Original Research

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Treatment-induced anogenital melanosis is a very frequent finding in patients with vulvar lichen sclerosus

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ABSTRACT

Background: Pigmented lesions such as melanosis have rarely been reported in patients with vulvar lichen sclerosus (VLS) that is typically characterized by hypopigmented lesions.

Objective: We aimed to analyze systematically anogenital melanosis in a large cohort of VLS patients.

Methods: We analyzed the clinical data of 198 female patients with VLS. The anogenital lesions of all patients were professionally photographed in a standardized position and illumination. Severity classification of architectural findings followed an easy-to-use clinical score. A modified Melasma Area and Severity Index and an image analysis software were used to evaluate the area and intensity of pigmentation.

Results: According to the clinical score, 79 (198/39.9%) patients showed grade 1 disease, 78 (198/39.4%) grade 2, 37 (198/18.7%) grade 3, and 4 (198/2%) grade 4 disease. About 111 (56.1%) of the 198 patients had anogenital melanosis with a median modified Melasma Area and Severity Index of 3.6 (0.4–14). Univariate analysis revealed that anogenital melanosis was positively correlated with the use of topical estrogens (P = .0018) and negatively correlated with the use of pulsed high-dose corticosteroids plus low-dose methotrexate (PHDC-LDM, P = .021). On multivariable analysis, the use of topical hormone therapy turned out to be a strong independent predictor for the presence of anogenital melanosis (odds ratio: 4.57, 95% confidence interval: 1.66–12.57, P = .0033), whereas PHDC-LDM use was an independent predictor for the absence of anogenital melanosis (odds ratio: 0.35, 95% confidence interval: 0.15–0.84, P = .018).

Limitations: The study includes the retrospective monocentric design.

Conclusion: Anogenital melanosis is a very frequent and so far, under-reported clinical finding in VLS patients. It is likely caused by the use of topical estrogens employed for VLS treatment. In contrast, patients with more severe disease and PHDC-LDM treatment appear to develop less likely anogenital melanosis.

Keywords: estrogens, hyperpigmentation, lichen sclerosus, treatment

Vulvar lichen sclerosus (VLS) is a relatively common inflammatory connective tissue disease with an autoimmune background, which predominantly affects the anogenital region of postmenopausal women.[1,2] VLS is typically characterized by hypopigmented skin lesions whereas pigmented lesions are rarely reported. However, reports of an association between VLS and vulvar melanoma have sporadically been published in the literature. Hence, pigmented skin lesions are of interest in patients with VLS. In the general female population, different pigmented lesions of the vulva can be observed systematically in about 10% of cases and are most frequently ignored.[3–7] Our clinical long-term observations, however, suggest that pigmented skin changes are much more common in VLS patients than previously reported. Hence, we aimed to analyze systematically anogenital melanosis in a large cohort of VLS patients.

What is known about this subject in regard to women and their families?

- Pigmented lesions such as melanosis have rarely been reported in patients with vulvar lichen sclerosus (VLS) that is typically characterized by hypopigmented lesions.

What is new from this article as messages for women and their families?

- Anogenital melanosis is a very frequent and so far, under-reported clinical finding in VLS patients.
- It is likely caused by the use of topical estrogens employed for VLS treatment.
- In contrast, patients with more severe disease and pulsed high-dose corticosteroids plus low-dose methotrexate treatment appear to develop less likely anogenital melanosis.

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Materials and methods

We analyzed the data of 198 female patients treated from 2014 to 2022 in the VLS outpatient clinics of the Department of Dermatology, Ruhr-University Bochum. In 112 (198/56.6%) patients, VLS diagnosis was histopathologically proven. Anogenital lesions of all patients with informed consent were professionally photographed (Nikon D600 and macro-objective Nikon AF-S Micro NIKKOR 60 mm 1:2, 8 G) in a standardized manner regarding position and illumination (macro-flash sets Nikon wireless remote speedlight SB-R200). At least one digital figure was available for every patient included in the study. Epiluminescence microscopy pictures were performed using a camera adapter for the Delta 20T dermoscope (Heine, Germany). Classification of the severity of architectural findings in VLS patients was carried out using the easy-to-use CIV classification (Italian: fimosi Clitoridea, coinvolgimento solchi Interlabiali, restringimento introito V) recently proposed by Boero et al.[8]

A modified Melasma Area and Severity Index (mMASI) was used to reliably evaluate the area and intensity of pigmentation.[9] The area of pigmentation was calculated by means of an image analysis software, in which the prepared images are imported as a .png file. The RGB (red/green/blue) function was used to determine the number of gray and black pixels. The ratio of gray pixels to the total number of all pixels (gray and black) was calculated. Thus, the percentage of hyperpigmented mucosal areas was determined within the total field-of-view. To record the extent of the mucosal melanosis, the area to be examined was first cut out as a polygon from the photo by means of Windows Paint program (Fig. 1). If possible, the anatomical boundaries of the organs are represented. However, due to synechiae and atrophies, the structural anatomical boundaries could not always be perfectly defined in case of pronounced disease findings. Then, labia majora and labia minora were recorded as a single unit. In this polygon section, the hyperpigmented mucosal areas were marked with gray color, whereas the remaining area was dyed black. Among the follow-up of VLS patients with clinically suspicious lesions, epiluminescence microscopy and/or skin biopsies were performed for the assessment of melanoma or other malignancies.

Data analysis was performed using the statistical package MedCalc Software version 20.217 (MedCalc Software, Ostend, Belgium). Distribution of data was assessed by the D'Agostino–Pearson test. Nonnormally distributed data were displayed as median and range. Where appropriate, univariable analysis was performed using the Spearman correlation and Kendall's Tau procedures and the $\chi 2$ test. Multivariable analysis was carried out by a logistic regression model including all independent variables with a P value smaller than .1, which were obtained from univariable statistics. P values <.05 were considered statistically significant.

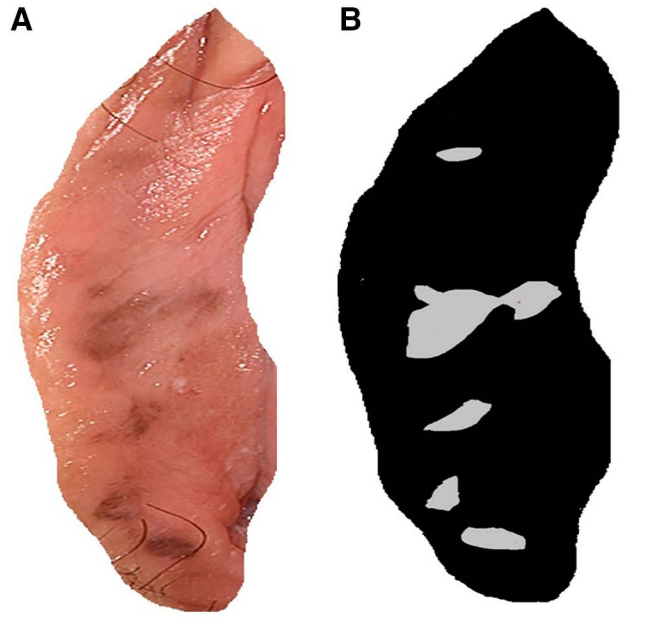

Fig. 1. Showing a polygon section from an original image (A) and marked areas in gray and black (B). This prepared image (A) was imported as a .png graphics file type using the R-Studio computer program. Next, the RGB (red/green/blue) function is used to evaluate the imported .png file. In each case, the number of gray or black pixels is determined and the ratio of the gray pixels to the total number of all pixels (gray + black) is calculated. Hence, the percentage of the hyperpigmented mucosal areas in the total area of interest was determined. In this example (A), the melanosis affected was 8% of the total area considered.

Results

The patient characteristics and treatment are displayed in Table 1. At first presentation, the median (range) of the 198 patients was 56 years (4–88) and 124 (62.6%) of them had a postmenopausal status. The median follow-up time was 16.5 months (0–300). According to the CIV score, 79 (198/39.9%)

Table 1

Clinical characteristics of 198 patients with vulvar lichen sclerosus investigated

Parameter	Data
Median age (range)	56 (4–88) years
Median follow-up in months (range)	16.5 (0–300) months
CIV grade	
1	79 (39.9%)
2	78 (39.4%)
3	37 (18.7%)
4	4 (2%)
Anogenital melanosis	
No/yes	87/111 (43.9%/56.1%)
Median mMASI (range)	3.6 (0.4–14)
Hypopigmentation/sclerosis	
No/yes	28/170 (14.1%/85.9%)
Erythema	
No/yes	46/152 (23.2%/76.8%)
Erosion/ulceration	
No/yes	142/56 (71.7%/28.3%)
Atrophy	
No/yes	44/154 (22.2%/77.8%)
Synechia	
No/yes	116/82 (58.6%/41.4%)
Pruritus	
No/yes	23/175 (11.6%/88.4%)
Pain	
No/yes	49/149 (24.7%/75.3%)
Autoimmune disease[a]	
No/yes	131/67 (66.2%/33.8%)
Depression	
No/yes	180/18 (90.9%/9.1%)
Topical corticosteroids	
No/yes	16/182 (8.1%/91.9%)
Systemic high-dose corticosteroids plus methotrexate	
No/yes	168/30 (84.8/15.2%)
Hormone therapy[b]	
No/yes	165/33 (83.3%/16.7%)
Other treatments	
No/yes	187/11 (94.4%/5.6%)

mMASI, modified Melasma Area and Severity Index.

[a] Almost two-third with hypothyreosis.

[b] Except for one patient, only topically used estrogens.

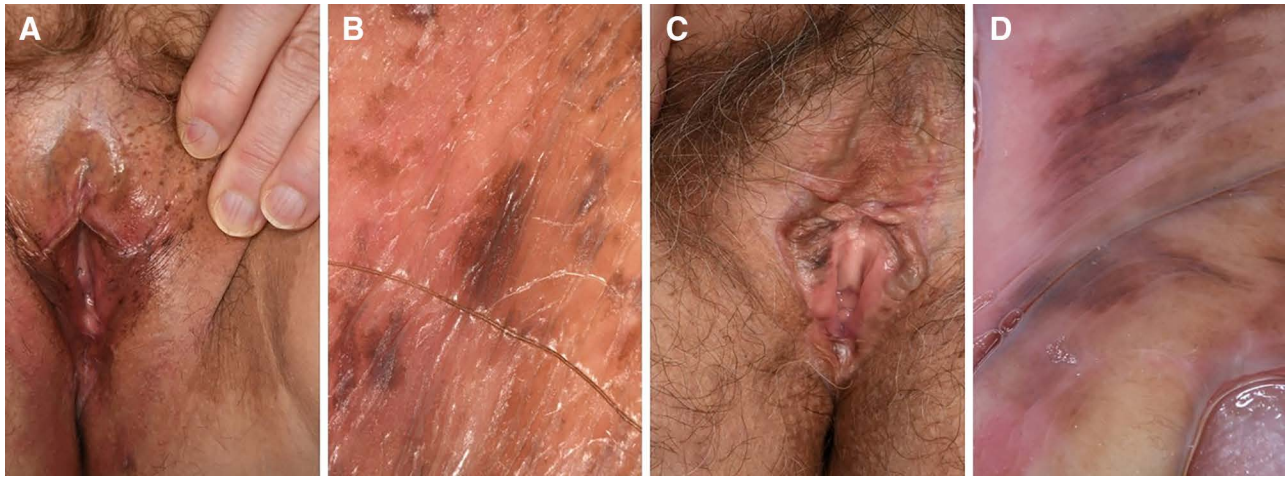

Fig. 2. Showing the genital region of a 61- (A) and a 58-year-old (C) female with vulvar lichen sclerosus and associated melanosis (mMASI score: 2.4 and 4.8, respectively). Dermoscopy (B and D) of genital melanosis of both patients revealed homogenous darkish-brown sharply demarcated blotches. Histopathology confirmed benign anogenital melanosis. mMASI, modified Melasma Area and Severity Index.

patients had grade 1 disease, 78 (198/39.4%) grade 2, 37 (198/18.7%) grade 3, and 4 (198/2%) grade 4 disease. About 111 (56.1%) of 198 patients had anogenital melanosis of any severity (Fig. 2). Notably, 17 (111/15.3%) had pigmentation intensity of grade 1, 51 (111/45.9%) of grade 2, 33 (111/29.7%) of grade 3, and 10 (111/9%) of grade 4. The median (range) percentage involvement of melanosis was 11% (1–52) in the labial region (n = 86), 18% (5–100) in the vaginal introitus region (n = 10), and 50% (6–100) in the perianal region (n = 38). The median mMASI was 3.6 (0.4–14). Among those patients with lesions suspicious of malignancy, histopathological examination confirmed benign melanosis in 10 (198/5.1%) patients, vulvar squamous cell carcinoma in 4 (198/2%) patients, and vulvar intraepithelial neoplasia grade 3 in 4 (198/2%) patients.

Univariate analysis revealed that anogenital melanosis was significantly associated with the use of topical estrogens (P = .0018). In contrast, the use of pulsed high-dose corticosteroids and low-dose methotrexate (PHDC-LDM) treatment was significantly more frequent in patients with higher CIV classes (P = .0011) and was significantly associated with absence of anogenital melanosis (P = .021). Accordingly, a low mMASI was significantly (P = .0074) associated with the use of PHDC-LDM. The use of topical estrogens did not significantly differ between patients with or without PHDC-LDM (P = .56). PHDC-LDM remained in the regression model as a significant predictor for the absence of anogenital melanosis in patients with VLS (odds ratio: 0.35, 95% confidence interval [CI]: 0.15–0.84, P = .018). In contrast, the use of topical estrogens remained in the regression model as a strong significant predictor for anogenital melanosis in patients with VLS (odds ratio: 4.57, 95% CI: 1.66–12.57, P = .0033). Other potential covariates for the prediction of melanosis, including age above 45 years/postmenopausal status, CIV score, clinical features of VLS (eg, erythema, pruritus), associated autoimmune conditions, and other comorbidities, were not included in the logistic regression model since the P values on univariate analyses were ≥.1.

Discussion

Hyperpigmented vulvar lesions are present in about 10% of White females. Approximately 2% of them are melanocytic nevi. Other benign pigmented lesions include melanosis, lentigines, postinflammatory hyperpigmentation, seborrheic keratoses, and pigmented warts. Malignant pigmented lesions, including melanoma, often have a worse prognosis compared to melanoma found on the rest of the integument. Therefore, hyperpigmented anogenital skin lesions require careful inspection with each full-skin or gynecologic examination, followed by dermoscopy and/or biopsy of any suspicious lesion.[3–7] With respect to vulvar melanosis, De Giorgi et al.[10] recently have shown in an over 20-year follow-up study that this condition has a benign nature and changes in lesions over time do not show malignant transformation. However, this study did not systematically evaluate which comorbidities (eg, VLS) were associated with vulvar melanosis.[10]

Indeed, the association of anogenital melanosis and VLS has not been assessed so far. In our daily clinical practice, increased evidence for the presence of hyperpigmented lesions in VLS was found. Compared to the general female population, we detected an over 5-fold increased frequency of hyperpigmented lesions in the anogenital region of patients with VLS.[3–7] In agreement with the data of De Giorgi et al.,[10] we did observe malignant transformation of hyperpigmented lesions on long-term follow-up. In all cases requiring histopathological confirmation, we observed benign melanosis. However, the detected cases of nonmelanoma skin cancers in the present VLS population match the frequency reported in previous studies on anogenital noninvasive and invasive squamous cell carcinomas in VLS patients.[1,2] Anogenital melanosis is very frequent in patients with VLS presumably because of topical hormone therapy. Interestingly, De Giorgi et al.[10] observed in their cohort (n = 129) that 67% of patients with vulvar pigmented lesions were premenopausal, and 65% had received some type of hormone treatment.

In our findings, topical estrogens are a strong (odds ratio: 4.57, 95% CI: 1.66–12.57) predictor of the presence of anogenital melanosis in patients with VLS. Other clinical covariates, including CIV score, erythema, and pruritus, did not remain in the logistic regression model. Indeed, topical estrogens can induce intense pigmentation.[10–13] For example, vulvar pigment lesions were observed as a frequent (25%) side effect after topical estrogen treatment for labial fusion.[13] The underlying pathomechanism is likely comparable to the development of melasma in patients treated with topical or systemic estrogens.[14] A previous study demonstrated increased expression of estrogen receptors in melasma-affected skin.[15] Hence, anogenital melanosis in VLS patients appears to be an adverse treatment effect and is unlikely a primary clinical feature of VLS. By contrast, PHDC-LDM treatment was significantly more frequently observed in patients with higher CIV classes. Of course, PHDC-LDM

therapy is reserved for more severe/recalcitrant cases.[16] In the present study, PHDC-LDM was significantly associated with the absence of anogenital melanosis and a low mMASI score. In the multivariable regression model, PHDC-LDM remained as a strong (odds ratio: 0.35, 95% CI: 0.15–0.84) predictor of the absence of anogenital melanosis in patients with VLS. Since anogenital melanosis was not significantly correlated with a low CIV score and less frequent use of topical estrogens, we assume that PHDC-LDM therapy might prevent the development of anogenital melanosis in VLS patients.[1,2,14]

Nevertheless, there are several limitations of the present study: (1) this investigation was a retrospective observation and thus any conclusions on causality are limited; (2) other confounding variables may have been present that were not measured; (3) even though the study comprised a reasonable sample size, this investigation was susceptible to local clinical practices, limiting the validity and generalizability of our findings.

In conclusion, this study presents that anogenital melanosis is a very frequent and so far, under-reported clinical feature in VLS patients. It is correlated to the use of topical estrogens for VLS treatment. In contrast, patients with more severe disease and PHDC-LDM treatment appear to develop less likely anogenital melanosis.

Conflicts of interest

None.

Funding

None.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies (Ethical Review Board: ID #4222-12).

Author contributions

TG, GE, and LS contributed to the study's conceptualization, methodology, and research design. SSWF was additionally involved with project supervision and editing the manuscript. TG, GE, and LS were involved in the investigation, data curation, writing, and manuscript editing.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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