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The value of dermoscopy in Grover's disease. Dermoscopy-histopathology correlation

Znaczenie dermoskopii w chorobie Grovera. Korelacja dermoskopowo-histologiczna

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ABSTRACT

Grover's disease (transient acantholytic dermatosis) is characterized by the eruption of pruritic papules and papulovesicular lesions, mainly on the trunk and proximal extremities. The aetiology of the disease remains unknown; however some drug-induced cases were reported. The diagnosis of Grover's disease is based on histopathological examination which usually shows the presence of focal suprabasal acantholysis with dyskeratosis within the epidermis. There are four main histopathological patterns of this disease, including the Darier-like pattern, the Hailey-Hailey-like pattern, pemphigus-like pattern and eczema-like pattern. The main purpose of the study was to describe clinical, dermoscopic and histopathological features of skin lesions in three patients with three different patterns of Grover's disease.

The study was carried out on three patients with observable characteristic dermoscopic features of skin lesions who had been diagnosed with Grover's disease based on the histopathological examination. In dermoscopy of the first one, yellow-brown polygonal structures with a white "halo" corresponding to focal acantholysis with dyskeratosis and hyperkeratosis were observed. Some areas with enlarged and dilated blood vessels were also seen, as well as regular oval white structures with yellow centres, which might correspond to empty hair follicles with abnormal keratosis in their ostia. In dermoscopy of the second patient, polygonal brown structures with scales corresponding to focal acantholysis with desquamation and dilated irregular blood vessels were observed. In dermoscopy of the third one, yellow-brown polygonal structures covered with scale and haemorrhagic crusts were observed.

Dermoscopy is a useful diagnostic tool in patients suspected for Grover's disease and gives characteristic dermoscopic features of yellow-brown polygonal structures corresponding to irregular acantholysis and disturb keratinization in histopathology.

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Key words: Grover's disease, dermoscopy, acantholysis, yellow-brown polygonal structures

STRESZCZENIE

Choroba Grovera (przemijająca dermatoza z akantolizą) charakteryzuje się obecnością rozsianych, swędzących grudek lub zmian pęcherzykowo-grudkowych głównie na tułowiu i proksymalnych częściach kończyn. Etiologia choroby pozostaje nieznana, ale opisywano przypadki indukowane różnymi lekami. Rozpoznanie choroby Grovera opiera się na badaniu histopatologicznym, które wykazuje obecność ogniskowej nieregularnej akantolizy ponad warstwą podstawną naskórka z towarzysząca dyskeratozą lub zaburzonym rogowaceniem keratynocytów powyżej. Wyróżnia się cztery główne wzory histopatologiczne tej choroby: obraz podobny do choroby Dariera, do choroby Hailey-Hailey, do pęcherzycy i obraz wypryskopodobny. Celem badania było opisanie klinicznych, dermoskopowych i histopatologicznych cech zmian skórnych u trzech pacjentów z trzema różnymi odmianami choroby Grovera. Badanie dermoskopowe zmian skórnych przeprowadzono u trzech pacjentów z rozpoznaniem histologicznym choroby Grovera, w celu określenia najbardziej charakterystycznych cech dermoskopowych tej choroby. W badaniu dermoskopowym pierwszego pacjenta stwierdzono obecność żółto-brązowych wielokątnych struktur z białawą obwódką, odpowiadających ogniskowej akantolizie z dyskeratozą i hiperkeratozą. Widoczne były również obszary z powiększonymi i poszerzonymi naczyniami krwionośnymi, a także regularne owalne białe struktury z żółtymi środkami, które mogły odpowiadać pustym mieszkom włosowym z nieprawidłowym rogowaceniem w ich lejkach. U drugiego pacjenta dermoskopowo stwierdzono obecność wielokątnych brązowych struktur pokrytych łuską odpowiadających ogniskowej akantolizie z nieprawidłowym rogowaceniem na powierzchni, oraz poszerzone nieregularnie naczynia krwionośne. U trzeciego pacjenta w dermoskopii stwierdzono żółto-brązowe wielokątne struktury pokryte łuską i krwotocznymi strupami. Dermoskopia jest użytecznym narzędziem diagnostycznym u pacjentów, u których podejrzewa się chorobę Grovera i obrazuje charakterystyczne żółto-brązowe, wielokątne struktury odpowiadające nieregularnej akantolizie z nieprawidłowym rogowaceniem w badaniu histopatologicznym.

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Słowa kluczowe: choroba Grovera, dermoskopia, akantoliza, wielokątne żółto-brązowe struktury

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INTRODUCTION

Grover's disease (*transient acantholytic dermatosis*) is characterized by the eruption of pruritic papules and papulovesicular lesions, mainly on the trunk and proximal extremities [1, 2]. The disease appears suddenly and is most common in elderly male patients. Its aetiopathogenesis remains unknown. There have been many cases reported in association with different chronic diseases or cases induced by drugs. Grover's disease has been reported in patients with malignancies [1, 3, 4], chronic renal failure [5, 6] and HIV infection [7], as well as in patients after kidney [8], heart [9] and bone marrow [10, 11] transplant. The drug-induced Grover's disease was described following the administration of ribavirin [12], cetuximab [13] and interleukin 4 [14]. The association between Grover's disease and metastatic melanoma treatment with ipilimumab [15], dabrafenib [16] and vemurafenib [17] has also been reported. The skin lesions are frequently exacerbated by heat, sweating, fever and ultraviolet light exposure [2].

The symptoms of Grover's disease may cause diagnostic difficulties. The differential diagnosis includes eczema, drug eruption, insect bites, keratotic disorders and pemphigus foliaceus. The diagnosis of Grover's disease requires a high index of suspicion and sometimes a confirmatory biopsy specimen.

The diagnosis is finally based on histopathological examination which usually shows the presence of focal suprabasal acantholysis with dyskeratosis with varying degree of severity in the epidermis. Grover's disease is characterised by four main different acantholytic patterns, including i) the Darier-like pattern in which dyskeratosis prevails over acantholysis, ii) the Hailey-Hailey-like pattern when acantholysis is prominent at different levels of the epidermis forming a "dilapidated brick wall" appearance, iii) the pemphigus-like pattern in which suprabasal acantholysis predominates showing the characteristic "row of tombstone" appearance formed by basal keratinocytes, and iiii) the eczema-like pattern with the most prominent separation of keratinocytes leading to spongiosis [2].

Histopathological analysis of 120 cases of Grover's disease done by Fernández-Figueras et al. pointed out that diagnostic criteria of the disease should be expanded [18]. They reported cases of Grover's disease with porokeratosis-like columns of parakeratosis, lesions with a nevoid or lentiginous silhouette, intraepidermal vesicular lesions, lichenoid changes with basal vacuolization and dyskeratosis, and dysmaturative foci with keratinocyte atypia which make the diagnosis of Grover's disease even more complex and difficult [18]. Regardless so many histopathological types, sometimes due to transitional course of the disease as its description indicate, the biopsy taken from the early or resolving lesion may miss Grover's features and stayed unrecognized. There is a study of the early changes in Grover's disease, in which elongation of rete ridges, mild focal acantholysis and eosinophils were included as a clues, but with a proper clinical correlation [19].

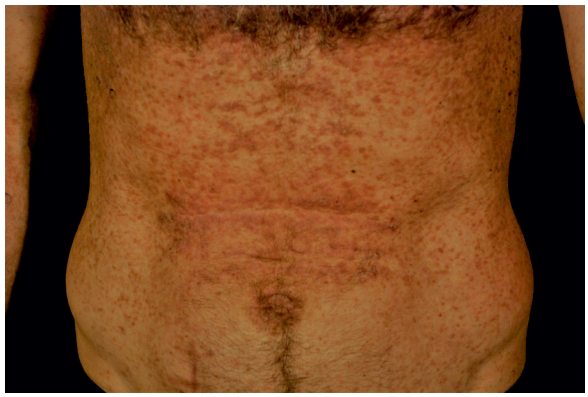


Figure 1. The first patient, a 58-year-old man with numerous yellow to brown hyperkeratotic papules over his trunk and extremities

The aim of this study was to analyse the clinical, dermoscopic and histopathological features of skin lesions observed in three patients diagnosed with Grover's disease of three different histopathological types. We wanted to answer the question whether dermoscopy can be used as a reliable, non-invasive diagnostic method for Grover's disease due to its transitional course and diverse presentation.

CASE REPORT 1

The first patient was a 58-year-old male patient in general good condition. In January 2015, he developed an intense yellow-brown hyperkeratotic papular rash on the trunk and extremities (Fig. 1). The skin lesions appeared one month after the appendectomy complicated by peritonitis. The biopsy was performed and histopathological examination showed focal acantholysis with intense dyskeratosis above at various levels of epidermis, as well as hyperkeratosis (Fig. 2). Corps ronds and grains were clearly visible, but his family history of Darier disease was negative. The patient was diagnosed with Grover's disease in Darier-like pattern.

In dermoscopy, yellow-brown polygonal, star-like structures with white halo corresponding to focal acantholysis with dyskeratosis were observed (Fig. 4, Fig. 5). Also, the thickening of the stratum corneum, areas covered with serum and haemorrhagic crusts and dilated blood vessels were seen. Furthermore, regular oval-shaped white structures with a yellow centre, which are deemed to correspond to empty hair follicles with abnormal keratinization in their ostia, were spotted (Fig. 3).

CASE REPORT 2

The second patient was an 82-year-old male patient with a history of prostate cancer with bone metastases

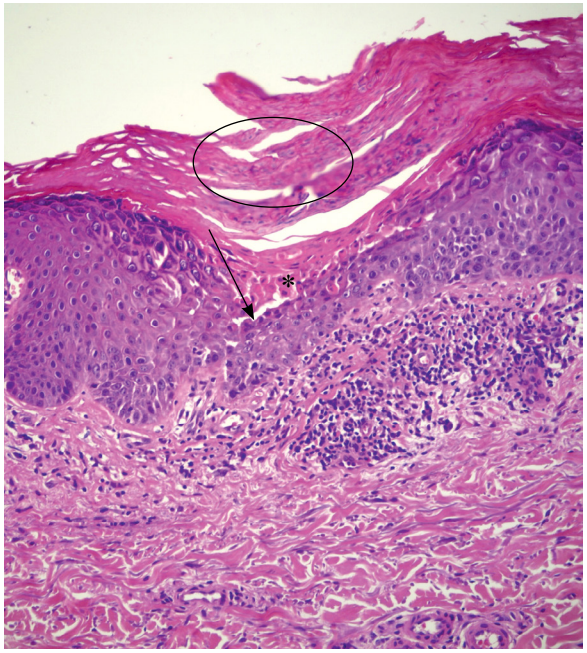


Figure 2. The biopsy revealed focal acantholysis (arrow) with prominent dyskeratosis (asterisk*) and hyperkeratosis with parakeratosis (circle) consistent with Grover's disease in Darier-like pattern. (100×)

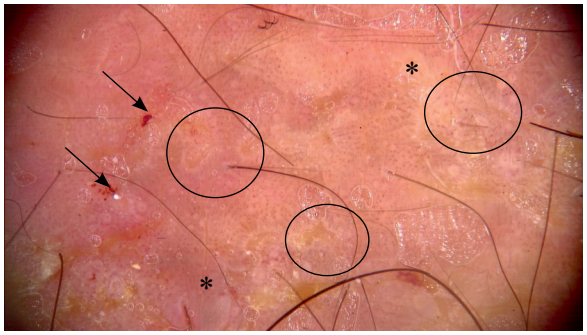


Figure 3. Multiple yellow-brown polygonal, star-like structures (circles) with white "halo" areas, with superficial serum or haemorrhagic crusts (arrows) and dilated blood vessels (asterisks*) in dermoscopy (20×)

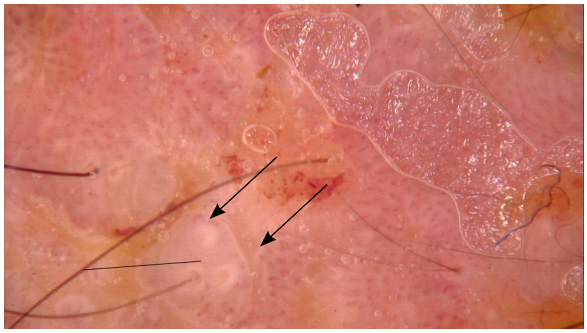


Figure 4. Regular oval white structures with a yellowish centre (arrows) corresponding to empty hair follicles with abnormal keratinization in their ostia in dermoscopy (20×)

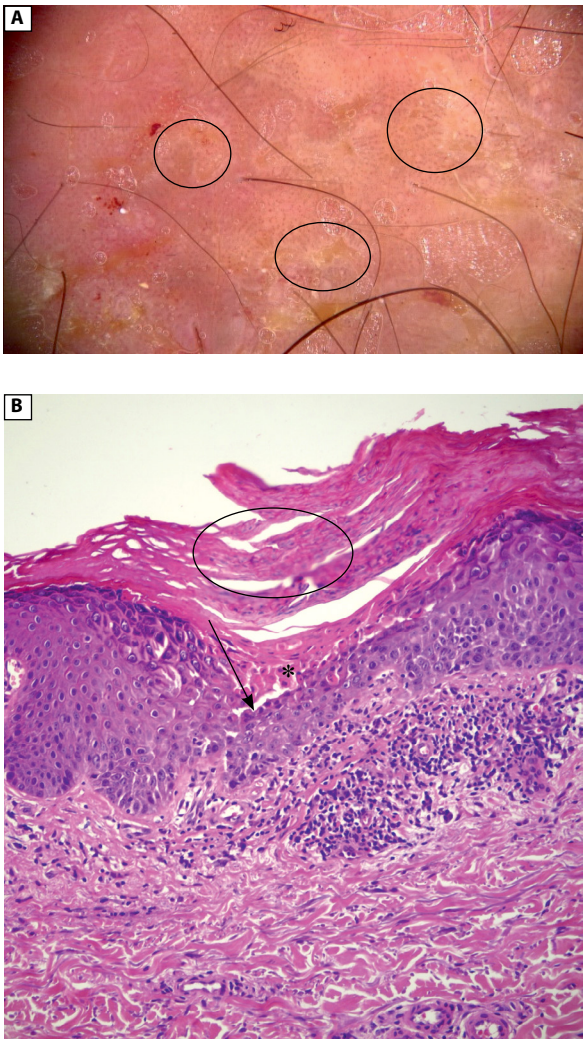


Figure 5. Dermoscopical-histopathological correlation. Multiple yellow-brown polygonal structures (circles) with white "halo" corresponding to focal acantholysis (arrow) with dyskeratosis (asterisk*) and hyperkeratosis with prominent parakeratosis (circle)

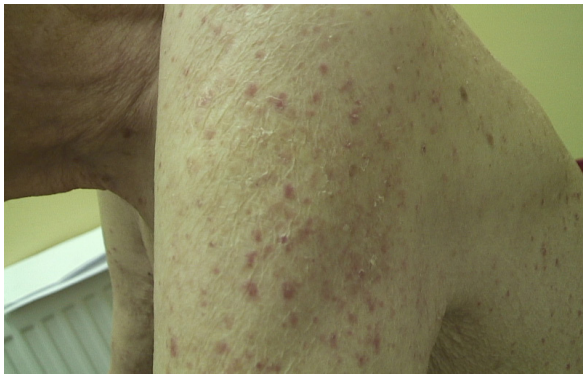


Figure 6. The second patient, an 82-year-old man who developed psoriatic and eczema-like lesions on his trunk and extremities. Xerosis of his skin is well visible

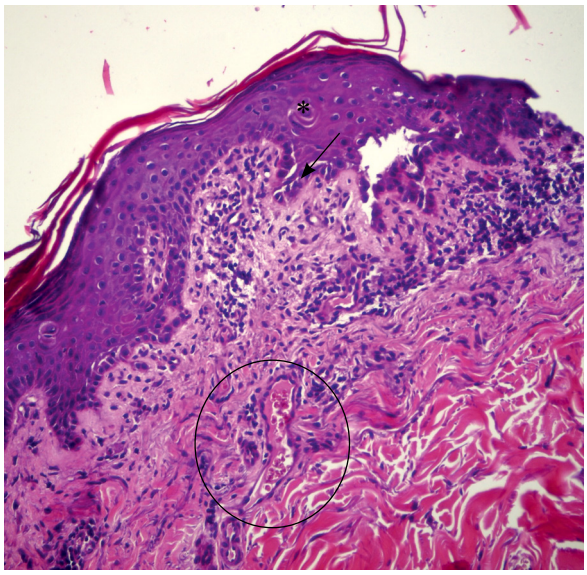


Figure 7. Focal suprabasal acantholysis forming a suprabasal cleft (arrow), single dyskeratotic cells (asterisk*), dilated blood vessel (circle) with mixed cellular inflammatory infiltrate in the dermis in histology (100×)

and concomitant urinary bladder cancer. In August 2015, he developed itchy psoriatic and eczema-like lesions on his trunk and proximal extremities (Fig. 6). The histopathological examination of the skin biopsy showed subtle suprabasal acantholysis, single dyskeratotic cells, dilated blood vessels with mixed superficial inflammatory cell infiltrate (Fig. 7). The direct immunofluorescence test was negative. The patient was diagnosed with Grover's disease. In dermoscopy, brown polygonal structures with scales corresponding to focal acantholysis were observed (Fig. 8, Fig. 9). Also, multiple irregular and dilated blood vessels were seen.

CASE REPORT 3

The third patient was an 82-year-old male patient with chronic heart and renal failure and a renal mass in the process of diagnosis. The patient was hospitalized due to the sudden eruption of pruritic erythematous papular rash with three month duration present on his trunk and extremities, unresponsive to medium strength topical corticosteroids (Fig. 10).

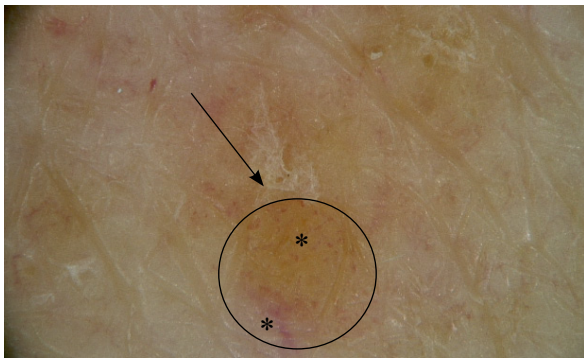


Figure 8. Polygonal yellow structures (circles) with a pityriasis scale (arrow) and multiple irregular, enlarged blood vessels (asterisks*) are seen under the dermoscope (20×)

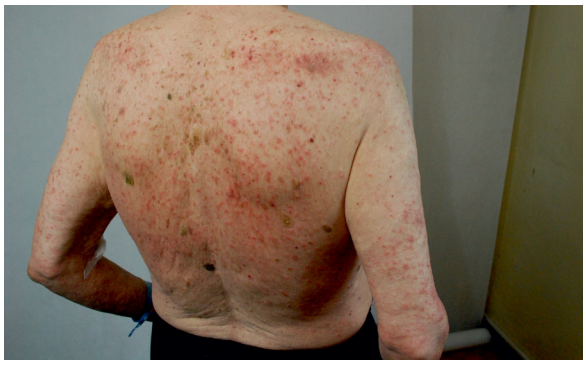
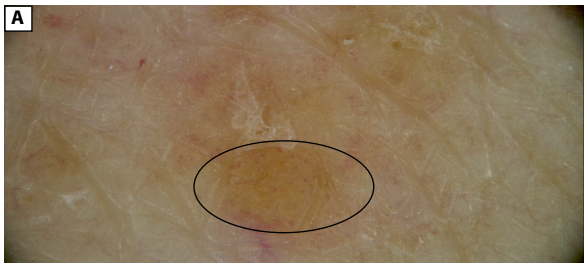


Figure 10. The third patient, an 82-year-old man with erythematous papular eruption on his trunk. There are many accompanying seborrheic keratoses



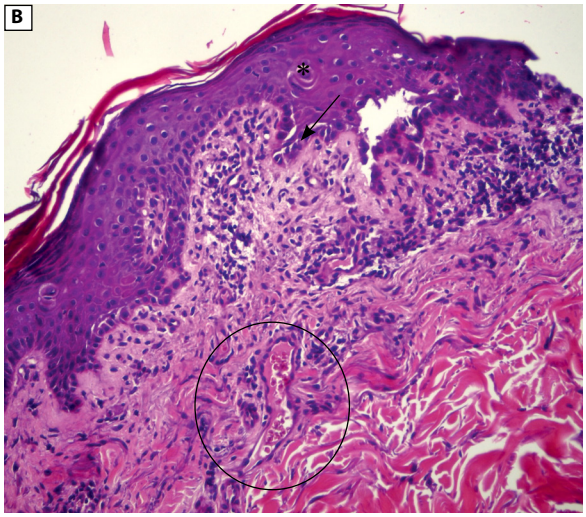


Figure 9. Dermoscopical-histopathological correlation. Polygonal structures (circles) corresponding to focal acantholysis (arrow) with a single dysceratotic cell (asterisk*)

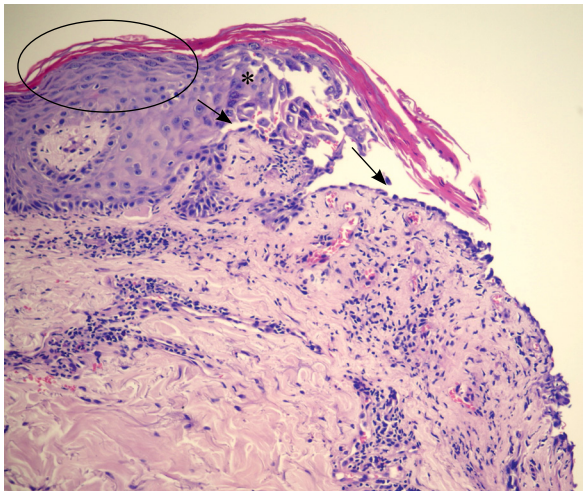


Figure 11. Suprabasal acantholysis (arrows) leading to the separation of the epidermis overlaying acantholytic cleft with epidermal acanthosis (asterisk*), hypergranulosis and hyperkeratosis (circle). There is a superficial perivascular inflammatory infiltrate with dilated vessels filled up with erythrocytes in the skin biopsy (100×)

The histopathological examination of the performed biopsy revealed suprabasal acantholysis with a "tombstone" appearance and acanthosis of the surrounding epidermis with hypergranulosis and hyperkeratosis (Fig. 11). The direct immunofluorescence test was negative. The patient was diagnosed with Grover's disease occurring in the pemphigus-like pattern. In dermoscopy, yellow-brown polygonal structures covered with scale and serum crusts were seen (Fig. 12, Fig. 13).

DISCUSSION

Grover's disease begins as a sudden onset of small itchy papules and fragile vesicles, usually on the trunk, which can quickly form crusts and keratotic erosions. The incidence of the disease is low (0.1%) with male predilection and a mean age at diagnosis is 61 years [2]. The sudden appearance of this itching disease in the central distribution suggests drug eruption or insect bites and, accordingly to the literature, Grover's disease is suspected clinically only in

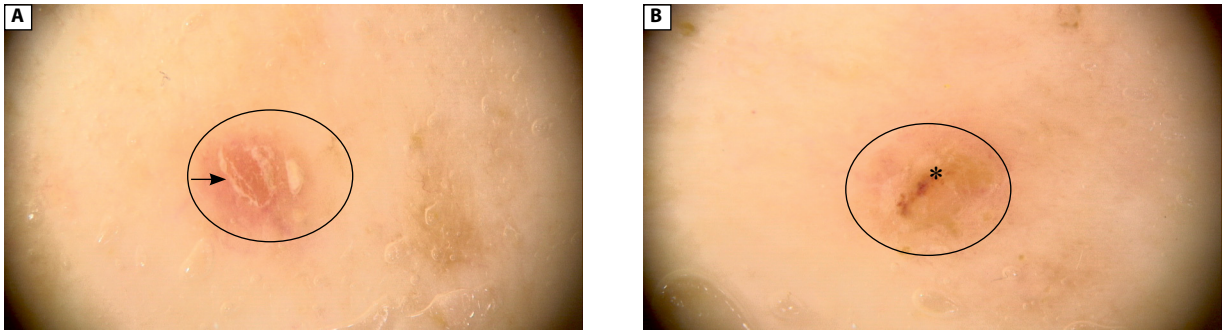


Figure 12. Polygonal yellow-brown structures (circles) covered with scale (arrow) serum crust (asterisk*) in dermoscopy (20×)

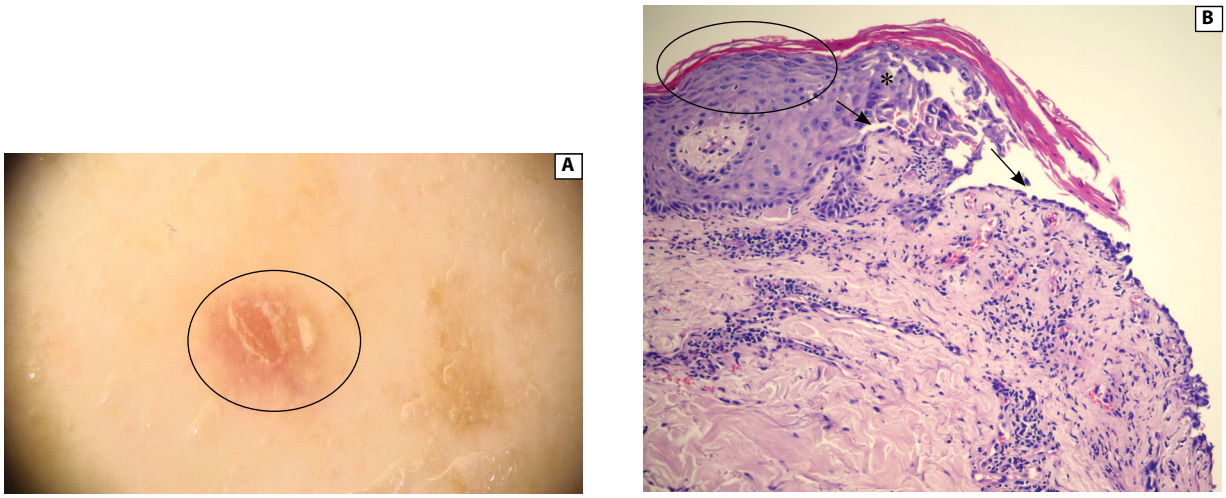


Figure 13. Dermoscopical-histopathological correlation. Polygonal yellow-brown structures (circles) corresponding to suprabasal acantholysis (arrows), disturbed keratinization (asterisk*) and hyperkeratosis (circle)

54% of patients [20]. Therefore any useful clinical information or examination which can help to establish fast diagnosis of Grover's disease would be very beneficial, regardless the biopsy implementation. Due to transient and chronic relapsing nature of Grover's disease, even the histopathological examination may cause delay in the diagnosis and be inconclusive. Much depends on disease activity, presence of the secondary changes such as excoriation, secondary infection and selection of the most representative skin lesion for the biopsy [2, 19].

Seasonal variation of Grover's disease is not very helpful either and is a controversial issue. Some publications report there are two picks of disease incidence or flare up. One is in winter time and is exacerbated by xerosis and higher susceptibility to external insults, whilst the second pick is in August [20]. The effect of ultraviolet influence may explain some histopathological findings in Grover's diseases which are UV-connected, such as porokeratosis, lichenoid changes with basal vacuolization and dyskeratosis, and atypia of the keratinocytes [18]. However, attempts to reproduce Grover's disease with sunlight were unsuccessful so far.

There are also many drugs or diseases, including malignant and other dermatoses associated with Grover's disease and this does not help in clinical diagnosis. So far the causing factor or triggering effect was not identified, and Grover's disease may have a multifactorial pathogenesis [1, 2].

The first description of dermoscopy in Grover's disease was depicted as brown star-like pattern [21]. These characteristic features may be reminiscent dermoscopically of „pseudocomedones" in Darier disease [22] and can be observed in any acantholytic dyskeratotic lesions [23].

We first described characteristic dermoscopic findings in three histopathological types of Grover's disease: Darier like-pattern, eczema-like pattern and pemphigus-like pattern. In our observations dermoscopic features of Grover's disease are yellow-brown polygonal structures corresponding to the main histopathological findings such as irregular acantholysis with different disturbances of keratinization.

Based on clinical examination with unspecific pruritic papular rash, the diagnosis of Grover's disease is difficult. Our observation of one characteristic pattern of yellow-brown polygonal structures regardless the type of Grover's disease, underlines the usefulness of dermoscopy in recognition of this disease. Also, the most representative skin lesion for the histopathological examination can be taken based on dermoscopy examination, which is called dermoscopy guided biopsy.

CONCLUSIONS

Grover's disease is characterized by multiform lesions mainly papules, which may evolve at a different time and are exacerbated by scratching and secondary infections. There are many other dermatoses with similar clinical presentation, including eczema, drug-induced exanthema, and keratinization disorders. A recent review paper about atypical or extensive Grover's disease suggests the association with underlying malignancy, chemotherapy and immune suppression [24].

Dermoscopy can be a useful method of non-invasive clinical diagnosis in patients with Grover's disease. The characteristic dermoscopic features of skin lesions in patients with Grover's disease are yellow-brown polygonal structures regardless the histopathological subtype of the disease, corresponding to focal acantholysis with different degree of dyskeratosis or keratinocytes dismaturation. These consistent characteristic dermoscopical findings in Grover's disease may be useful in a quick and correct diagnosis and help to select the most representative skin lesion for the biopsy. Similar dermoscopical findings were described for Darier disease, which can be histopathologically similar to Grover's disease, but the clinical evaluation, personal and family history helps to distinguish between these two [25].

Since our observation, several other patients and their multiple lesions were examined with a dermoscope and each time the presence of several polygonal, star-like or roundish-oval-shaped yellowish or brownish areas of various size surrounded by a thin whitish halo were seen helping to recognize transient pruritic disease with acantholysis, such as Grover's disease.

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