Dermatology Practical & Conceptual

Dermoscopy in the Diagnostics of Incontinentia Pigmenti Skin Lesions

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ABSTRACT

Introduction: Incontinentia pigmenti (IP) is a rare X-linked geno-dermatosis characterized by numerous findings. Skin biopsy and histopathological analysis are considered as minor criteria for the diagnosis of IP. We assume that dermoscopy can assist the earlier diagnosis of IP.

Objectives: To gain experience in earlier diagnosis of IP by observing dermoscopic findings of cutaneous changes.

Methods: We revised confirmed cases of IP and examined them using dermoscopy, comparing histopathological and dermoscopic results.

Results: Stage I presented solitary and grouped vesicles in linear arrangement on erythematous skin. Early stage II presented star-shaped verrucous lesions on erythematous or pigmented skin. In well-developed lesions, dotted vessels surround keratotic part, some with thrombosed capillaries, resembling a viral wart. Stage III presented linear brown dots on the pigmented areas. Dermoscopic image was uniform in all the examined pigmented Blaschko linear changes. Stage IV presented numerous dotted vessels on the hypopigmented skin. Terminal hair was scarce or absent in all four stages. The surrounding normal skin had perifollicular depigmentations in stages III and IV.

Conclusions: Dermoscopy of all four stages is very specific compared to the dermoscopy of inflammatory dermatoses and pigmentations. Stage III has very close clinical, histological and dermoscopic mimickers and needs to be carefully examined with obligatory genetic testing. Dermoscopy of the stage IV closely corresponds to histopathological findings and may be crucial as a quick tool in revealing potential IP gene carriers. Dermoscopy should be used in addition to clinical examination since the two methods are complementary.

Introduction

Incontinentia pigmenti (IP; Bloch-Sulzberger syndrome) is a rare X-linked genetic disorder with an estimated prevalence of 1.2/100.000 [1,2]. It appears almost exclusively in females and is usually lethal in males [3]. It is caused by a mutation of the *IKBKG* gene localized on the X chromosome locus Xq28, which is the only gene known to be associated with IP [2]. The most prominent clinical manifestations of IP are considered to be skin changes, which constitute major IP diagnostic criteria [4,5]. Skin changes in IP occur along the lines of Blaschko throughout four stages: vesiculobullous (I), verrucous (II), hyperpigmented (III), and atrophic or hypopigmented (IV) [2,4].

Objectives

Beside clinical examination, skin biopsy and *IKBKG* gene analysis are the methods used in diagnosing IP. Since these methods are time consuming and invasive, we suggest that there is also a need for a faster and easier method as an adjunct to clinical diagnosis.

Methods

We clinically examined 2 female probands and one proband mother with signs of IP on the skin, which were confirmed by biopsy, and genetical examination –exons 4–10 deletion on the *IKBKG* gene. We have used a DermLite Hybrid M Dermatoscope (3 GEN) with immersion fluid and initial 10x magnification in a polarized mode coupled with a Nikon J3 camera (Nikon corporation). The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of University Clinical Center of Serbia (protocol code 251/4 and date of approval May 21, 2021). Informed consent was obtained from all subjects involved in the study.

Results

Case 1

The proband was 2 weeks old at the initial visit, phototype II, presented with vesiculobullous lesions grouped in stripe-like shapes following the lines of Blaschko (Figure 1A). Three months later, the proband had several verrucous changes (Figure 1B)], hyperpigmented maculas, and very few vesicles. When six-months-old, there were Blaschko linear, slightly erythematous and pigmented changes forming atrophic lines with a verrucous part (Figure 1C). Biopsy was performed at the first and dermoscopy at all 3 clinical visits of the patient (Figure 1, D-H). In stage I we found solitary and grouped vesicles in a linear arrangement with yellowish content and serocrusts on an erythematous skin. Skin hair was significantly reduced on the affected area. In stage II, early verrucoid lesions are star-shaped, yellowish or whitish on an erythematous and a slightly pigmented skin. In well-developed lesions, dotted vessels surround a central keratotic part, or can be distributed on the lesion, with thrombosed capillaries, strikingly resembling a viral wart.

Case 2

The proband was one and a half months old at the initial visit, phototype IV, presented with hyperpigmented maculas following Blaschko lines as well as a few verrucous papules. Two biopsies were performed depicting stage II and III of IP (Figure 2, B and C). Clinical and dermoscopic examinations were performed at the age of 6 months, at stage III (Figure 2, A and D). As in previous stages, the affected area is devoid of terminal hair. We observed striking linear brown to gray-brown dots on the light brown pigmented areas. That dermoscopic image was uniform in all the examined pigmented Blaschko linear changes.

Case 3

The case 1 proband mother, phototype II, presented a slightly visible hypopigmented 6 cm macula on the lower extremity (Figure 3A). Anamnesis revealed a transitory skin eruption in childhood. The skin lesion was confirmed by biopsy as stage IV skin finding in IP (Figure 3B). Dermoscopy revealed numerous very small dotted vessels present on the surrounding hypo- and normally pigmented skin (Figure 3C). Terminal hair was very scarce or absent on the hypopigmented skin. The surrounding normal skin had perifollicular depigmentation.

Clinical summary data for all the patients are presented in Table 1.

Conclusions

Since some of the stages occur in utero, the diagnosis of IP may be delayed or overlooked. Clinical differential diagnosis should exclude other linear dermatoses along Blaschko lines: linear and whorled nevoid hypermelanosis (both familial and sporadic forms), hypomelanosis of Ito and lichen planus pigmentosus with Blaschkoid presentation [4,6-9].

By stages, the clinical differential diagnosis of IP in the stage I should exclude (ie congenital herpes simplex, varicella, bacterial infections, epidermolysis bullosa and bullous pemphigoid) [4,10,11]. In the stage II of IP, dermatologists should exclude verrucae vulgares, X-linked-dominant chondrodysplasia punctata, linear verrucous epidermal nevus and lichen striatus [4,12]. Darier disease and prurigo nodularis

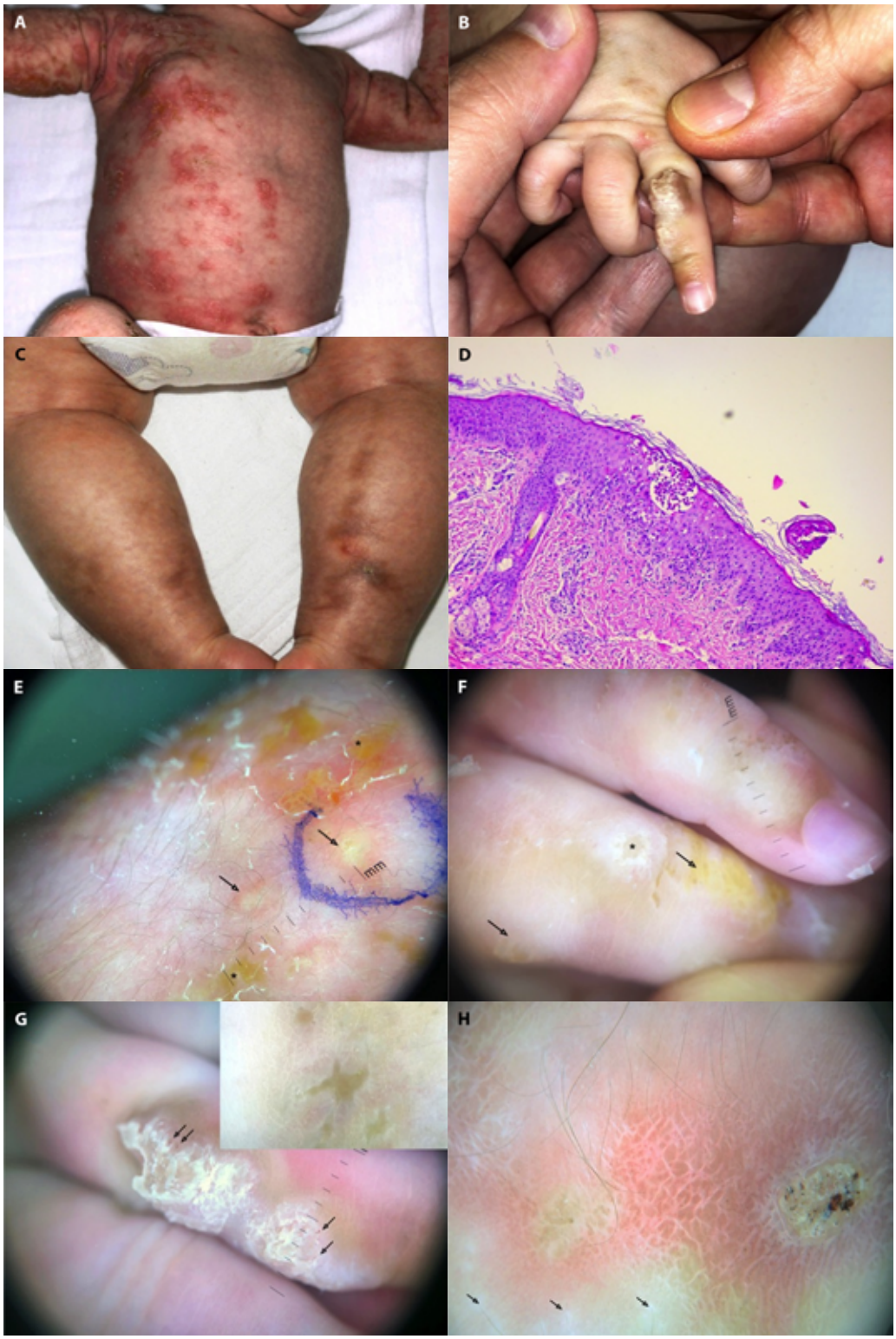

Figure 1. Case 1. (A) Blaschko lines distributed lesions (2-weeks-old). (B) verrucous formation on the middle digit (3-months-old). Verrucous lesions were present at the same time with scarce vesicles. (C) Blaschko linear, erythematous and pigmented atrophic line with a verrucous part (6-months-old). (D) Histology: spongiosis, vesicles with eosinophiles, and individual apoptotic keratinocytes in the epidermis. Lymphocytes and eosinophiles were present focally in the superficial dermis (H&E, x 20). (E) Dermoscopy: (magnification x10) Stage I, 2-weeks-old: new vesicles have yellowish center and erythematous halo (arrows), while the older lesions have yellowish serocrusts (star) surrounded by polycyclic scalling. The vesicle in the blue circle has been biopsied. (F) Stages I and II, 2-weeks-old: grouped vesicles with the yellowish content (0.5-2 mm in diameter) (star) and small verrucous lesion (star). (G) Stage II, 3-months-old (middle digit): well developed verrucoid lesion with scarce, tiny thrombosed dotted vessels (arrows) and slightly pigmented edge. Inset: star shaped early verrucous lesion. (H) Stage II-III, 6-months-old: verrucous lesion with thrombosed capillaries on an erythematous and slightly pigmented background. Atrophic part had shiny-white linear or polygonal streaks resembling chrysalis. Note: perifollicular depigmentation (black arrows).

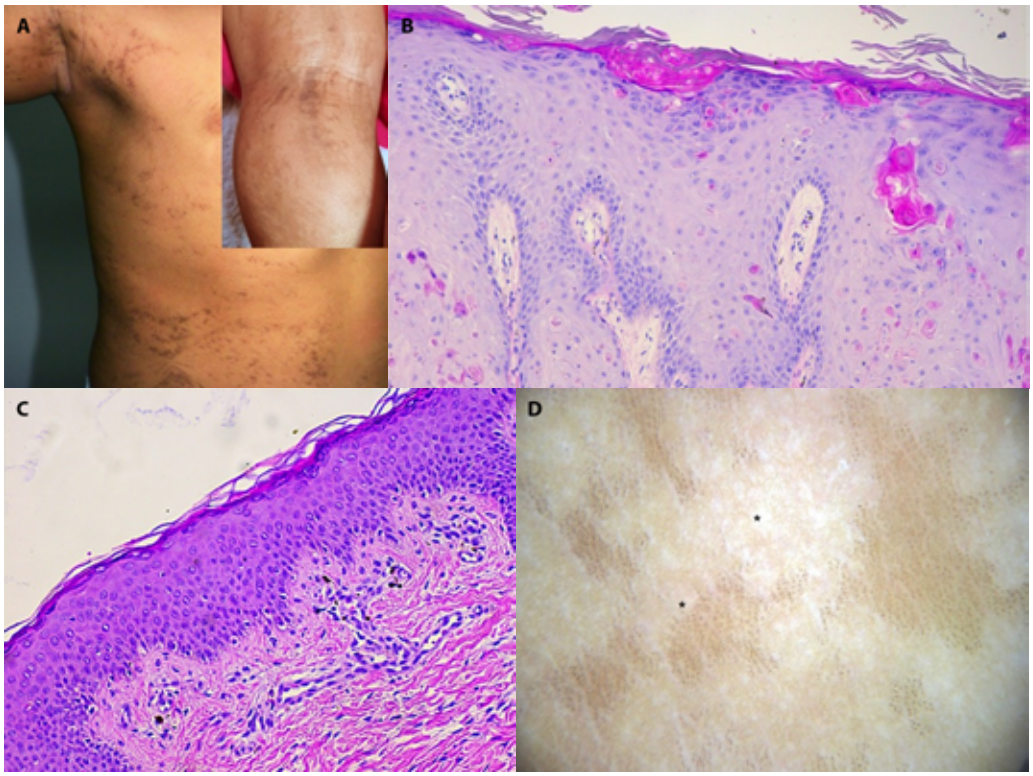

Figure 2. Case 2. (A) Stage III, 6-months-old: pigmented Blaschko lines on the trunk and extremities (inset). (B) Stage II histology: compact hyperkeratosis, hyper-granulosis and prominent acanthosis with papillomatosis. Dyskeratotic cells were present in the epidermis as well as apoptotic like keratinocytes individually and in groups. Dilated blood vessels were visible in the dermal papillae, and lymphocytes and individual eosinophiles were present peri-vascularly. (H&E, x 20). (C) Stage III histology: individual cytoid bodies, and mild degree spongiosis focally in the epidermis. Proliferation of capillaries was visible in the papillary and superficial reticular dermis with eosinophiles as well as individual melanophages and free pigment. Homogenization of collagen was initiated focally in the papillary dermis (haematoxylin and eosin, x 20). (D) Stage III dermoscopy- linear gray- to gray-brown dots on the light brown pigmented background. The pigmentations were intermingled with normal skin and perifollicular depigmentation (stars).

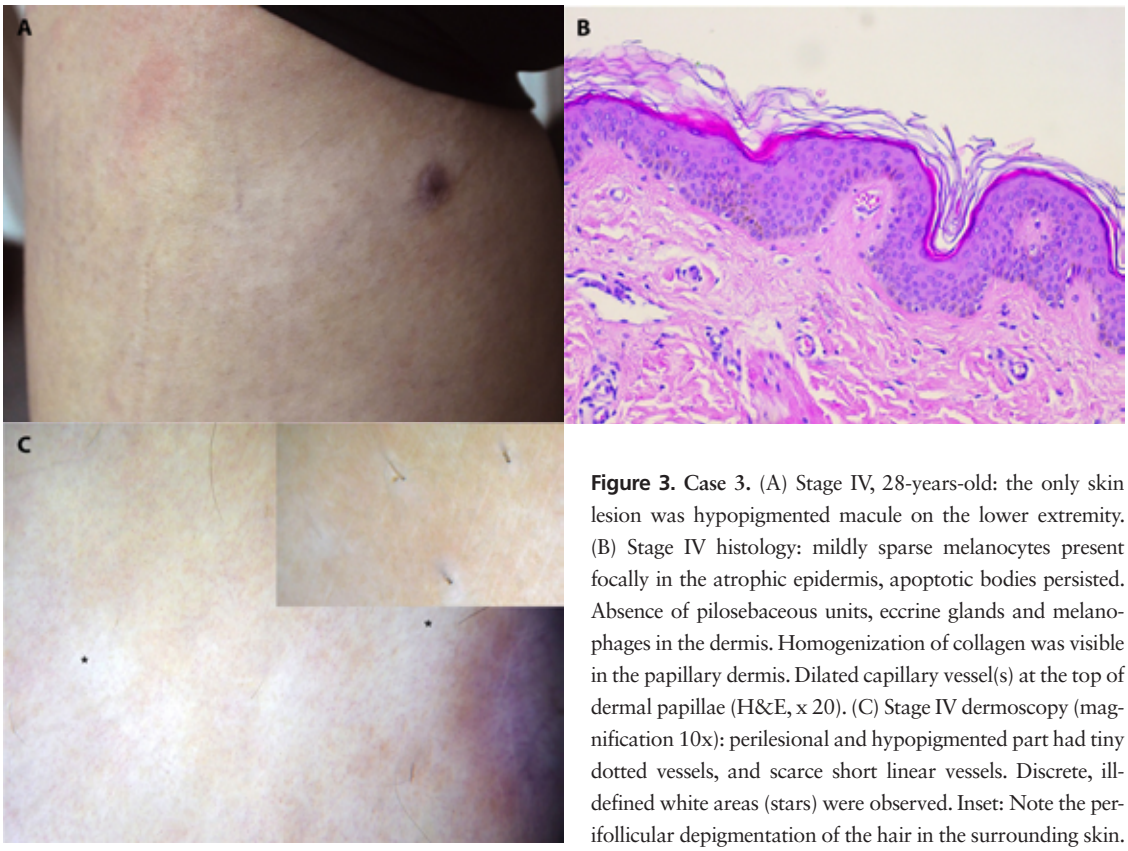

Figure 3. Case 3. (A) Stage IV, 28-years-old: the only skin lesion was hypopigmented macule on the lower extremity. (B) Stage IV histology: mildly sparse melanocytes present focally in the atrophic epidermis, apoptotic bodies persisted. Absence of pilosebaceous units, eccrine glands and melanophages in the dermis. Homogenization of collagen was visible in the papillary dermis. Dilated capillary vessel(s) at the top of dermal papillae (H&E, x 20). (C) Stage IV dermoscopy (magnification 10x): perilesional and hypopigmented part had tiny dotted vessels, and scarce short linear vessels. Discrete, ill-defined white areas (stars) were observed. Inset: Note the perifollicular depigmentation of the hair in the surrounding skin.

Table 1. Basic subject data when establishing Incontinentia pigmenti diagnosis and key laboratory and clinical findings

Subject	Age at onset	Age of proband at 1st exam	IP stage at I exam	Clinical findings			IKBKG exon 4-10 deletion	Skin histopathology
				Skin stage(s) dermoscopy	Eye	CNS		
Case 1	At birth	2 weeks	I stage	I, II, III stage	Retinopathia praematuri	-	+	Stage I
Case 2	At birth	1.5 months	II, III stage	III stage	Retinopathia ishemica prolipherativa oculus sinister	Hypertonio discreta	+	Stage II and III
Case 3 (mother)	Unknown	28 years	IV stage	IV stage	-	-	+	Stage IV

may also be included. The stage III, as the hallmark stage of IP, one should distinguish from linear and whorled nevoid hyper-melanosis and lichen planus pigmentosus with blaschkoid presentation [6,9,13]. The stage IV should be distinguished from hypo-melanosis of Ito, vitiligo with localized alopecia, different types of ectodermal dysplasia, nevus anemicus, nevus depigmentosus, extragenital guttate lichen sclerosus, achromic pityriasis versicolor, idiopathic guttate hypomelanosis and postinflammatory hypopigmentations [4,13,14]. This stage may be difficult to detect in women with light skin, the most important reason why IP diagnosis is not made until adulthood in 52% of patients [15].

There have been only 2 cases of IP dermoscopy published so far: one with positive genetic findings, lacking a histology analysis, the other on dermoscopy on IP whorled alopecia and with no report on *IKBKG* gene analysis [16,17].

Recently, the case of 13-month-old girl with linear and whorled hyperpigmentation preceded by vesicular lesions (anamnestic data) on the trunk and extremities at birth was published [18]. Genetic analysis was not performed, histology images were not provided. In our view, this was a typical case of blaschkoid lichen planus pigmentosus, but not IP [19].

In dermoscopy of IP stage I, it was very easy to find a suitable, small lesions for biopsy. They are clinically presented as seropapules and dermoscopically as yellowish seropapules with an erythematous halo. The main dermoscopic differential diagnosis is eczematous dermatitis and herpes simplex (Table 2) [20]. Tzanck smear searching for giant multinuclear cells should be performed to eliminate the suspicion on neonatal herpes simplex [21]. Histological inflammation corresponds to dermoscopic erythema. Vesiculobullous formation was presented as either yellowish structures surrounded by an erythematous halo or grouped vesicles or serocrusts.

In dermoscopy of IP stage II, histologically, verrucous hyperplasia, compact hyperkeratosis, acanthosis and papillomatosis correspond to the central verrucous part on dermoscopy are presented in table 2. Dilated blood vessels visible in the dermal papillae may correlate to the vessels changes dermoscopically observed. The reticular dermis is dense, fibrous and totally devoid of pilosebaceous units and sweat glands, and correlates with the absence of terminal hair observed on dermoscopy.

In dermoscopy of IP stage III, the main dermoscopic differential diagnosis is presented in Table 2. Linear brown to gray-brown dots are in accordance with previous 2 reports of IP dermoscopy of pigment stage [16,17]. Perifollicular depigmentation and disruptions in the normal reticular pigmentation of the surrounding skin have been observed. They have not been noted in any of the aforementioned conditions. Histopathological findings of this IP stage in our study also correspond to literature data and dermoscopy findings. Large deposits of free or intra-macrophagic melanin in the papillary dermis correspond to the gray-brown dots found on dermoscopy which is suggestive for pigment incontinence [9,15,22].

In dermoscopy of IP stage IV, the main dermoscopic differential diagnosis is presented in Table 2. Histopathological findings of this IP stage correspond to our findings and literature data [15,23]. Homogenization of collagen in the papillary dermis corresponds to the white areas on the hypopigmented skin. Numerous dotted vessels seen on dermoscopy correspond to dilated capillary vessel(s) at the top of dermal papillae.

According to the presented findings and literature data, the greatest clinical, dermoscopic and histological mimics of IP are blaschkoid lichen planus pigmentosus, and more localized, blashkoid lichen striatus [9,12,22]. Dermoscopically, the first condition has bluish-gray dots, globules, blotches and white lines or gray-brown dots arranged in a linear and reticular pattern [9,20]. The second condition has gray granular pigmentations arranged in a linear manner and white lines [12]. Bluish gray pigmentations in both conditions correspond to melanin incontinence in the papillary dermis [9]. Furthermore, both conditions have apoptotic keratinocytes presented as colloid bodies and increased melanin and melanophages in the superficial dermis [9,12].

This report addresses all four IP skin stages, and follows up different consecutive IP stages presented in a single

Table 2. Dermoscopic differential diagnosis of Incontinentia pigmenti

Stage	Clinical diagnosis	Dermoscopy findings
I	Eczematous dermatitis	Dotted vessels are distributed in clusters with yellow scales and serocrusts [20]
	Herpes simplex	Whitish, vesicles with brown dots/globules and peripheral erythema [21]
II	Verruca vulgaris	Thrombosed vessels and/or hemorrhagic dots on the verrucoid part [24], but no additional findings on the surrounding skin
	Darier disease	Central, star-like, yellowish area surrounded by a peripheral white halo [20]
	Prurigo nodularis	The "white starburst" pattern (peripheral radial white striae over a reddish-brownish background) is present; a central yellow crust is also present [20]
	Inflammatory linear verrucous epidermal nevus	Yellow to brown "cerebriform" pattern with moderate scales and dotted vessels [12]
	Lichen striatus	Gray granular pigmentation and a white scar-like line with mild scales [12]
III	Linear and whorled nevoid hypermelanosis	-Numerous brownish rings, curved and streak-like lines. Also, focally distributed hypopigmmented dots corresponding to perifollicular areas were found [8] - Linear or circular arrangement of streak-like pigmentations arranged in a "parallel manner" following the lines of Blaschko [25]
	Lichen planus pigmentosus	Fine/coarse, gray-blue/brown dots over a brownish background [26]
	Lichen planus pigmentosus with Blaschkoid presentation	Discrete bluish-gray dots, globules, blotches and rods against a brownish background [9]
IV	Vitiligo	Well-demarcated dense/glowing white area with perifollicular depigmentation (stable vitiligo) or perifollicular pigmentation (active vitiligo) [27]. Terminal hair is present with leucotrichia [28]
	Nevus depigmentosus	Reticulate pigmented spots along with the border of the normal skin were in accordance with the serrated and irregular border of nevus depigmentosus [14,28].
	Extragenital lichen sclerosus	White-yellowish structurless areas. White chrysalis-like structures, fine whitish scales [28].
	Achromic pityriasis versicolor	Diffuse hypopigmented blotches, satellite lesions. Fine scales localized in the skin furrows [28].
	Idiopathic guttate hypomelanosis	Cloudy sky-like" or "cloudy" pattern [26]
	Postinflammatory hypopigmentations	Dermoscopic findings typical of the original lesions [26].
	Pityriasis alba	Fairly ill-demarcated hypopigmented macules with fine scales [28].

patient. In all IP skin stages dermoscopic findings appear to be very characteristic and correlate to histopathological findings. Furthermore, dermoscopy can be used as an aid for determining the optimal lesion for diagnostic biopsy. Unlike the other stages, the stage III of IP has very close clinical, histological and dermoscopic mimickers and this stage needs to be carefully examined with obligatory genetic testing. The stage IV of IP in lighter phototypes is sometimes clinically barely visible, but has enormous clinical importance for diagnostics of potential IP gene carriers.

Further studies are needed to establish precise dermoscopic applicability in IP in the everyday practice of a dermatologist.

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