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CLINICAL CASES OF DARIER-WHITE FOLLICULAR DYSKERATOSIS

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Key words: *Darier-White disease, differential diagnosis, dermoscopy, treatment*
Ключові слова: *хвороба Дар'є, диференціальна діагностика, дерматоскопія, лікування*

Abstract. Clinical cases of Darier-White follicular dyskeratosis. Tkach V.Ye., Voloshynovych M.S., Romanchuk S.M., Girnyk G.Ye., Matkovska N.R., Kozak N.V. *Follicular dyskeratosis (Darier-White disease) is a hereditary skin disease that is extremely rare in medical practice, so errors in its diagnosis can occur. It was first described in 1889 by two scientists (independently of each other), Ferdinand-Jean Darier and James White. The disease is inherited in an autosomal dominant pattern with variable gene penetrance. The main cause of this pathological process is a mutation of the ATP2A2 gene, located in the long arm of chromosome 12. Both men and women are affected with the same probability, but clinical manifestations are more severe in males. It appears, as a rule, at the age of 20; children under 10 rarely suffer from DAR; people who are over 30 years have very little chance of contracting this disease. Clinical manifestations slowly progress up to the age of 40-50, and gradually disappear in older age. Typical rashes are follicular papules, 0.2-0.5 cm in size, yellow-brown or dark brown in color, covered with dry or oily layers in the form of horny scales. On the*

surface layers, black dots are visible which are hair follicle funnels. Papules are rounded, dense, flat or spherical, initially isolated, eventually merging into plaques. They are mostly localized on the skin of the limbs, trunk, chest, in the interscapular area, large folds, less often on the neck, scalp, auricles, and in the ear canals. In 20-30 percent of patients, rashes are localized on the mucous membrane of the oral cavity next to the affected skin. More than 90 percent of patients have nail abnormalities, such as erythro- and leukonychia. Other possible manifestations are fragility, splinter hemorrhages, marked subungual hyperkeratosis, which can be observed on 2-3 nails or affect all nail plates. The dermatoscopy of skin lesions is characterized by the presence of several polygonal, branched, star-shaped or rounded-oval yellow-orange-brown lumps of various sizes, surrounded by a thin whitish halo and pink small-structured areas. The prognosis for recovery is not favorable, the treatment is ineffective. Two cases of Darier-White disease are described in this article.

Реферат. Клінічні випадки фолікулярного дискератозу Дар'є-Вайта. Ткач В.Є., Волошинович М.С., Романчук С.М., Гірник Г.Є., Матковська Н.Р., Козак Н.В. *Фолікулярний дискератоз (хвороба Дар'є-Вайта) – спадкова хвороба шкіри, яка зустрічається в практиці лікаря надзвичайно рідко, тому допускаються помилки в її діагностиці. Уперше описана в 1889 році незалежно один від одного двома науковцями: Фердінандом Жаном Дар'є та Джеймсом Вайтом. Хвороба успадковується за аутосомно-домінантним типом з варіабельною пенетрантністю. В основі мутація гена ATP2A2, локалізованого в довгому плечі 12 хромосоми. Хворіють з однаковою ймовірністю як чоловіки, так і жінки, проте клінічні прояви більш виражені в чоловіків. Дебют хвороби – частіше в другому десятилітті життя. Рідко хвороба починається в першому десятилітті й ще рідше після 30 років. Клінічні прояви до 40-50 років повільно прогресують, у старшому віці поступово згасають. Типовими висипаннями є фолікулярні папули, величиною 0,2-0,5 см, жовто-бурого або темно-коричневого кольору, покриті сухими або жирними нашаруваннями у вигляді рогових лусок. На поверхні нашарувань помітні чорні точки-лійки волосяних фолікулів. Папули округлі, щільні, плоскі або сферичні, спочатку ізольовані, з часом зливаються в бляшки. Локалізуються, як правило, на шкірі кінцівок, тулуба, грудній клітці, в міжлопатковій ділянці, великих складках, рідше на шиї, волосистій частині голови, на вушних раковинах, у вушних проходах. Дуже рідко на долонях і підошвах. У 20-30 відсотків висипні елементи локалізуються на слизовій ротової порожнини поряд з ураженням шкіри. Більше ніж у 90 відсотків хворих уражаються нігтьові пластинки у вигляді еритро- та лейконіхії. Інші ймовірні прояви: крихкість, поздовжні гребінці, скалкоподібні крововиливи, виражений піднігтьовий гіперкератоз, що можуть спостерігатись на 2-3-х нігтях чи охоплювати всі нігтьові пластини. При дерматоскопії висипних елементів – типова наявність кількох полігональних, гіллястих, зіркоподібних або округло-овальних жовто-помаранчево-коричневих грудок різного розміру, оточених тонким білуватим ореолом та рожевими малоструктурними ділянками. Прогноз щодо вилікування несприятливий, лікування малоефективне. Подано опис двох випадків хвороби Дар'є-Вайта.*

Darier-White disease (DAR) (also known as Darier disease, follicular vegetative psorospermosis, Darier's follicular dyskeratosis, follicular keratosis (ichthyosis)) is a hereditary skin disease that is extremely rare in medical practice, so errors in its diagnosis can occur. It was first described in 1889 by two scientists (independently of each other), Ferdinand-Jean Darier and James White [14].

The disease is inherited in an autosomal dominant pattern with variable gene penetrance. Both men and women are affected with the same probability, but clinical manifestations are more severe in males. It appears, as a rule, at the age of 20; children under 10 rarely suffer from DAR; people who are over 30 years have very little chance of contracting this disease. At an older age, rashes are often scanty, not typical (abortive form). Up to the age of 50, the number of rashes increases, then they disappear. It is believed that the main cause of this pathological process is a mutation of the ATP2A2 gene located in the long arm of chromosome 12 (12q23-24.1). It encodes sarcoplasmic Ca^{2+} ATPase type 2 (SERCA2), which is responsible for regulation of the intracellular concentration of calcium ions in various body tissues, including the epidermis. However, the mechanism by which a dyskeratotic reaction of epidermal keratinocytes occurs in response to a violation of calcium homeostasis remains unknown. [3, 5, 14]

Typical rashes are follicular papules, 0.2-0.5 cm in size, yellow-brown or dark brown in color, covered with dry or oily layers in the form of horny scales. On the surface layers, black dots are visible which are hair follicle funnels. Papules are rounded, dense, flat or spherical, initially isolated, eventually merging into plaques. They are mostly localized on the skin of the limbs, trunk, chest, in the interscapular area, large folds, less often on the neck, scalp, auricles, and in the ear canals. Papules appear very rarely on the palms and soles, simulating horny eczema, psoriasis or keratoderma. They can be associated with itching and unpleasant odor. The entire skin can be affected in sporadic cases. It should also be mentioned that patients have increased sensitivity to sunlight [8, 14].

In 20-30 percent of patients, rashes are localized on the mucous membrane of the oral cavity next to the affected skin. Nodules appear on the palate, tongue, cheeks. Lentil-sized rash elements with a vague depression in the center are of whitish color; they are covered with gray-black layering, which can be easily removed. In addition to the typical form of

the disease, atypical ones are rarely found: hypertrophic, vesicular, abortive, linear comedo-like, etc. [1, 4, 11, 12, 15].

More than 90 percent of patients have nail abnormalities, such as erythro- and leukonychia (longitudinal red-white streaks with a distal V-shaped split). Other possible manifestations are fragility, splinter hemorrhages, marked subungual hyperkeratosis, which can be observed on 2-3 nails or affect all nail plates. The disease can start with onychodystrophy [13]. Darier's follicular dyskeratosis is benign but can be associated with endocrinopathies, mental illnesses, epilepsy, and mental retardation [2, 6].

The dermatoscopy of skin lesions is characterized by the presence of several polygonal, branched, star-shaped or rounded-oval yellow-orange-brown lumps of various sizes, surrounded by a thin whitish halo and pink small-structured areas. [10] (Fig. 1).

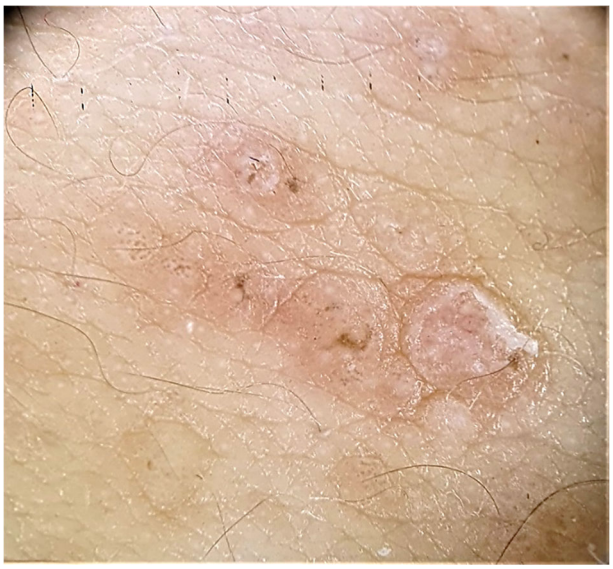

Fig. 1. Dermatoscopy of rash elements in Darier-White disease polygonal yellow-brownish areas with whitish halo

However, it is necessary to consider that such signs are also characteristic of Grover's disease and acantholytic dyskeratosis induced by BRAF inhibitors, which does not allow a direct interpretation of the obtained microscopic data without regard to the results of a clinical examination, and as with other pathologies in general dermatology, they must be evaluated comprehensively [7, 9].

The purpose of the work was to demonstrate the difficulty of diagnosing Darier-White disease as a rare pathology, given the possible atypical course of the disease; to suggest the use of dermatoscopy as an additional research method, subject to an assessment of the clinical picture and subsequent skin biopsy.

Heine Delta 20 dermatoscope, Samsung SM-G973F digital camera, clinical cases of Darier-White disease to demonstrate typical and atypical manifestations of this disease.

Two cases of Darier-White disease are described in this article.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

A 34-year-old patient A. fell ill more than a year ago. At first, small rashes appeared on the lateral surfaces of the neck, the number of which increased over time. The elements merged into plaques, they did not disturb and only caused cosmetic discomfort. Over the past six months, the number of rashes has increased, spreading to the upper limbs, abdomen and scalp. Exacerbation was noted after exposure to the sun. A district dermatologist diagnosed lichen planus and sent her to our clinic to confirm the diagnosis. The anamnesis revealed that the patient was the second child in the family who was born in a natural way after an uncomplicated pregnancy. She grew up and developed in normal living conditions, graduated from school and medical college with "good" and "excellent" grades, works as a nurse. No similar diseases were found in close or distant family. The woman is not married, her periods are regular. Her general condition is satisfactory, intelligence corresponds to the level of education. For the last 2-3 months, the patient experienced headaches and nausea. She also suffers from chronic pyelonephritis. Patient A. was examined and her general blood analysis, blood sugar were within normal limits. A urinalysis revealed traces of protein, leached erythrocytes, minor leukocytosis. No worm eggs were found in the feces. Blood proteins, cholesterol, bilirubin, B-lipoproteins, triglycerides, AlT, AsT, C-reactive protein were without deviations. Cortisol in blood and urine were decreased by 1.0 μg/dl, 21.6 μg/24 h, potassium – 3.84 mmol/l, sodium – 149 mmol/l, chloride – 92 mmol/l, respectively. Abdominal ultrasound was showed no abnormalities. X-ray of the lungs, ECG were within normal limits.

When examining the lateral and frontal surfaces of the neck and occipital area, small, dense, rounded, covered with horny scales, dome-shaped papules of dark brown color were noted. On the lateral surfaces of the neck, they merge into plaques covered with dirty-brown crusts; a moist surface with a central depression is visible when they are removed (Fig. 2).

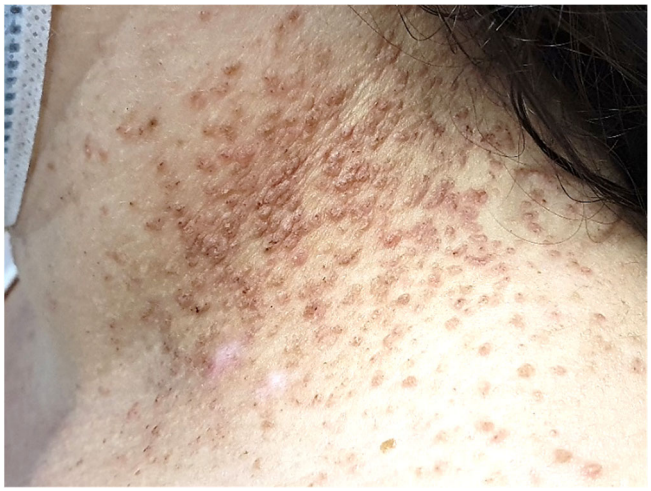

Fig. 2. Patient A. Dense domed papules of dark brown color on the lateral surface of the neck, merging into plaques

Similar papules are focally located on the upper limbs, abdomen and back. (Fig. 3) Small papules and exfoliation were noticed on the scalp. The mucous membranes of the oral cavity, nail plates, palms and soles were not affected.

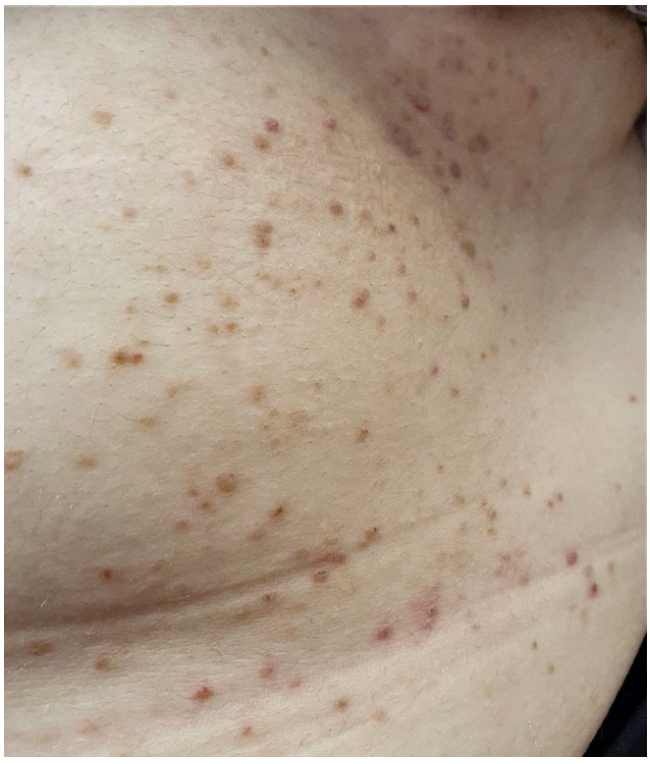

Fig. 3. Patient A. Papules on the anterior-lateral surface of the abdomen were located focally

The dermatoscopy of different areas of skin lesions is characterized by the presence of multiple polygonal, branched, star-shaped or rounded-oval yellow-orange-brown lumps of various sizes, surrounded by a thin whitish halo and pink small-structured areas (Fig. 4-5).

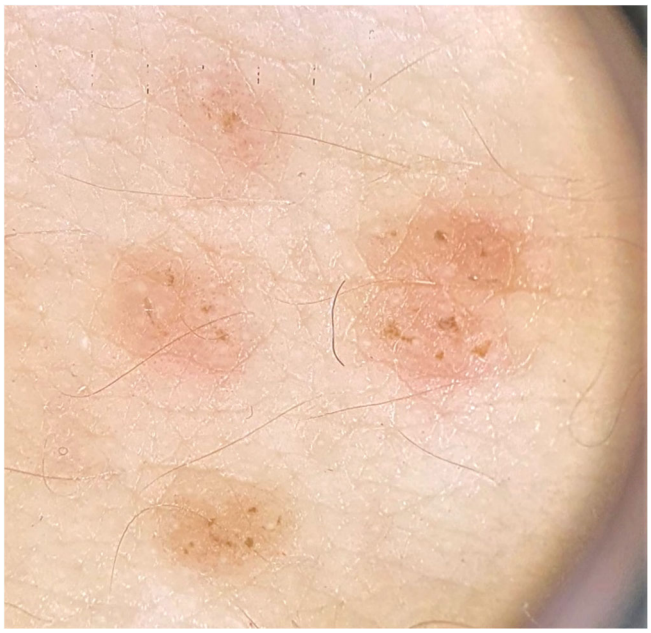

Fig. 4. Patient A. Trunk surface. Dermatoscopy. A picture of polygonal, yellow-orange-brown areas of different sizes, surrounded by a thin whitish halo and delimited by healthy skin

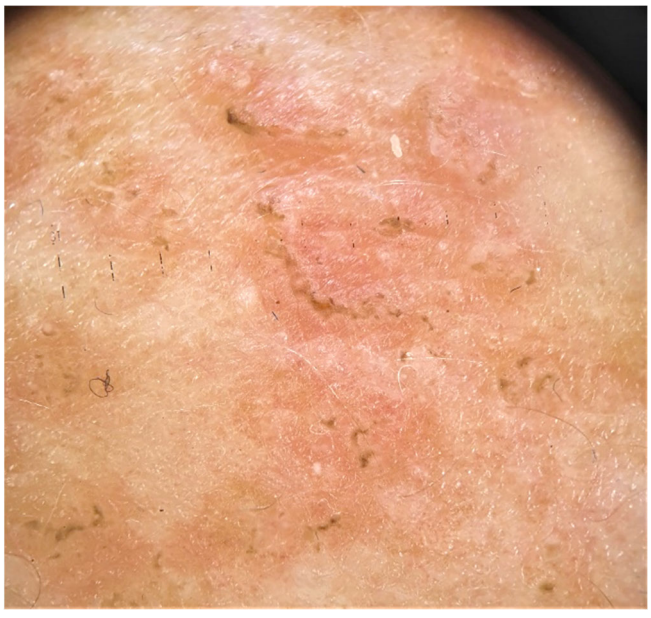

Fig. 5. Patient A. Area of the lateral surface of the neck where papules form plaques. Dermatoscopy. A dense network of multiple, polygonal, branched, yellow-orange-brown areas of various sizes, surrounded by a thin whitish halo, and pink small-structured zones

A diagnosis of follicular dyskeratosis (Darier-White disease) was made. In order to confirm it, a biopsy study of lesions on the skin of the neck was conducted. Focal hyperkeratosis, acanthosis, hypergranulosis with deformed cells and signs of dyskeratosis (crop ronds) were found in the epidermis. In the basal layer, there were signs of acantholysis (the formation of clefts was observed). A perivascular lymphohistiocytic infiltrate was detected in the superficial layer of the dermis. (Fig. 6).

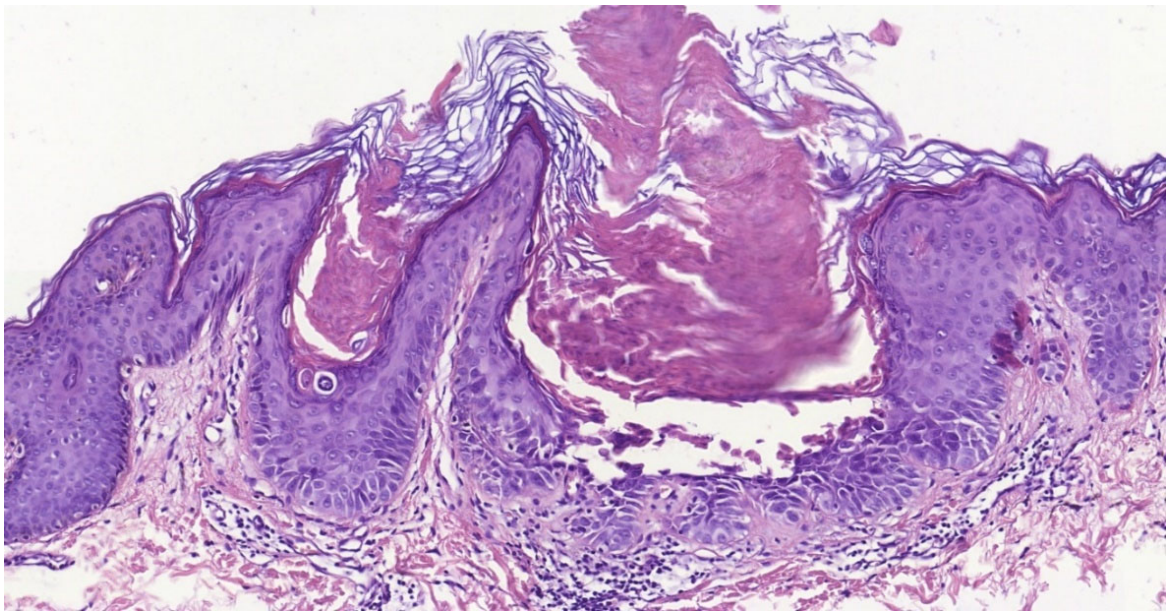

Fig. 6. Patient A. Pathohistological examination of a punch biopsy of the skin of the neck

A 29-year-old patient B. turned to a dermatologist with complaints of rashes on the skin of the face, upper limbs and trunk without subjective sensation. The skin rash appeared at the age of 7. The disease progressed; the number of rashes increased without any reason, spreading to the chest and upper limbs. Two years ago, the rash began to appear on the skin of the face. Doctors recommendehelsd him various creams and ointments, the use of which somewhat reduced the feeling of skin tightening. He was born a full-term child, grew up and developed in satisfactory living conditions. The patient graduated from school, university. He is married, has two children. His parents, children and relatives do not have similar skin diseases. When examined, the rashes were widespread, localized on the skin of the face, upper limbs, back, front surface of the chest. (Fig. 7-8).

Flat lentil-sized follicular papules are of yellow-brown color; they are covered with crusty scales. When they are removed, a dry or wet surface with a depression in the center is exposed. In the area of the back and chest, the elements merge into dark brown plaques of various sizes. Keratosis is revealed on the palms and soles. White horizontal streaks (leukonychia) are visible on the fingernail plates. The mucous membranes of the oral cavity are unchanged.

The patient was hospitalized with a preliminary diagnosis of Darier-White disease. During the examination, the general analysis of blood and urine showed no abnormalities. Wasserman's reaction was negative. Total protein – 74.7 g/l, total bilirubin – 18.0 μmol/l, direct bilirubin – 5.6 μmol/l, urea – 5.5 mmol/l, creatinine – 88.4 μmol/l, AsAT – 75.5 units/l, AlAT – 62.2 units/l, cholesterol – 6.1 mmol/l, glucose – 5.1 mmol/l, lactate dehydrogenase – 307.24 units/l, amylase – 41.98 units/l. Ultrasound of the abdominal cavity showed chronic cholecystitis, pancreatitis, gastroduodenitis, structural changes of the liver by the type of hepatosis, hemangioma of the right lobe. Thyroid gland was without pathological changes. X-ray of the lungs, ECG didn't reveal any pathological changes. A therapist examined the patient and prescribed treatment. A neuropathologist, a surgeon, and an endocrinologist did not find any pathologies. A biopsy was taken from the pathologically changed skin. Growth of the reticular layer of the dermis with cavities and fissures, specific degeneration of epidermal cells, hyperkeratosis, cellular formation with intensively stained nuclei and granular cytoplasm were found in the material. Basophilic bodies with and without nuclei were revealed in the superficial layers of the epidermis.

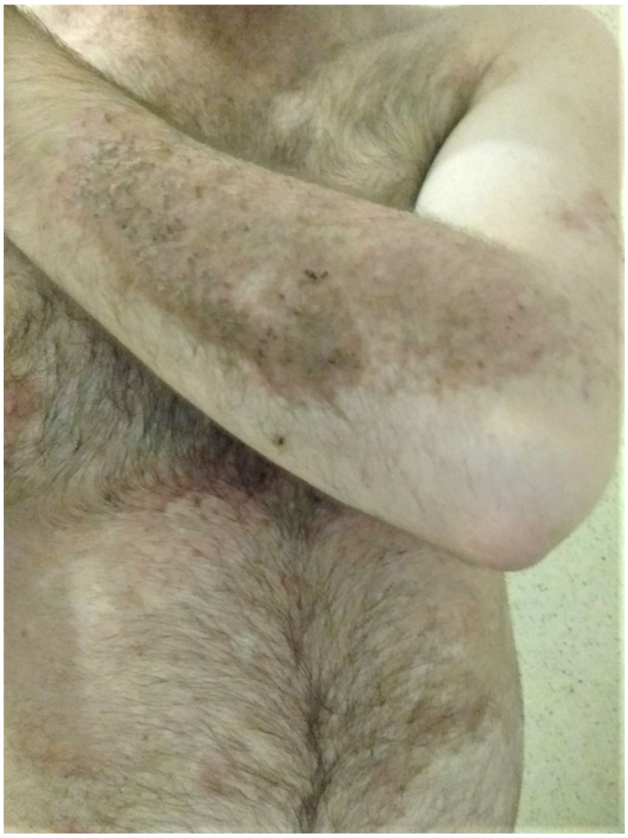

Fig. 7. Patient B. Rash on the upper limbs in the form of flat yellow-brown papules that form plaques

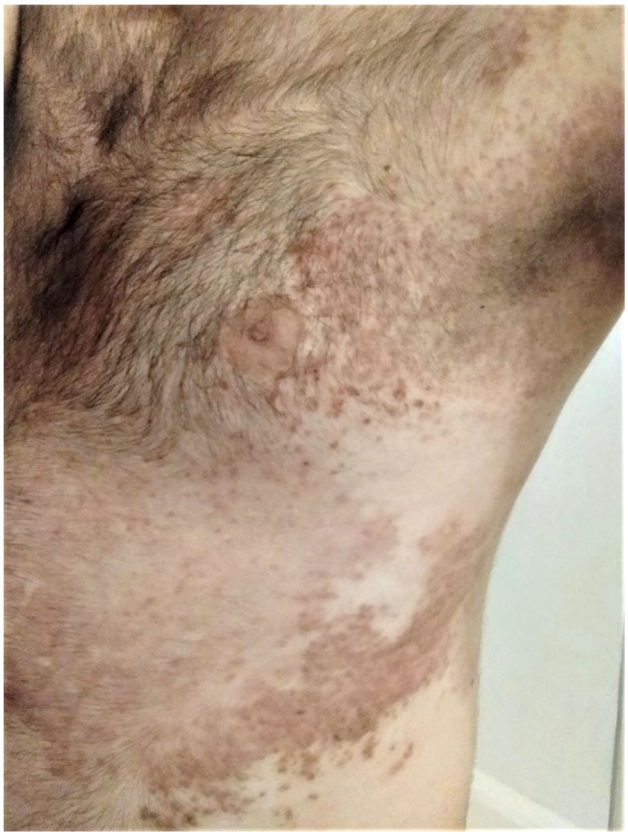

Fig. 8. Patient B. Rashes on the lateral surface of the trunk merge into plaques

Clinical manifestations, the results of histopathological examination convincingly confirm follicular dyskeratosis (Darier-White disease).

Both patients received 50,000 units of retinol 2 times a day in courses of 1.5-2 months, 2 times a year. Hepatoprotectors xanthine-nicotinate, pyridoxal phosphate, vitamin C, keratolytic steroid ointments, moisturizing creams, emollients were also prescribed. Obvious long-lasting improvement was not observed. Patients were advised to take periodic baths with sea salt, salt coniferous concentrate, decoction of salvia, lemon balm and to avoid sunlight. They had to use moisturizing creams for a long time. Patients refused treatment with retinoids, considering their side effects and temporary effect.

Diagnosing Darier-White disease is a typical option for an experienced dermatologist and does not pose great difficulties. More often, as in our case, follicular dyskeratosis is regarded as lichen planus. Common features of these two diseases are flat papules, localization, chronic course. However, in case of lichen planus, the papules are polygonal, have the color of raspberries in milk, with an umbilicated depression in the center and a waxy luster under lateral illumination. Lichen planus can go into remission due to the treatment or even without it, which does not happen in Darier-White disease. Pathohistological examination confirms or refutes the diagnosis.

Kyrle's disease, like Darier-White disease, is a rare dermatosis that occurs at any age, more often in males at the age of 10. As with Darier-White disease, the primary elements are follicular papules of yellow-brown color, covered with a hyperkeratotic layer; mucous membranes are rarely affected. In contrast to follicular dyskeratosis in Kyrle's disease, rashes are localized on the upper and lower extremities, rarely disseminated. Millet-sized or pea-sized papules are covered with a bloody crust. Plaques of large sizes with scalloped edges are dense and rise above the skin level. Keratinized epidermis on plaques is similar to warts and is difficult to remove. In the area of hair follicles, cone-shaped crusts are visible. Small scars remain at the site of the papules, and large scars remain after the plaques. The following pathohistological changes are characteristic of Kyrle's disease: follicular and parafollicular hyperkeratosis and parakeratosis, thinning of the follicular epithelium, leuko-, lympho-, and histiocytic infiltration around hair follicles.

When Dühring's disease is localized in large folds of an atypical vesicular form, it should be differentiated from Hailey-Hailey disease. It shouldn't be confused with seborrheic eczema or keratosis pilaris on the scalp, "seborrheic" places.

If palms and soles are affected, corneal eczema and psoriasis are excluded.

CONCLUSIONS

1. The demonstrated cases indicate that follicular dyskeratosis can appear in the first and third decades of life.
2. Despite the inheritance of the disease, it is often impossible to confirm it, because the history is limited to one, rarely two generations.
3. The use of dermatoscopy, as an additional routine method, improves the quality of diagnosis, subject to a comprehensive assessment, taking into account the specifics of the clinic and the subsequent performance of a skin biopsy.

Contributors:

Tkach V.Ye. – conceptualization, writing – original draft, writing – review & editing, data curation;

Voloshynovych M.S. – writing – original draft, resources, investigation, writing – review & editing;

Romanchuk S.M. – resources;

Girnyk G.Ye. – writing – original draft, writing – review & editing;

Matkovska N.R. – resources, writing – review & editing;

Kozak N.V. – writing – review & editing.

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