Diplomarbeit

Evaluation of Epidemiologic and Morphologic Data of Genital Melanosis in Men and Women

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Zusammenfassung

Einleitung: Genitale Schleimhautmelanose ist eine gutartige Hyperpigmentierung der genitalen Schleimhäute, die sowohl Männer als auch Frauen betreffen kann. Sie besitzt ähnliche klinische Merkmale wie das Melanom, was eine Unterscheidung zwischen den beiden schwierig machen kann. Die genaue Abgrenzung beider Entitäten ist aber sehr wichtig, da sich beide in Bezug auf die Therapie und die Prognose deutlich unterscheiden. Ziel dieser retrospektiven Studie war es, epidemiologische und klinische Daten von Männern und Frauen mit genitaler Melanose zu analysieren.

Material und Methodik: In dieser retrospektiven Studie wurden die Daten von PatientInnen mit pigmentierten Schleimhautveränderungen gesammelt, die an der Abteilung für Dermatologie und Venerologie an der Medizinischen Universität Graz im Zeitraum von Januar 2010 bis Juni 2016, behandelt wurden. Diese Daten wurden epidemiologisch und morphologisch untersucht und anschließend statistischen ausgewertet, um eine detaillierte Charakterisierung zur Verbesserung der Diagnose und Differentialdiagnosen von Pigmentläsionen der Schleimhaut zu erhalten.

Ergebnisse: Es wurden insgesamt 79 PatientInnen (64, 81% Frauen und 15, 19% Männer) mit pigmentierten Läsionen im Genitalbereich in unsere Analyse eingeschlossen. Das mittlere Alter der PatientInnen lag bei 52 Jahren (± 15.7 Jahre). Bei 64 (81%) der Patientinnen erfolgte eine histologische Diagnosesicherung und bei 15 (19%) Fällen wurde die Diagnose klinisch gestellt. Die häufigste Diagnose war Schleimhautmelanose (n=74, 95%). Bei den restlichen 5 (5%) Fällen wurde histologisch die Diagnose eines melanozytären Nävus (n=3), Melanoma in situ (n=1) und Verruca seborrhoica (n=1) gestellt. Die Glans penis und Labia minora waren die häufigsten betroffenen Regionen. Insgesamt 71% (n=56) der Läsionen präsentierten sich als multifokale Pigmentierung und 29% (n=23) waren solitär. Männer mit Schleimhautmelanose waren im Durschnitt 38.5 Jahre alt, Frauen hingegen 54.4 Jahre ($p < 0.01$). Die mittlere Dauer des Bestehens von genitaler Melanose war bei Männern (17.4 Jahre) signifikant länger als bei Frauen (5.8 Jahre) ($p<0,01$).

Fazit: Basierend auf den Ergebnissen unserer Studie, sind Frauen häufiger von Schleimhautmelanose betroffen als Männer. Die Glans penis und Labia minora zählten bei allen Diagnosen zu den häufigsten betroffenen Stellen. Das Alter, die Lokalisation, das klinische Bild und die Dauer der Pigmentierung sollen bei der Differentialdiagnose pigmentierter Schleimhautveränderungen mit in Betracht gezogen werden. Als mögliche Ursachen für Schleimhautmelanosen gelten Trauma und Irritationen.

Abstract

Introduction: Genital melanosis is a benign hyperpigmentation, which can occur in both, men and women. It shares similar clinical characteristics to malignant melanoma, which makes a differentiation between the two difficult, but all the more important, since therapy and prognosis differ. The aim of this retrospective study was to analyse epidemiological and clinical data of men and women, who received the diagnosis genital melanosis.

Materials and Methods: Data was collected from patients who received the diagnosis of genital melanosis at the Department of Dermatology and Venerology at the Medical University of Graz during January 2010 and June 2016.This data was epidemiologically and morphologically evaluated, and subsequently, a statistical analysis was conducted. This evaluation was done to improve knowledge of the characterization of these lesions, which can be useful for the diagnosis and elimination of possible differential diagnoses.

Results: A total of 79 patients (n=64, 81% women and n=15, 19% men) with genital lesions were included in our analysis. The average age of all patients was 52 years (± 15.7 years). A histopathological diagnosis was confirmed in 64 cases (81%) and a clinical diagnosis was made in 15 cases (19%). Mucosal genital melanosis was confirmed as a diagnosis in 74 cases (95%), and in 5 cases (5%) a different diagnosis was found histologically (1 melanoma in situ, 3 melanocytic nevi and 1 verruca seborrhoica). In men, lesions were frequently found on the glans penis, in women the labia minora were most common affected. Most patients presented multifocal lesions (n=56, 71%), fewer patients presented unifocal lesions (n=23, 29%). Male patients with genial melanosis were on average 38.5 years old with a significant difference to female patients, with an average of 54.4 years ($p < 0.01$). The average duration of existence of genital melanosis was significantly longer in men (mean duration 17.4 years) than in female patients (mean duration 5.8 years) ($p<0.01$).

Conclusion: Our patient group showed, more women were affected by mucosal genital melanosis than men. The glans penis and labia minora were among the

most frequent affected areas in all diagnoses. Possible causes of genital melanosis are trauma and irritation.

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Glossar und Abbreviations

GM- Genital melanosis

AMNGT- Atypical melanocytic nevi of the genital type

MM – Malignant melanoma

PH- Postinflammatory hyperpigmentation

VM- Vulvar melanoma

VIN- Vulvar intraepithelial neoplasia

SCC- Squamous cell carcinoma

HPV- Human papillomavirus

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1 Introduction

1.1 General Facts

On the genital mucosa, a variety of hyperpigmented lesions can occur. They can be benign or malignant, be caused by a variety of reasons and may include nonmelanocytic and melanocytic proliferations. These pigmented lesions of the genital are no rarity in the general population, and often share common clinical and epidemiological features.

Melanosis belongs to the group of benign pigmented lesions, and can be found in the oral and genital mucosa.[1] They are caused by an increased pigmentation of keratinocytes without increase of melanocytes.[1] The name of genital melanosis (GM) can vary, it can also be known as genital lentigo, genital melanotic macules, or anogenital hypermelanosis[1,2]. These lesions usually appear as large asymmetrical macules with an irregular border, and a color range, depending on the skin type, from light brown to black-gray.[2,3] Such patterns can be however also seen in genital melanoma. The similar appearance between these two different entities makes a clinical differentiation often challenging. However, an accurate diagnosis is important, as the prognosis and management of these two conditions are completely different.[4,5]

1.1.1 Incidence and Etiology

In general, pigmented lesions of the genital, especially the female genitalia, are rather common. It is estimated that about 10-12% of white women and 3% of men are affected by GM.[1,5-7] However, information about the exact incidence of GM in both genders is limited.[3,8] Only a few studies have made a comparison between the occurrences of GM in both sexes.[9] It is estimated, that the incidence of GM lies by 0,011% of dermatological patients presenting themselves in a clinic.[8]

There appears more literature about GM of the female genital than on the male genital. In reproductive-aged women, vulvar melanosis accounts for around 68% of pigmented lesions located on the female genitalia.[5,10] Studies suggest, that the manifestation of GM occurs more often in perimenopausal women with an average age between 41-44 years.[5,8,11,12] Furthermore, Haugh and colleagues studied

patients with GM in 2016 and inquired the patients' past medical and family history. Five patients had a personal history of melanoma, only one of which was diagnosed in the genital area, the remaining four cases were on other body sites.[8] Furthermore, the lesions of GM in these patients had a tendency to more suprabasal spread of melanocytes than GM in patients with no history of malignoma.[8] They concluded, that patients with a history of melanoma may have a higher incidence of developing GM.[8]

The pathogenesis of GM is still unknown, several different possible causes are discussed. Some postulate that a chronic trigger might play a role by inducing a reactive hyperpigmentation, however, the authors did neither identify nor define such trigger.[3,13] In a study by Barnhill et al., 3 penile lesions appeared after injury or irritation, and one could be related to PUVA therapy.[9] Other studies indicated a relationship between the occurrence of GM and lichen sclerosus.[10,14] Furthermore, case reports and studies showed a possible correlation between hormonal factors and the onset of GM, this is due to oral contraceptive use and the appearance of lesions in the postpartum period.[5,10] A case report has also associated the occurrence of GM with human papillomavirus (HPV) infection,[15] although a study from 1999, which investigated if HPV could trigger GM with 23 cases of vulvar melanosis, found no correlation, as all cases were tested negative on HPV.[16] A defect of melanotic transport to the keratinocytes in the suprabasal layer has also been discussed as a possible trigger for GM.[3] It is also assumed, that an increase of sensitivity to melanocortin, a hormone that stimulates the melanocytes in the skin layer, is a reason for the appearance of melanosis.[1] Instead, UV exposure, which is a common cause for hyperpigmentation on other body sites, seems to play no role in the pathogenesis of GM, given the generally sun-protected location and body site.[1]

Some papers state, that although GM has a similar appearance to malignancy, there is no association of GM developing into melanoma,[10,11] but there is one case of malignant melanoma developing on the background of vesicovaginal melanosis.[17] It is still unclear if there is a relationship between LS and melanoma, but there are case reports of vulvar/penile melanoma developing in LS patients.[18,19]

Age should also be regarded when examining pigmented lesions. It can be a helpful indicator, since patients with malignant neoplasms are usually older than

patients with benign lesions, yet should be considered carefully.[12] Blum et al examined pigmented mucosal lesions, and patients with a benign diagnosis had a mean age of 43,2 years whereas patients with the diagnosis of malignant tumors had a mean age of 60.1 years.[12]

1.1.2 Clinical Aspects

Cengiz et al. evaluated pigmented lesions in both men and women (28 male patients) and found that the pigmentation in men most commonly affects the glans penis, followed by the meatus and less frequently on the shaft of the penis.[20]
In women, GM lesions can be found on the whole genital and peri-anal region, predominantly on the mucosal labia majora, labia minora and clitoris, and less frequent on the introitus, mons pubis, and perineum.[2,10,11,21-23]
Generally, the mucosal membranes are more often affected than the keratinized and hairy skin of the vulva.[11] In other studies, the majority of macules in male patients were found on the glans penis, but cases of macules on the penile shaft were also documented.[9,24]
GM can present as single macule or, as seen more often, as multifocal pigmentation.[9,11] Lesions are generally asymptomatic, asymmetric, and with irregular borders.[6,9,10] They can reach a size of about 2 cm, with a range of various shades of brown or black, with a difference in color even in a single lesion. [3,10,11,25]
Sison-Torre et al reported on a lesion measuring more than 4cm in size.[22]
A few studies differentiate between genital lentigo and melanosis by their size and appearance. Lentigos are often described as single, round, and well- defined macules, whereas the term melanosis is often used to describe multifocal, large and irregularly pigmented macules with ill-defined borders.[6,26]

1.1.3 Diagnosis

The diagnosis of GM is usually made by the clinical appearance, in doubtful cases, a punch biopsy is performed to obtain a histopathological confirmation.[10] The first diagnosis in women is often made during routine gynecological visits,[27] and men often present at dermatologists because of a self-detected pigmentation on the penis.[9]

In the recent years, studies about dermatoscopy have shown, that this non-invasive, in vivo diagnostic tool can be a helpful in the differential diagnosis between GM and melanoma, since GM show different patterns in dermatoscopy than melanoma.[20,26,28]

In dermatoscopy, different patterns of GM have been described (Table 1). These descriptions were mostly based on the analaysis of vulvar melanosis and to much lesser extent, on penile melanosis. In vulvar melanosis, the structureless, parallel and ring-like patterns are the most common described dermatoscopic features.[2,4,26,29] More recently, reflectance confocal microscopy has been employed for the diagnosis of genital pigmentations.[23,30] This method allows a visualization of morphological structures close to the histopathologic resolution,[23] accordingly, this method is also referred to as "*optical biopsy*".[30] Cinotti et al described an increase of brightness in cells around the papillae in cases of melanosis whereas they are absent in clinically normal mucosa.[23] One cases of melanoma showed atypical cells with a destroyed, disarranged architecture of the papillae, neither of these two features were found in cases of melanosis.[23]

1.1.4 Histology

The histopathological examination of GM shows hyperpigmentation due to melanin deposition, which can be mainly found in the basal layer of the epidermis.[6,9,11,14,21,22,24] The number of melanocytes are described as either normal or slightly increased, and they are usually arranged solitarily in the basal layer, not in nests.[11,21,22] Furthermore, the melanocytes do not feature any atypia, such as an abnormal cell nuclei, and they are not seen in stages of mitosis.[21,22] Some studies described the presence of melanophages with a higher amount of melanin in the dermis,[6,11,24] and melanocytes with longer dendrites that reach up into to the epidermis.[21,22]

Barnhill et al described the histopathological features of a series of penile and vulvar melanoses, and found that the histopathological aspect was with one exception similar in vulvar and penile cases. The only differences observed between female and male GM was the absence of melanocytic dendrites in vulvar lesions, while they were common in men.[9] They also described lesions that featured hyperplasia of the epidermis with lentigous elongation of the rete ridges.[9]

Lenane et al presented genital macules that showed acanthosis in the epidermis, without elongated rete ridges and a perivascular infiltrate of lymphocytes.[3]
Some authors correlated the dermatoscopic patterns of GM with histopathology, but did not find significant differences between the dermatoscopic aspect and histopathology. The histopathological correlates of dermatoscopic features of GM are depicted in Table 2.

Pattern	Location and Description	Ref.
Structureless (homogenous) Pattern	Light brown to dark brown pigmentation, which can also show greyish-blue color. The pigmentation appears diffuse homogenous and there are no hints of specific dermatoscopic structures.	2,4,12,26,29
Parallel Pattern	The pigmented lesions appear in lines, globules, linear or curvy streaks that run in the course of the skin's surface and profile. Ronger-Salve et al also mentioned a fingerprint- like appearance. This pattern was also found in penile melanosis.	2,4,26,29
Reticular-like Pattern	This pattern has similarities to the pigment network of melanocytic lesions on the skin, but with a grid of round/ oval shapes, rather than polygonal shapes. The lines end abruptly at the edge of the lesion, but are distributed evenly along the middle.	2,4,26
Ring-like Pattern	Multiple round or oval macules arranged in groups in some areas. The color of pigmentation ranges from white to light brown with darker, hyperpigmented distinct borders. No other typical dermatoscopic shapes and structures correlating with melanocytic lesions are found.	4,26
Polycircular Pattern	It is only present on the papillomatous surface of the outer edge of the labia minora where the pattern shows polycircular, brown pigmented areas. It is the only described pattern to be associated with an anatomical site.	26
Cobblestone Pattern	Polygonal shapes that are light to dark brown, accumulated to a single lesion	2
Globular Pattern	Similar to globules seen in melanocytic lesions. Multiple round or ovoid, clustered structures, that appear light to dark brown.	2,26

Table 1 Dermatoscopic patterns described in genital melanosis

Pattern Type	Histopathology	Ref.
Structureless (homogenous) Pattern	Moderate hyperpigmentation along the basal cell layer. Blue color probably due to melanophages in the upper dermis.	2,4,26
Parallel Pattern	Examination shows resemblance to ink spot lentigo. The rete ridges are elongated and clubbed and hyperpigmentation is found along the basal layer of the epidermis and especially on the tips of the rete ridges. No increase of melanocytes.	2,4,26
Reticular-like Pattern	In the basal cells of the epidermis, the pigment melanin could be found. The pigmented rete ridges form the lines of the grid that can be seen on the surface of the skin, with the holes being the dermal papillae. However, the rete ridges appear to have lost their normal profile. Furthermore, the epidermis shows signs of acanthosis with the presence of thick hyperpigmented epidermal crests blending at the base.	4,26
Ring-like Pattern	Histopathological, this pattern is similar to the parallel pattern. Hyperpigmentation is found in the epidermal basal layer with elongated and clubbed rete ridges, but it shows areas that lack pigmentation which is a differentiation from the continuous hypermelanosis seen in the parallel pattern.	2,4,26

Table 2 Histopathology and correlating dermatoscopic patterns

1.1.5 Prognosis and Treatment

GM is a benign lesion and the prognosis is excellent, therefore, GM does not require any specific treatment but regular clinical and dermatoscopic visits are recommended.[11] This is because GM may sometimes show changes during follow up, although currently little is known about the frequency of changes over time, few studies reported on increase in size of pre-existing lesions and the development of new lesions.[3,8] Although up to date there are no reports on

malignant transformation, careful examination of any newly developing macule in an adult should be always considered.[3,8,22,24] Some affected individuals might warrant removal of the genital lesions due to concern or cosmetic reasons.[11] In these cases, a shaving biopsy or cryotherapy can be effective.[1,11,31]

1.2 Differential Diagnosis

1.2.1 Melanocytic Nevi

Melanocytic nevi of the mucosa, including the genitals, are often referred to as nevi of special body sites or nevi with site-related atypia.[32] This is because a certain proportion of nevi might show marked atypia upon histopathology, although their clinical course is entirely benign.[7,32] In the realm of genital nevi, two types can be differentiated: Common nevi without histopathologic atypia and atypical nevi of the genital type.[7,28]

Common melanocytic nevi make up about 23% of pigmented vulvar lesions in adult women, and approximately 2% of women have vulvar nevi.[33] Their pigmentation is due to a benign proliferation and accumulation of melanocytes and nevus cells, but show no sign of atypical cell growth.[10,11,14]

They appear as solitary, symmetric lesions, with a color range of different shades of brown to black, sometimes a white-blue veil is described.[5,10,26] They are usually smaller than 1 cm, with well-defined borders, either flat or dome-shaped, and most common on the labia majora but can also be found on the labia minora and clitoris.[5,10,28] In dermatoscopy, a globular and homogenous pattern is the most common described feature.[5,26] Besides the differences in the dermatoscopic patterns between genital nevi and GM, also age presents an important criterion in the differential diagnosis. As such, studies suggests that nevi occur more frequently in younger aged women compared to GM, which are more commonly diagnosed in adult women (average age 28 to 39 years, respectively) [7,20,27,28,33].

1.2.1.1 Atypical Melanocytic Nevi

Atypical melanocytic nevi of the genital type (AMNGT) are a subgroup of the nevi occurring on the genital areas, which have histopathological features, which can make a differentiation from melanomas difficult.[7] It must be underlined that these

nevi follow a benign course and that the atypical morphological appearance does not correlate with a higher risk of malignant progression.[32,34] AMNGT are usually described on the vulva and perineum, but are sometimes also found in the axilla and rarely on male genitalia.[34] Compared to GM and common nevi, AMNGT are associated with younger age, with an average age of 17 to 28 years.[20,28] Clinically, AMNGT stand out from melanocytic nevi by their large size, irregular borders and hyperpigmentation.[34,35] Dermatoscopically, they show some asymmetry of colors and structures and often exhibit a mixed globular- structureless pattern with colors varying from brown to gray and blue.[20,28] Histologically, they show atypical melanocytes in nests that are spread unevenly along the rete ridges of the epidermis, lentiginous growth, skin adnexal involvement, focal pagetoid spread and fibrosis of the papillary dermis.[34,35]

1.2.2 Melanoma

1.2.2.1 Epidemiology and Pathogenesis

In women, vulvar melanoma (VM) is the second most frequent malignancy of the vulva following squamous cell carcinoma.[36,37] MM of the female genital causes 8 - 10% of all malignancies of the vulva [38] and accounts for 2-7% of all melanomas affecting women.[36,37] An analysis of the National Cancer Data Base reports that mucosal melanoma make up 1.3% of all melanomas, and of these, 18% are located on the female genital tract.[39] MM of the vagina is extremely rare and accounts for less than 1% of all melanomas.[40] VM affects typically postmenopausal women with a peak incidence in the sixth and seventh decade.[41] According to different studies the mean age ranges from 60 [42] to 76 years.[38,43,44] The pathogenesis of VM is largely unknown but tissue-specific factors and environmental influences, such as viruses, toxins and drugs, have been discussed in its development.[45] In contrast to cutaneous melanoma, ultraviolet radiation does not seem to play a significant role a given the generally sun-protected location.[1,11] In men, penile melanoma is infrequent and accounts for approximately 0,7% of all penile cancer, and less than 0,2% of all melanoma cases.[46,47] Penile melanoma is mainly described in middle aged men with most recent data suggestion an average age between 44.5 [46] to 53 years.[48,49] Older studies and case reports

observed patients with an average age of 63 years.[47] Oldbring et al. also mentioned that the most cases of melanoma on the penis and urethra, have been observed between the sixth and seventh decades of life. [47,50,51]

1.2.2.2 Clinical and histopathological presentation

The presentation of MM on the genitals may be as macules, papules, nodules and often ulcerations.[5,47] Morphological criteria associated with MM are asymmetry, irregular borders, multifocality, poor circumscription and a size of more than 7 mm.[5,10] Moreover, lesions are polychromatic with different shades of brown, black, white, red and blue.[5,10] Initial MM remains usually asymptomatic, although pruritus may be reported.[36] At late stage, the tumors may cause discomfort due large size, bleeding and erosion.[36] In dermatoscopy, structureless, polychromatic patterns as well as irregular dots, reticular depigmentation and polychromatic vessels can be observed.[12,28]

Histolopathologically, tumors can be classified based on the prevailing morphologic features into mucosal lentiginous, superficial spreading, nodular and amelanotic melanoma.[11,37,38] In all subtypes atypical melanocytes, arranged in nests or solitarily, mitosis, lack of cell maturation and a disturbed architecture of the skin can be seen.[5,11]

1.2.2.3 Treatment and Prognosis

The prognosis of MM is depending on several different factors, like tumor size, tumor thickness defined by the Breslow-Index or Clark-levels, tumor invasion, lymph node involvement, the manifestation of ulcerations, age of the individual and localization of the primary tumor.[36] Treatment of the primary tumor is surgery.[10] The radicality of surgery dependents on how much tissue has been infiltrated by tumor cells.[38,45] Radical surgery including vulvectomy and penectomy has not been associated to an improved outcome and overall survival rate compared with wide excision only.[36,38,41,45] Immuno-therapy, targeted therapy, chemotherapy and radiotherapy are used in advanced tumor stages.[36,41] Prognosis of genital melanoma is poor, it is associated with a high rate of local recurrences and lymphogenic as well as hematogenic metastatic spread. [37,41] Recent studies analysed a 5 - year survival rate of only 11%.[39]

1.2.3 Physiologic Hyperpigmentation

In women with a natural darker skin tone, physiological hyperpigmentation can occur in the vulvar region.[6,11] It is mostly found on the tips of the labia minora, introitus and perianal region, sometimes the labia majora can also be affected.[10,11] The patches are flat, symmetrical and asymptomatic and show no difference in texture to normal skin.[10] If biopsied, the lesions would show an increase of melanin and melanosomes in the melanocytes and keratinocytes of the basal cell layer.[10,11] Hormone changes such as pregnancy, contraceptive use, puberty and menopause, can affect the hyperpigmentation.[6] Other disorders disrupting the hormone balance, like the excess production of adrenocorticotrophic hormone as seen in Cushing's disease, Addison's disease and congenital adrenal hyperplasia, can also cause hyperpigmentation with similar appearance.[6]

1.2.4 Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation (PH) is an increased pigmentation reactive to an inflammatory process.[6] It commonly affects patients with a darker complexion, but it may occur in all skin types.[10,11] These lesions are characterized by shades of brown that are spread on areas of previous trauma or inflammation.[10,11] The lesions are usually asymmetric, although symptoms like pruritus may be reported, especially if the inflammatory process is still active.[10]

Lichen planus and lichen sclerosus as well as lichen simplex have been described as a possible cause for hyperpigmentation.[6,10,11] Treating the underlying disease can reduce the advance of PH and relieve the patient of irritating symptoms, but the hyperpigmentation may not disappear at all.[10]

1.2.5 Gendodermatoses Characterized by Lentigines

There are a number of lentiginosis syndromes that involve also the genital mucosa and resemble clinically GM. Such syndromes should be always considered in the differential diagnoses of genital pigmentation. [52]

1.2.5.1 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant inherited condition that is associated with mucocutaneous pigmentation, especially on oral, buccal, nasal and perianal regions.[53] Besides these skin lesions, it is also characterized by intestinal polyposis with a prevalence of the small intestine and a significant higher predisposition to cancer.[52,53]

1.2.5.2 Laugier-Hunziker Syndrome

Laugier- Hunziker syndrome is an uncommon disorder of acquired hyperpigmentation of the oral and genital mucosa,[54] the skin of the palms and soles.[52] In many cases, the presence of longitudinal melanonychia is reported.[55] This condition is benign, but it is important to distinguish from possible hyperpigmentation disorders with an increased risk for cancer.[56]

1.2.5.3 LEOPARD Syndrome

LEOPARD syndrome is an autosomal dominant inherited disorder, the name is an acronym for its main symptoms: L (lentigines); E (ECG abnormalities); O (ocular hypertelorism); P (pulmonary stenosis); A (genital abnormalities); G (growth retardation) and D (deafness).[57] Multiple lentigines usually occur on the upper body, face and neck, the oral and genital mucosa, the extremities are usually spared.[52,57] Not all symptoms manifest at the same time, making the diagnosis difficult in patients with only a few phenotypical features.[57]

1.2.5.4 Carney Complex, NAME Syndrome and LAMB Syndrome

All these syndromes have similar characteristics and share the manifestation of atrial myxomas.[58] Carney complex is an autosomal dominant inherited disorder and features multiple hyperpigmented lesions on the skin and mucosa, myxoma of the heart, skin and other regions, and several other tumors of the endocrine system.[59,60] The NAME syndrome (nevi, atrial myxoma, myxoid neurofibroma and ephelides) and LAMB syndrome (multiple lentigines, atrial myxoma, mucocutaneous blue nevi) are acronyms and share similar symptoms with the Carney Complex.[61,62] In the past, a differentiation was made between these syndromes, today they are classified under the synonym Carney complex.[59,60]

1.2.5.5 Bannayan-Riley-Ruvalcaba Syndrome

The Bannayan-Riley-Ruvalcaba Syndrome is of autosomal dominant inheritance due to a PTEN gene mutation.[63,64] The syndrome includes the Riley-Smith, Bannayan-Zonana and Ruvalcaba-Myhre-Smith syndromes, out of which the name is formed.[65] Typical symptoms of the syndrome are macrocephaly, lesions of hyperpigmentation on the penis and polyposis of the intestine.[63,65]

1.2.6 HPV Associated Lesions

1.2.6.1 Condylomata Acuminata

Concylomata acuminata are genital warts and the most common sexually transmitted disease, caused by an infection with low risk- human papillomavirus (HPV).[66] This virus is highly contagious and transmitted via skin contact of infected skin or mucosa.[67] Genital warts manifest as skin-colored or hyperpigmented, flat, verrucous or papillomatous lesions and can appear on infected skin and mucosa, such as on the vulva, penis, perianal region, groin and suprapubic area.[10,68]

1.2.6.2 Vulvar Intraepithelial Neoplasia (VIN)

Vulvar intraepithelial neoplasia is a dysplastic disorder of the vulva, with a certain risk of progression towards squamous cell carcinoma (SCC).[69] It can be categorized into two groups: the first mainly affecting young women with multifocal lesions and high-risk HPV association, and the second in older women, mostly single lesions, with history of vulvar dermatitis, and no association with HPV.[69,70] These lesions can be flat, plaques or papules and with different coloring, sometimes brown and hyperpigmented.[10,69,70]

1.2.7 Other Rare Diseases

Angiokeratoma: These are benign lesions due to vascular ectasia predominantly in the papillary dermis with hyperkeratosis of the epidermis.[71,72] They appear as solitary or multiple, red, sometimes brown or black papules.[10,72]

Seborrheic keratosis: Seborrheic keratoses are common benign tumors on the trunk and face of elderly persons, but they are seldom seen on the genital region.[73-75] They manifest as skin-colored, brown or black lesions with a raised, verrucous surface and well defined borders.[73,76]

Pigmented basal cell carcinoma: Basal cell carcinoma (BCC) is a malignant skin tumor, which grows locally invasive, but usually does not metastisize.[77,78] Although it is the most frequent non-melanoma skin malignancy, it rarely develops on the genitals.[78-80] Although tumors are often non-pigmented, pigmented variants do exisit.[10,81] In these cases, they share clinical features with melanoma.[81,82]

1.3 Aims of this Study

Pigmented lesions on the genital area can be a diagnostic challenge for the clinician and may cause concern and uncertainty in the patient.[3] The similar clinical appearances of GM with other causes of pigmentation make a clear distinction between benign and malignant lesions difficult.[3-5] Suffice to say, that early diagnosis and adequate treatment are the mainstay in reducing morbidity and mortality of melanoma, while other causes of hyperpigmentation do not require invasive procedures and can be managed conservatively.[5]
In this retrospective study, we aimed to assess the epidemiological and clinical characteristics of GM in both, men and women, and to compare it with other causes of pigmentation on the genitals in order to gain further insights into the frequency, clinical features, associated co-morbidities and duration of lesions. The evaluation according to age, location site, size, histopathological findings as well as dermatoscopic pattern should help to better differentiate benign melanosis from other tumors including melanoma.

2 Material and Methods

2.1 Literature Search

The search for literature started in March 2017 and continued until July 2017. During this time, internet databases were consistently looked through to find recent articles on the topic. Databases used for the search were UpToDate and PubMed. UpToDate also served as a good source to give a brief overview of the matter and to read up on the subject. The following key words were used for the literature search: „benign vulval melanosis", "vulval melanosis", "penile melanosis", "genital melanotic macule", "genital melanosis", "genital lentitgo", "mucosal melanosis", and "mucosal lentigo". Because not all articles were available for free or via the library of the University of Graz, the focus was made on original and review articles.

2.2 Data Search

The database of the Department of Dermatology at the Medical University of Graz was searched for patients with a diagnosis or differential diagnosis of „genital melanosis" attending the clinic between January 2010 and June 2016. For each patient, type of diagnosis (clinical vs. histopathological), gender, age, anatomical site, diameter and history of the lesions and duration of the observation period were collected. We included only patients from which a digital photography of the lesion was available. The photography was performed irrespective of the study out during the routine clinical visits. However, all patients gave a written signed inform consent prior to the photography. Digital images included a clinical overview of the lesion and if available, also a dermatoscopic image.

2.3 Lesions Characteristics

Lesions were classified based on their final histopathological diagnosis. In addition, the clinical differential diagnosis as well as specific location and clinical characteristics based on a review of the clinical images was analysed. The location of lesions in women was categorized into (i) labia minora, which also includes introitus of the vagina, (ii) labia majora, including the commissure, and perianal region including the perineum. Lesions in men were divided into (i) glans penis, (ii) penis shaft, (iii) preputium, (iv) scrotum and (v) perianal region.

Clinically, lesions were categorized as solitary or multifocal/patchy macules. Solitary lesions were defined as, solitary macules without other neighboring pigmentation, whereas multifocal lesions presented were defined as confluent and patchy macules that involved more than one area.

To evaluate the age distribution of our patients, a total of eight age groups were defined. The first age group starting at ages < 20 years, followed by the age group of 21 to 30 years and going up in 10-year intervals to the age group of 81 to 90 years. Moreover, the size of the lesion was subdivided into 3 groups: < 10 mm, 10-20 mm, > 20 mm.

Analysis included assessment of patients' demographics and lesions characteristics in terms of absolute numbers and frequencies in percentage. In addition, we compared these data between women and men.

2.4 Statistic Analysis

Records were categorized using Microsoft Excel 2016. This program was also used for the statistical calculations such as average age, standard deviation, percentages, and statistical significance, which was considered as $p<0.05$. Furthermore, it was used to create diagrams and tables enabling a graphical view of the results of our study.

3 Results

3.1 General Results

3.1.1 Patient Demographics

During the study period from January 2010 to June 2016, overall 79 patients, consisting of 64 (81%) women and 15 (19%) men, with a diagnosis or differential diagnosis of „genital melanosis“, were included. The average age of the cohort was 52 ± 15,7 years (range 15 to 83). The majority of patients (n=19; 24%) were grouped into the age group 51 to 60 years. The age distribution of patients according to age groups is shown in Figure 1.

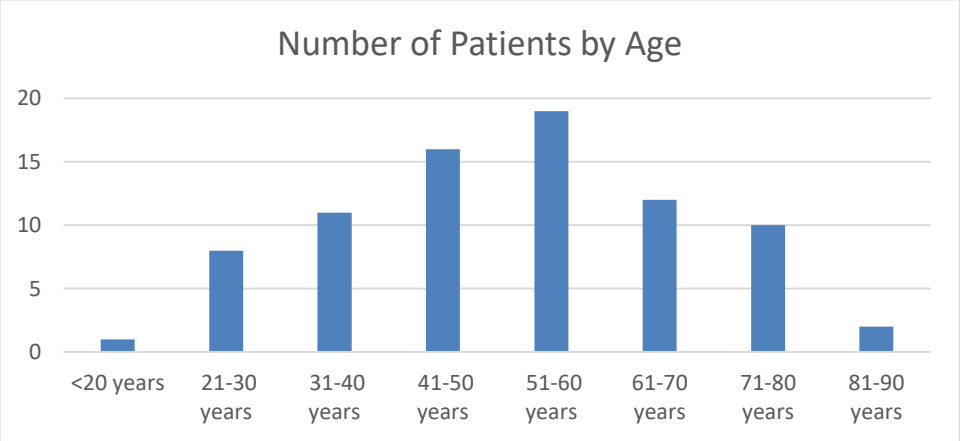

Figure 1 Number of all patients sorted by age

3.1.1.1 Co- Morbities

Co-morbities relating to the genital region or other skin regions were also analysed for our cohort. In 36 patients (46%), no remarkable medical history regarding the skin was mentioned. In 18 cases (23%), review of the medical charts revealed the presence of multiple partially dysplastic nevi. Seven patients (9%) had recurrences of genital pigmentation, after having lesions removed in the past. Irritation in the genital region was mentioned by 3 patients (4%), and 4 patients (5%) were diagnosed with lichen sclerosus et atrophicans or lichen simplex in the genital area. Seven patients (9%) have been in treatment for suspect diagnosis of melanoma, 4 (5%) of which in the genital area, and 3 (4%) on other skin sites. Four patients (5%) had undergone surgery for phimosis. Less frequent co-

morbities were HPV infection (n=2, 3%), morphea (n= 2, 3%), oral mucosal melanosis (n= 2, 3%), Bowens's disease (n=1, 1%), psoriasis (n=1, 1%), and vitiligo (n=1, 1%).

3.1.2 Lesion Demographics

In 5 patients (6%) with a skin biopsy, histopathology revealed a diagnosis of a melanocytic nevus (n=3, 4%), melanoma in situ (n=1, 1%) and verruca seborrhoica (n=1, 1%). The majority of the cases were diagnosed with GM (n=74, 94%).

With regard to morphology, most patients featured multifocal or patchy genital lesions (56 patients, 71%), whereas unifocality was less common (23 patients, 29%).

Of the overall 79 cases, 47 lesions (59%) occurred solely on the labia minora, followed by 8 (10%) multifocal lesions on the labia minora and majora, 7 lesions (9%) on the glans penis, 5 cases (6%) on the labia majora, and 4 cases (5%) on the penile glans and shaft. Less common appearances of genital pigmentation were found on the glans and prepuce (n=2, 3%), perianal region (n=2, 3%), penile glans and prepuce (n=2, 3%), and penile shaft (n=1, 1%). One patient (1%) had a large multifocal lesion, which affected the penile glans, shaft, prepuce and scrotum.

In 36 patients (46%), the size of the lesions was unable to be determined. In 23 cases (29%), the lesions were less than 10 mm in diameter, 16 patients (20%) featured lesions between 10 – 20 mm, and only 4 cases (5%) showed lesions larger than 20 mm.

Melanosis	Melanocytic Nevus	Melanoa in Situ	Verruca Seborrhoica	Single Lesions	Mutifocal/ Lesions
74 (94%)	3 (4%)	1 (1%)	1 (1%)	23 (29%)	56 (71%)

Table 3 Diagnoses and lesion occurrence of all patients

3.1.3 Management

Of the 79 patients included, 64 patients (81%) had undergone histopathological examinations of their pigmented lesions. In the remaining 15 patients (19%), the diagnosis was based on clinical examination alone. Interestingly, while a biopsy for histopathological diagnosis was performed in 57 (89.1%) out of 64 women, skin biopsies were obtained only in 7 (46.7%) out of the 15 men. All patients were asked to regularly self-check their lesions for any changes in size, color or appearance. Follow up at the clinic was carried out for 62 patients (78%) with an average time of 4 ± 3.1 years. The remaining 17 patients (22%) were referred to their respective dermatologists for regular follow- ups.

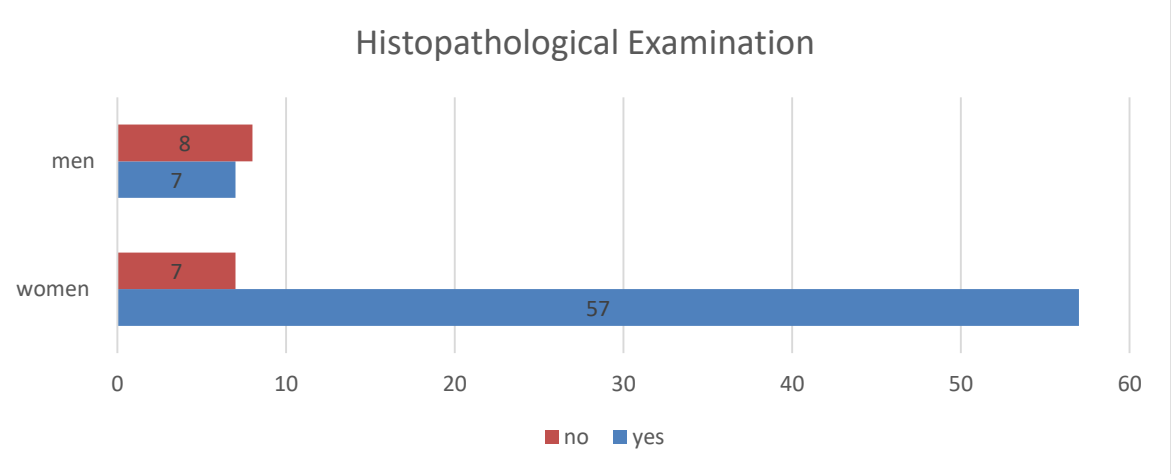

Figure 2 Total number of histopathological examination

3.1.4 Duration of Disease

Of our entire cohort, the average time of existence of the pigmented genital lesions was 6.9 years ± 5.8 years. In 26 cases (33%) the onset of disease could not be made. In 17 patients (21%) pigmentation of the genital has just been noticed recently, less than 2 years. A large group of patients (n=22, 28%) have known about their pigmentation between 2 - 10 years, 12 patients (15%) for 10 – 20 years, and only 2 patients (3%) have known of their lesions for more than 20 years. When split by gender, the average duration in men (15.3 years ± 5.5 years) was significantly longer than in women (5.8 ± 4.9 years) ($p<0.01$).

3.2 Specific data: Gender-related Differences in GM

3.2.1 Female Patients

A total of 64 women were included in our study. The most common diagnosis was GM in 61 patients (95%), whereas 2 patients (3%) and 1 patient (2%) had a melanocytic nevus and verruca seborrhoica, respectively.

3.2.1.1 Patient Demographics

Considering only patients with GM, a large portion featured multiple lesions (n=46, 75%), the remaining (n=15, 25%) were characterized as solitary macules (Fig. 7).

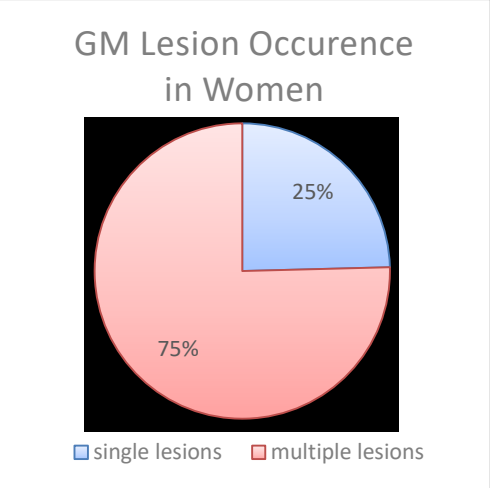

Figure 3 GM lesion appearance in women

The data obtained from the women diagnosed with melanosis showed mostly middle-aged patients, the average age of female patients was 54.4 ± 14.5 years (range 24 to 83 years). The majority of women were between the ages of 41-70 years, 14 of these women (23.0%) were in the age group of 41-50 years, 16 women (26.2%) in the age group of 51-60 years and 10 patients (16.4%) in the age group of 61-70 years. Fewer women were either younger than 41 or older than 70 years. Three women (4.9%) represented the age class of 21-30 years, eight women (13.1%) the group of 31-40 years, eight women (13.1%) the group of 71-80 years and one patient (3.3%) is counted into the age group of 81-90 years.

Overall 28 women (46%) had no remarkable medical history. Seven women (11%) had recurrences of previously removed genital lesions. One woman had a diagnosis of melanoma arising on GM, but subsequent re-biopsies did not confirm the diagnosis of melanoma but revealed patterns consisting with the diagnosis of GM. In further 3 (5%) women, clinical features were suggestive of melanoma but

biopsies did not confirm the clinical suspect. Two women (3%) also exhibited melanosis on the oral mucosa.
Interestingly, 14 (23%) of patients had GM in association with multiple melanocytic nevi, including dysplastic nevi. Further associated co-morbidities were lichen sclerosus et atrophicans or lichen simplex in 4 patients (7%), HPV induced warts in 2 patients (3%), morphea (2 patients, 3%), Bowen's disease (1 patient, 2%), and irritation of the outer genital (2 patients, 3%).

3.2.1.2 Lesion Characteristics

The analysis of demographic and clinical data of the women in our cohort revealed following results: In 44 (72.1%) of women, GM involved the labia minora. The simultaneous occurrence of lesions on the labia minora and majora were the second most common location sites for GM and was seen in 8 women (13.1%). Five women (8.2%) had solitary lesions of the labia majora and 2 (3.3%) exhibited pigmented macules at the perianal region. One woman (3.3%) presented extensive pigmented lesions on both the labia minora, labia majora and the perianal region.

Most lesions appeared as light to dark brown, partially confluent macules with some exhibiting additional shades of black, grey or blue. They often appeared patchy with areas of hyper and hypo-pigmentation. Some of the lesions covered large areas with confluent macules, while in other women, pigmentation appeared as small speckled macules. In dermatoscopic analysis, the most common structures were structureless, parallel, globular, linear and reticular- like patterns. All lesions presented as ABCD positive pigmentation, which is defined by asymmetry, border irregularity, color variation and diameter larger than 6 mm and used to differentiate between benign and malignant pigmented skin lesions.[83] Approximately half of the patients, 29 women (47.5%), had lesions that were not measured and therefore not available for statistical analysis. Of the remaining women, 18 (29.5%) had macules smaller than 10 mm, eleven patients (18.0%) had lesions between 10-20 mm and three women (4.9%) featured lesions larger than 20 mm in diameter.

3.2.1.3 Management

In 54 cases (89%) biopsy was taken for histopathological diagnosis, 7 women (11%) did not obtain this procedure. The majority of women were advised for regular self-examinations. Moreover, all women were scheduled for regular follow up visits at the Department of Dermatology at the Medical University of Graz (n= 51, 84%) or at their local respective dermatologist (n=10, 16%). The mean time of follow up at the clinic was 4.2 ± 3.2 years. Five women (8%) had their lesions surgically removed, either for diagnostic or for cosmetic reasons, and one woman (2%) had undergone laser treatment to avoid further check-ups.

3.2.1.4 Duration of Disease

Out of the 61 cases, 17 women (29.5%) could not recall any history of the existing lesions. Of the remaining 44 women, the majority recalled the existence of the pigmentation since less than 10 years, with an average time between first notice and presentation at our clinic of 5.8 years ± 4.7 years. Macules that have been noticed less than two years prior to the visit was recorded in 14 cases (23.0%), 21 patients (34.4%) claimed they have known about their lesions between 2 – 10 years and 8 (11.5%) women were aware of having GM for the past 10 - 20 years. One patient (1.6%) had GM since more than 20 years.

3.2.2 Male Patients

Our cohort included 15 men, of whom 13 men (86.7%) with a diagnosis of GM, 1 with a melanocytic nevus (6.7%) and 1 man with a histopathological diagnosis of melanoma in situ (6.7%).

3.2.2.1 Patient Demographics

Men diagnosed with melanosis represent the largest group out of the male patients seeked out for this study. Melanosis prevailed as multifocal, patchy pigmentation in 10 cases (77%), whereas single lesions were observed in 3 (23%) of men. The data set obtained shows rather young patients. The mean age of men diagnosed with GM was 38.5 ± 16.3 years. Nine patients were under the age of 41 (69.2%). The largest amount of these being the 21 - 30-year olds, these five patients made up 38.5% of the men diagnosed with melanosis, three patients (23.0%) were in the age group of 31-40 years and one patient (7.7%) was under the age of 21. There was one patient (7.7%) in each of the remaining age categories (41 - 50 years, 51 - 60 years, 61 - 70 years, 71-80 years).

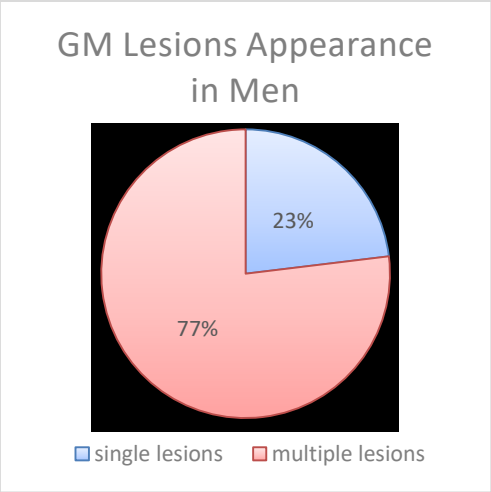

Figure 4 GM lesions appearance in men

Co- morbities relating to the genital region or other skin regions were also analysed for our male cohort. Of the 13 men, 5 (38%) had no remarkable history, while 4 (31%) revealed a history of circumcision during their childhood. Four men (31%) had multiple, partially dysplastic melanocytic nevi and 1 patient (8%) complained about recurring balanoposthitis for the last 20 years. Less frequent co-morbities was vitiligo (n=1, 8%) and psoriasis vulgaris (n=1, 8%).

3.2.2.2 Lesion Characteristics

The most common site for the emergence of GM in men was observed on the glans penis, five patients (38.5%) presented with a lesion involving solely on the glans. Four patients (30.7%) with multifocal macules on both the glans penis and penis shaft, and 2 patients (15.4%) had manifested lesions on the glans penis with the prepuce also being affected. Only one patient (7.7%) presented with GM on the penile shaft, and one patient (7.7%) had widespread lesions on the glans penis, penile shaft, and scrotum.

GM presented mainly as dark brown macules, some with grey pigmentation, that appeared patchy and with irregular, undefined borders. In five cases, pigmentation

involved the whole circumference of the penis shaft. Dermatoscopically, they appeared as structureless, globular, linear and reticular- like patters. In only one man (7.7%), the lesion was smaller than 10 mm, while four men (30.7%) had lesions measuring between 10 - 20 mm in size and one patient (7.7%) had a lesion exceeding 20 + mm. Data about the clinical diameter of the lesion ware missing in 7 patients (53.9%).

3.2.2.3 Management

In 5 cases (38.5%) biopsy was taken for histopathological diagnosis, 8 cases (61.5%) were clinical diagnoses and therefore, close follow up was made in in order to reassure a benign course. In none surgical removal was performed. Moreover, all patients were advised to regularly perform self-examination and to seek medical consultation in the case of changes in size, color, or appearance. Follow- ups were carried out in nine patients (69%) at the clinic, with an average time of follow up 3.3 ± 2.4 years, while 4 patients (31%) were referred to their attending dermatologist.

3.2.2.4 Duration

Out of the 13 men with GM, 6 men (61.5%) could not recall any history of the pigmentation. Out of these, six mentioned the lesions first appeared several years ago, but could not make any exact claims. The remaining five patients had an average duration of existence of their GM of 17.4 years ± 3.3 years, four men (30,7%) mentioned the lesions have existed between 10 – 20 years, while only one patient (7,7%) has known about the hyperpigmentation for more than 20 years.

3.2.3 Comparison of Data

3.2.3.1 Age

Women with GM were on average older than men (medium age = 54.4 ± 14.5 years versus 38.5 ± 16.3 years, respectively). There was a difference between both genders with regard to the distribution per age group: while the majority of men were aged between 21 to 30 years (Figure 2), most women were assigned to the age group 51 to 60 years (Figure 3).

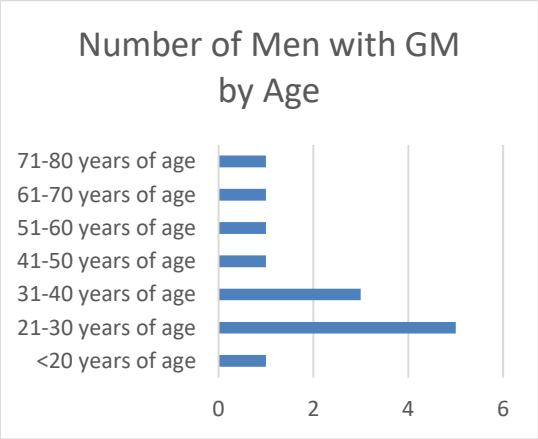

Figure 5 Number of male patients sorted by age

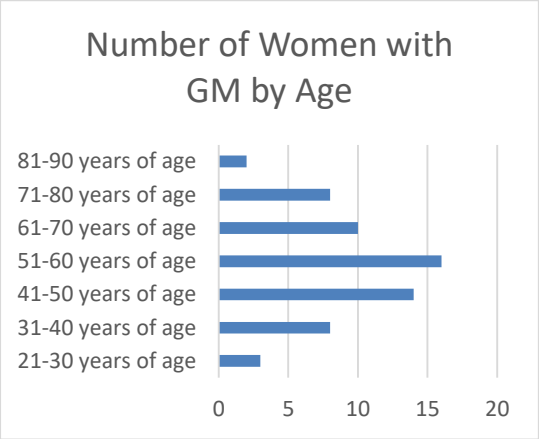

Figure 6 Number of female patients sorted by age

3.2.3.2 Uni- Mutifocality

Although men (n=13) represented a smaller cohort than women (n=61), the majority of GM lesions presented as multifocal lesions in both genders (men n=10, 77% versus women n=46, 75%). Only approximately one-fourth featured solitary lesions, 3 men (23%) and 15 women (25%).

Melanosis Patients	Total Number	Solitary Lesions	Multifocal Lesions
Women	61 (100%)	15 (25%)	46 (75%)
Men	13 (100%)	3 (23%)	10 (77%)
Total	**74**	**18**	**56**

Table 4 Number, frequency and occurrence of GM lesions sorted by gender

3.2.3.3 Size

In both men and women, size of the lesions could not be determined in nearly half of the patients (men n=7, 53.9%; women n=29, 47.5%). Interestingly, a large part of women tended to have smaller lesions than men, 29.5% (n=18) of women presented with macules measuring < 10 mm compared to only 7.7% (n=1) of men. Lesions measuring between 10 - 20 mm were seen in 30.7% (n=4) of men, however only 18.0% (n=11) in women. In both genders, lesions larger than 20 mm were seldom, 7.7% (n=1) in men and 4.9% (n=3) in women.

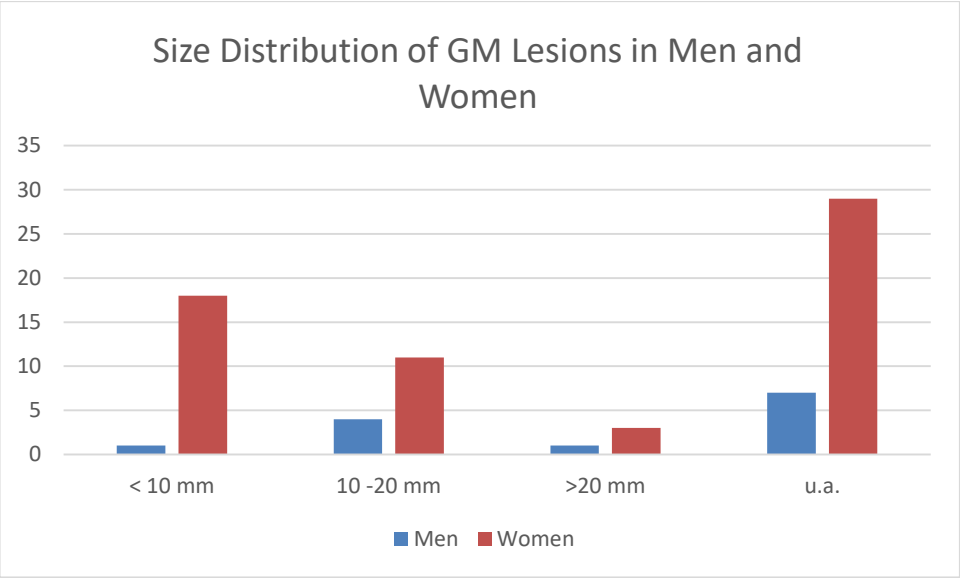

Figure 7 Size distribution of GM lesions in men and women

3.2.3.4 Management

Regular follow-ups were carried out in all GM patients, but follow up visits were more commonly hospital/university based in women compared to men, who were referred to practice based dermatologists (n= 51, 84% versus n=9, 69%, respectively). The average time of follow-up visits did have a significant difference between both genders, 4.2 years for women and 3.3 years for men (p=0.4). Procedures for removal of the genital pigmentation were performed only in women. Overall 5 women (8%) were treated surgically and in 1 woman (2%), GM was treated with laser.

3.2.3.5 Duration

Men had a mean duration of their GM lesions for 17.4 years ± 3.3 years, while women presented with an average time of 5.8 years ± 4.7 years at the clinic. This shows a significant difference ($p<0.01$). The majority of men, who could recall the first appearance of their lesions (n=4, 30.7%) referred to a first onset 10 - 20 years ago. The majority of women (n=21, 34.4%) noticed their lesions much between 2 to 10 years.

3.3 Specific Results: Patients with Other Causes of Pigmentation

A total of 5 patients featured diagnoses non-related to GM. These other diagnoses were: melanocytic nevus (n=3), melanoma in situ (n=1) and verruca seborrhoica

(n=1). Due to the small cohort of patients with non-GM, these cases will be analysed separately.

3.3.1 Melanocytic Nevi

Three patients were histopathologically diagnosed with a melanocytic nevus on the genital region and were included in our cohort, involving two women (67%) and one man (33%). The average age for these patients was 58 ± 2.2 years (range 56 to 61 years). All lesions (n=3, 100%) presented as solitary macules, two measured less than 10 mm, one between 10-20 mm (average size 7 mm ± 5,9 mm). The macules were located on the glans penis of the man (n=1, 33%), and labia minora of the women (n=2, 67%). Macroscopically, the lesions appeared as light to dark brown macules, with homogenous pigmentation, while one patient featured hypopigmentation in the center, after biopsy, and irregular borders. In dermatoscopy, the lesions exhibited either a reticular pattern or a globular pattern around the outer border of the lesions, there were no signs of malignancy using the ABCD algorithm.
In both women, the nevi were first detected by the treating gynecologists, whereas the nevus in the man was self-detected and first noticed about 5 years ago. Since then he remained under regular dermatological surveillance without any significant changes during this time.

3.3.2 Melanoma

One 44-year-old man, with history of melanoma in situ excised 4 years previously on the glans penis, sought consultation because he recently noticed a solitary brown macule, less than 10 mm in diameter on the glans. Histopathological examination showed lentiginous melanocytic hyperplasia, but a melanoma in situ could not be ruled out. Due to the patient‘s medical history, treatment with cryotherapy was initiated. Follow up visits for the first year showed no sign of recurrent pigmentation.

3.3.3 Verruca seborrhoica

A 72-years old woman with a personal history of melanoma in situ on her breast, was referred to our clinic by her gynecologist because he noticed a pigmented macule on her labium minorum during a routine control. Clinically, the lesion

presented as single, brown, homogeneous pigmented macule with a diameter of less than 10 mm. Because melanoma could not be ruled out with certainty, the lesion was removed. Histopathology revealed a diagnosis of verruca seborrhoica.

Clinical Data Women	Melanosis (n=61)	Melanocytic Nevus (n=2)	Verruca Seborrhoica (n=1)
Location			
Labia Minora	44 (72.1%)	2 (100%)	1(100%)
Labia Majora	5 (8.2%)		
Labia Minora + Majora	8 (13.1%)		
Perianal Region	2 (3.3%)		
Lab. Min./ Maj. + Perianal Region	2 (3.3%)		
Age			
21-30 years	3 (4.9%)		
31-40 years	8 (13.1%)		
41-50 years	14 (23.0%)		
51- 60 years	16 (26.2%)	1 (50%)	
61-70 years	10 (16.4%)	1 (50%)	
71-80 years	8 (13.1%)		1 (100%)
81-90 years	2 (3.3%)		
Size			
<10 mm	18 (29.5%)	2 (100%)	1 (100%)
10 – 20 mm	11 (18.0%)		
>20 mm	3 (4.9%)		
unavailable	29 (47.5)		
Histopathology Examination			
available	54 (88.5%)	2 (100%)	1 (100%)
unavailable	7 (11.5%)		
Time of Duration			
<2 years	14 (23.0%)	1 (50%)	1 (100%)
2-10 years	21 (34.4%)		
10-20 years	8 (13.1%)		
>20 years	1 (1.6%)		
Unknown	17 (27.9%)	1 (50%)	

Table 5 Clinical data of pigmented lesions in women

Clinical Data Men	Melanosis (n=13)	Melanocytic Nevus (n=1)	Melanoma in Situ (n=1)
Location			
Glans Penis	5 (38.5%)	1 (100%)	1 (100%)
Penile Shaft	1 (7.7%)		
Glans Penis and Shaft	4 (30.7%)		
Glans Penis and Prepuce	2 (15.4%)		
Glans, Shaft, Prepuce, Scrotum	1 (7.7%)		
Age			
< 21 years	1 (7.7%)		
21-30 years	5 (38.5%)		
31-40 years	3 (23.0%)		
41-50 years	1 (7.7%)		1 (100%)
51- 60 years	1 (7.7%)	1 (100%)	
61-70 years	1 (7.7%)		
71-80 years	1 (7.7%)		
Size			
<10 mm	1 (7.7%)		1 (100%)
10 – 20 mm	4 (30.7%)	1 (100%)	
>20 mm	1 (7.7%)		
unavailable	7 (53.9%)		
Histopathology Examination			
available	5 (38.5%)	1 (100%)	1 (100%)
unavailable	8 (61.5%)		
Time of Duration			
<2 years			1 (100%)
2-10 years		1 (100%)	
10-20 years	4 (30.7%)		
>20 years	1 (7.7%)		
Unknown	8 (61.5%)		

Table 6 Clinical data of pigmented skin lesions in men

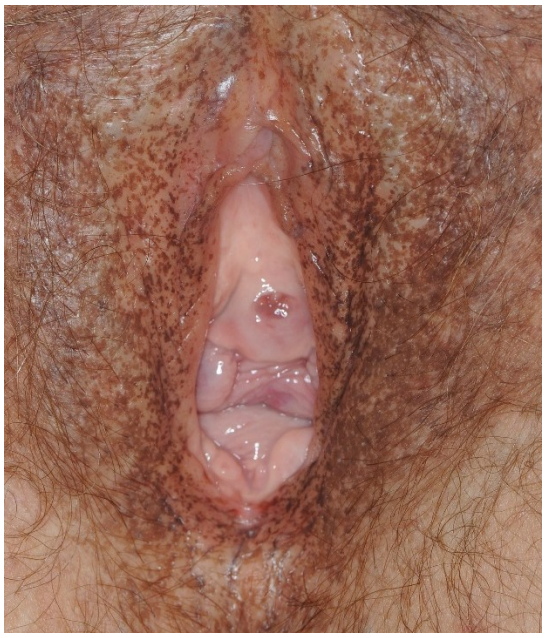

Figure 8 Vulvar "speckled melanosis"

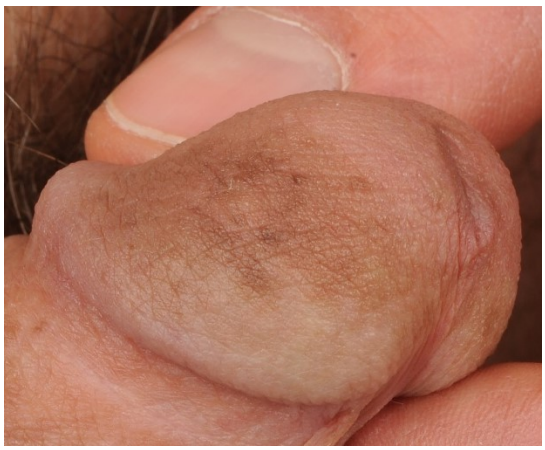

Figure 9 Genital melanosis of the glans penis with light to dark brown pigmentation and poorly demarcated borders

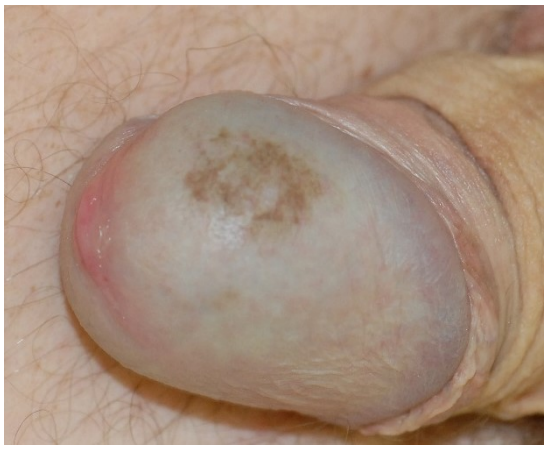

Figure 10 Solitary melanocytic nevi on the glans penis. Hypopigmentation in the middle due to past biopsy, reticular pattern in the marginal area

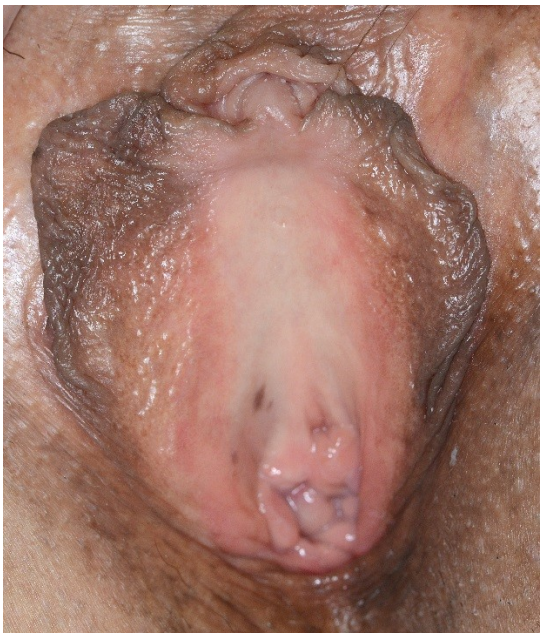

Figure 11 Hyperpigmented labia minora with a brown, melanocytic nevi near the introitus

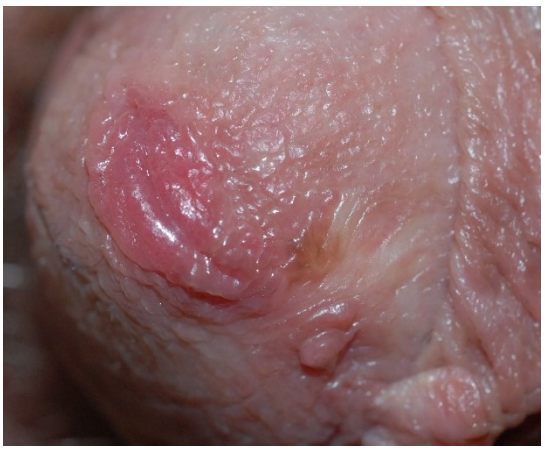

Figure 12 Single lesion of a melanoma in situ on the glans penis with irregular borders and heterogeneous brown pigmentation

4 Discussion

In this study, we evaluated patients' demographics and lesions characteristics of consecutive patients attending a single university center because of genital pigmentations.

The average age of our entire cohort was 52 ± 15.7 years and women presenting with pigmented genital lesions were significantly older (mean age = 54.8 years) than the men (mean age = 40 years; p<0.01). Women in our study were older, compared to the study by Rock et al., who reported an average age of 44 years in patients with vulvar lentigines.[33] In contrast, our findings in men are in line with the study by Revuz et al[24] who described 5 cases of penile melanosis with an average of 39.8 years and by Barnhill et al [9] who reported a mean age of 42.2 years in his cohort.

The most common site for GM in our patients were the glans penis in men (n=5, 38.5%) and labia minora in women (n=44, 72.1%). A similar distribution has been reported by Barnhill et al.[9], Revuz et al.[24] and Murzaku et al.[5]
In their studies they noticed however that GM may affect more than one location. This observation is supported by our study as we also observed pigmented macules on different areas of both, the female and male genitalia. Notably, although melanosis of the perineum and preputium are considered rare[12,22], we observed 2 patients with perianal GM and 3 men with GM involving the preputium .

Another noteworthy finding in our study is that the majority of GM presented as multifocal or patchy pigmentation, and only 23 as single lesions. There were no gender-specific differences regarding multi-or unifocality. However, mean duration of genital pigmentation was significantly longer in men compared to women (15.3 years ± 5.5 years in male vs. and 5.8 ± 4,9 years, respectively; p<0.01).
In line with previous studies,[9,24] lesions in our study were light to dark brown, sometimes associated with grey, black or even blue coloration. Often an asymmetry of colors and mottled borders were seen. It should be noted, that for multifocal GM, the ABCD rule gives false positive result in the majority of cases

and should be therefore considered an inadequate method for the clinical recognition of melanoma at genital sites.[26]

Dermatoscopy can aid the diagnosis and differential diagnosis of pigmented genital macules due to well-defined dermatoscopic structures of GM. Clues for the diagnosis of GM are structureless, parallel, globular, and reticular pattern. Ronger et al. reported that these dermatoscopic patterns, along with the so-called ring-like pattern, are most commonly observed in benign genital lesions like melanosis and nevi.[26]

Despite the variability in the clinical appearance, also the size may vary significantly between patients. Lesions may be small up to more than 20 mm in diameter.[3],[22] We observed such large lesions (i.e. > 20 mm) in 3 women and one men of our cohort. With regard to smaller lesions (< 20 mm), women in our cohort tended to have smaller lesions than men, as nearly 30% (n=18) of women with GM presented with macules measuring < 10 mm compared to only 7.7% (n=1) of men. This contrast to the findings reported by Cengiz et al., who described lesions measuring less than 10 mm in 68,4% of women and 71.5% of men.[20]
This difference may be related to different referral settings between the study by Cengiz et al and our study, as our clinic is a tertiary referral center. Thus, it is likely that larger lesions, which are often more worrisome or difficult to treat, are over-represented in our cohort,
Up to date, little is known about associated co-morbidities and the occurrence of GM. Trauma and irritation, as well as PUVA therapy and hormonal factors in women, have been proposed as possible causes.[9,11,13]
Notably, 4 out of 13 men with GM in our study had circumcision in their childhood due to phimosis, and one had recurring balanoposthitis for 20 years. This observation suggests that chronic inflammation may function as stimulus for a reactive hyperpigmentation, at least in men.

Of particular interest is the fact that some suspect a higher incidence of GM in patients with melanoma.[8] In fact, in our study 6 patients had a personal history of melanoma, but even more remarkable, 15 patients had a high nevus count. The latter is the most important risk factors for melanoma. However, due to the paucity

of data reporting such association, we are unable to further compare our findings with current literature.

With regard to the management, studies suggest that GM usually remain stable over time although new lesions may develop.[1,3] Revuz et al reported two cases showing enlargement over time. [24] These observations are also supported by our data, as only 9 (12%) of lesions revealed a darkening of pigmentation or increase in size during follow up.

We observed a significant difference between the duration of genital pigmentation between men and women. As such men reported an average duration of 17 years, while it was 6 years for women. Interestingly, Barnhill et al also reported on a longer duration of penile melanosis compared to vulvar melanosis (14.4 years versus 6.6 years, respectively).[9] Also our analysis of mean follow- up time (women 4.2 years, men 3.3 years) is similar to prior studies, Haugh et al. reported on an average follow-up time of 30.5 months.[8] A possible explanation of the gender-related differences regarding the duration of disease may be related to an earlier self-detection pattern in men compared with women.

With regard to the non-melanosis cases in our study, it should be highlighted that all presented as solitary macule, which contrasts to the high frequency of multifocality in GM. Similar findings were reported by Ferrari et al. in their study on vulvar pigmentations. In their study, they described melanoma and nevi more often as solitary lesions, while vulvar melanosis occurred in 61% of their cases as multifocal and 39% as solitary macules.[28] Ronger-Savle et al. examined pigmented vulvar lesions and their findings show, that all cases of benign melanosis were multifocal, whereas most nevi and melanomas were unifocal.[26] They proposed an algorithm for pigmented vulvar lesions to determine possible malignancy and, among other criteria, one of the variables was defined as of unilfocality and unilateralism.[26]

The findings of all three cases diagnosed with melanocytic nevi in our cohort (average age 58 years) showed that the patients were older than in other studies, which had a mean age of 39.3 years.[20] The male patient diagnosed with

melanoma in situ was younger than the reported occurrence of penile melanoma (between the sixth and seventh decades),[47,50] however, in recent years reports of younger patients have been made. There are only few cases of penile melanoma reported up to no. Oldbring et al. examined 6 cases of penile melanoma and described the lesion's diameter of approximately 1-3 cm in diameter.[47] Our case of recurrent melanoma in situ lacked specific pattern of melanoma, but the correct diagnosis was facilitated by the history of a previous melanoma at the same site.[26,47]

In conclusion, our study suggests some significant differences in the epidemiology and morphology of GM between women and men. Compared to women, men are usually younger and present with larger lesions of longer duration. GM in both genders presents in the majority of cases as large and multifocal pigmentation. The diagnosis is usually made by clinical and dermatoscopic examination, but biopsy for any suspicious area is recommended. Although preliminary, our pilot data suggest a possible association between chronic inflammation of the genitalia and multiple nevi and GM, but further prospective studies on a larger cohort are needed to better define such association.

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