should also not forget about prevention measures, such as HPV vaccination to prevent new outbreaks of infection and HPV-associated diseases, including some cancers. Such vaccines are recommended in the United States for adults and children ages 9 to 26 and for some persons up to 45 years of age with specific indications [15].

Conclusions:

1. HPV is a highly contagious pathogen. Mostly, HPV genotypes are harmless, but some of them are highly carcinogenic. This situation is one of the main reasons for improving the prevention, early diagnostic and timely treatment of papilloma virus of different localizations which can be cancerous.
2. Dermoscopy can provide essential additional information on the structural elements, especially in case of

small warts. HPV infection diagnosis and differentiation from other skin abnormalities can be performed

easily based on specific findings summarized in table below (Tabl.1).

Table 1

Differential diagnostic criteria for warts and wart-like skin formations

Name of skin growth	Macroscopic manifestations	Dermoscopic manifestations
Common warts	Papules of various sizes of flesh colour with a rough surface	Grouped papillae with dotted or looped vessels, hemorrhagic points and lines. Often centrally located and surrounded by a whitish halo. A pattern of "frog caviar" can be observed (Fig. 1).
Plantar warts	Flat, yellow or brown keratinized growths with clear boundaries	Small dotted hemorrhagic structures corresponding to thrombosed vessels and are visible inside of whitish or yellowish papillae, which destroy the skin pattern (Fig. 2).
Flat warts	Papules of flesh, yellow, pink or light brown colour; have a round or polygonal form; grouped or arranged linearly	Do not contain specific dermoscopic features or may be represented by single dotted vascular or hemorrhagic inclusions (Fig. 3).
Filamentous warts	Thin, pointed, sometimes with keratinization on the tip flesh-coloured growths.	Have the same features as normal warts, but due to the elongated papillae; long loop-shaped vessels are usually better visualized (Fig. 4).
Genital warts	Papules are mostly flesh-coloured of various sizes.	Mosaic pattern (buttons), namely the presence of grouped centrally located dotted or glomerular vessels surrounded by a whitish reticular lines, as well as a finger-shaped pattern associated with looped vessels (Fig. 5).
Seborrheic keratosis	Spots or papules of various colours with or without keratinization on the surface	Pattern of centrally located vessels, miliary cysts, comedones, inclusions of yellowish keratin, as well as fissures and ridges which form a cerebral pattern (Fig. 6).
Intradermal nevi	Papules are of various sizes, mostly flesh-coloured.	The vascular pattern is represented by curved vessels in the middle of clots of flesh or weakly pigmented colour; keratotic masses accumulate in the folds of the formation (Fig. 7).
Keratoacanthoma	Papule of dense consistency with keratinization in the center	The centrally located crater is filled with yellow keratin masses and surrounded by a whitish border. Polymorphic vessels can be seen in it. Single hemorrhages are usually associated with the central part (Fig. 8).
Molluscum contagiosum	Papule with umbilical indentation in the center	Dome-shaped protrusion with umbilical indentation, filled with white, yellow, or combined amorphous structures. The peripheral zone is more often represented by corona-like vessels. There are also radial, dotted vessels, or growths without visible peripheral vessels (Fig. 9).

References:

- Berman TA, Schiller JT. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases: HPV in Cervical and Oropharyngeal Ca. *Cancer*. 2017; 123(12):2219-29. DOI: <https://doi.org/10.1002/cncr.30588>.
- Arnold JD, Byrne ME, Monroe AK, Abbott SE. District of Columbia Cohort Executive Committee. The Risk of Anal Carcinoma After Anogenital Warts in Adults Living With HIV. *JAMA Dermatol*. 2021; 1; 157(3):283-289. DOI: <https://doi.org/10.1001/jamadermatol.2020.5252>.
- Sterling JC, Gibbs S, Haque Hussain SS, Mohd Mustapa MF, Handfield-Jones SE. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014; 171(4):696-712. DOI: <https://doi.org/10.1111/bjd.13310>.
- Stepanenko VI, Chobotar AI, Bondar SO, et al. *Dermatologhiia i venerologhiia*. Kyiv: *Vseukrainske spetsializovane vydavnytstvo «Medytsyna»*; 2020. P.239-40.
- Rosendahl C, Voloshynovych MS, Girnyk GY. «Chaos and Clues» algorithm in routine practice of analyzing dermoscopic image. *Ukr J Dermatol Venerol Cosmetol*. 2019; 75(4):65-70. DOI: <https://doi.org/10.30978/UJDVK2019-4-65>.
- Piccolo V. Update on Dermoscopy and Infectious Skin Diseases. *Dermatol Pract Concept*. 2019; 31; 10(1):e2020003. DOI: <https://dx.doi.org/10.5826%2Fdp.c.1001a03>.
- Tschandl P, Argenziano G, Bakos R, et al. Dermoscopy and entomology (entomodermoscopy). *J Dtsch Dermatol Ges*. 2009 Jul; 7(7):589-96. DOI: <https://doi.org/10.1111/j.1610-0387.2009.07027.x>.
- Fried I, Kasper RS, Hegyi I, Kempf W. Black dots in palmoplantar warts-challenging a concept: A histopathologic study. *J Am Acad Dermatol*. 2018; 79(2):380-2. DOI: <https://doi.org/10.1016/j.jaad.2018.01.013>.
- Maatouk I, Apalla Z, Errichetti E, Lallas A. Dermoscopy for venereologists: an update on patterns of tumors, inflammatory and infectious diseases of the genitalia, and tips for differential diagnosis. *Int J Dermatol*. 2021; 60(10):1211-1218. DOI: <https://doi.org/10.1111/ijd.15333>.

10. Rosendal K, Voloshynovych MS, Girnyk GE. Algorithmic method of dermoscopic image analysis «Prediction without pigment» and its implementation in clinical practice. *Ukr J Dermatol Venerol Cosmetol.* 2020; 78(3):62-8. DOI: <https://doi.org/10.30978/UJ-DVK2020-3-62>.
11. Carrera C, Segura S, Aguilera P, et al. Dermatoscopic Clues for Diagnosing Melanomas That Resemble Seborrheic Keratosis. *JAMA Dermatol.* 2017; 153(6):544-551. DOI: <https://doi.org/10.1001/jamadermatol.2017.0129>.
12. Nirenberg A, Steinman H, Dixon A. Keratoacanthoma: Update on the debate: Update on the debate. *Am J Dermatopathol.* 2021; 43(4):305-7. DOI: <https://doi.org/10.1097/DAD.0000000000001872>.
13. Wang X, Wang Y, Wang H, et al. The first report of diagnosing of keratoacanthoma in Chinese Han patients using dermoscopy and reflectance confocal microscopy. *Skin Res Technol.* 2021; 27(3):422-427. DOI: <https://doi.org/10.1111/srt.12975>.
14. Natsis NE, Gordon SC, Kaushik A, Seiverling EV. A practical review of dermoscopy for pediatric dermatology part II: Vascular tumors, infections, and inflammatory dermatoses. *Pediatr Dermatol.* 2020; 37(5):798-803. DOI: <https://doi.org/10.1111/pde.14284>.
15. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus vaccination for adults: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2019; 68(32):698-702. DOI: <http://dx.doi.org/10.15585/mmwr.mm6832a3>.

УДК 616-071+616.5+616-006.52

РОЛЬ ДЕРМАТОСКОПІЇ В ДИФЕРЕНЦІЙНІЙ ДІАГНОСТИЦІ УРАЖЕНЬ ШКІРИ, ВИКЛИКАНИХ ВІРУСОМ ПАПІЛОМИ ЛЮДИНИ

М.С. Волошинович¹, Г.Є. Гірник¹, В.Г. Чмут¹,
В.Є. Ткач¹, Н.В. Козак¹

*Івано-Франківський національний медичний університет,
кафедра дерматології та венерології,
м. Івано-Франківськ, Україна,
ORCID ID: 0000-0001-7619-2289,
e-mail: mvoloshynovych@gmail.com;
ORCID ID: 0000-0002-9353-6490,
e-mail: galingir@ukr.net;
ORCID ID: 0000-0003-3259-4643,
e-mail: chmut.valery@gmail.com;
ORCID ID: 0000-0001-5560-3923
e-mail: tkach_vasyl@ukr.net;
ORCID ID: 0000-0002-3190-5238,
e-mail: nkozak@ifnmu.edu.ua*

Резюме. Вірус папіломи людини (HPV) є високо контагіозною вірусною інфекцією, що передається між людьми через прямі контакти або інфіковані об'єкти. Згідно з інформацією Центру з контролю та профілактики захворювань (США), HPV є найбільш частою сексуально трансмісивною інфекцією. Існує понад 350 генотипів HPV; в основному вони викликають різні типи бородавок. Серед відомих генотипів більшість є не шкідливими або вважаються типами низького ризику, але 12 генотипів володіють високим канцерогенним ефектом. Ця ситуація ставить необхідність профілактики, ранньої діагностики і вчасного лікування папіломавірусної інфекції на чільне місце та об'єднує спільною метою лікарів різних спеціальностей. Термін «бородавки» включає в себе всі морфологічні типи бородавок та іноді використовується з метою позначення бородавкоподібних розростань, таких як себорейні кератоми, епідермальні та внутрішньодермальні невису, гіперплазії сальних залоз та інших доброякісних чи злоякісних пухлин. Дерматоскопія може надати додаткову інформацію про структурні елементи дрібних бородавкоподібних розростань. Звичайні бородавки при дерматоскопії виявляються у вигляді згрупованих сосочків із точковими або петлеподібними судинами, геморагічними точками та лініями в різних комбінаціях. Підшовні бородавки представлені невеликими точковими геморагічними структурами, що відповідають тромбованим судинам. Плоскі бородавки частіше не містять специфічних ознак. Ниткоподібні бородавки містять ті ж ознаки, що й звичайні бородавки. Генітальні бородавки проявляються мозаїчним малюнком. Знання цих нюансів може бути корисним для обрання вірної методики лікування.

Ключові слова: папіломавірус, невис, плоскоклітинна карцинома.

Стаття надійшла в редакцію 08.01.2022 р.
Стаття прийнята до друку 07.02.2022 р.