

## Clinical and Histopathological Characteristics of Genital Melanocytic Nevi: A Report of 109 Cases and a Review of the Literature

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### Abstract

Melanocytic lesions on the genital area are rare and poorly documented; they occur more frequently on the vulva and less often on the perineum, pubic area, and male genitalia. Genital melanocytic nevi exhibit features similar to nevi occurring on other areas of the body; in addition, they display high clinical and histopathological variability and are mostly classified as common nevi. However, a benign subtype of genital nevi that occurs in young women is known as atypical melanocytic nevi. These nevi exhibit distinct morphological characteristics that sometimes overlap with those of cutaneous melanoma.

A retrospective systematic review was performed of 111 biopsy specimens of pigmented lesions on the vulva, perineum, pubic area, penis, and scrotum collected between 1998 and 2009 to assess their clinicopathological characteristics. In this sample, there were 101 cases of common genital melanocytic nevi, two genital melanotic macules, seven atypical melanocytic nevi, and one dysplastic melanocytic nevus; no cases corresponded to cutaneous melanoma. Of the 111 patients, 14.4% were male, and 85.6% were female with a mean age of 34.3 years. The female exhibited a larger number of atypical melanocytic nevi than the males. The nevi displayed melanocytic proliferation, forming irregular and coalescent nests with a loss of cellular cohesion at several sites in the rete ridges. Cytologic atypia was mild to moderate. Difficulties in the histological interpretation of these lesions remain to this day; thus, diagnosis relies significantly upon the experience and subjective judgment of pathologists to distinguish morphologically between atypical genital nevi and melanoma.

**Keywords:** Genital melanocytic nevi; Nevi of special sites; A typical genital nevi; Dysplastic nevi; Cutaneous melanoma

### Introduction

Genital pigmented lesions arise mainly on the vulva (labia majora, labia minora, and clitoris) [1-4], although they may occur less often on the perineum, pubic region, and male genitalia (penis and scrotum) [3,4]. Approximately one out of ten women with lightly pigmented skin will exhibit at least one pigmented lesion on the vulva in her lifetime [3-5]. Genital pigmented lesions include lentiginosis, blue nevus, common melanocytic nevus, Spitz nevus, dysplastic melanocytic nevus (DMN), and cutaneous melanoma (CM) [1,2]. Melanocytic nevi (MN) represent just 2.3% of pigmented lesions on the vulva [3,5]. As a rule, MN is detected on the grounds of a previous (personal or family) history of CM or DMN or during a routine gynecologic or urologic examination [5]. The scientific community has acknowledged clinical differences among melanocytic lesions based on their anatomical location for decades, and continued and increasing efforts are being devoted to correlate them with histological findings [6-8]. Genital melanocytic nevi (GMN) generally exhibit characteristics similar to nevi on other parts of the body. However, one GMN subtype known as atypical genital nevi (AGN) is characterized by the presence of atypical melanocytes and might resemble the appearance of DMN and CM [1,2,4,9]. Atypical melanocytic nevi of the genital type were first described by Friedman and Ackerman (1981) [10]. In 1988, Clark et al. [2] shortened the name of these nevi to atypical genital nevi (AGN), reflecting a concern with its histological characteristics, which might lead to a diagnosis of DMN or CM.

AGN is an MN subtype exhibiting benign behavior that appears on special sites [8], is rare (5% of MN are located on the genital area) [1,4], is found in young women, and displays distinct morphological

characteristics that sometimes overlap with those of CM [1,2,8,9]. Few studies in the literature have assessed the clinicopathological characteristics of this type of pigmented lesion [1,2,4,5,9].

Some AGN might pose difficulties for their histological interpretation [1,2,9,10] and could be diagnosed as CM, with consequent therapeutic and prognostic implications [9]. Anatomic pathology reviews found that one-third of AGN were previously diagnosed as CM [2]. The main motivation for our study was the lack of scientific publications reporting data on ethnically mixed populations (i.e., exhibiting phenotypic heterogeneity regarding skin pigmentation-a heterogeneous population) and the lack of clinicopathological studies performed in South America. It is critical to be able to recognize the characteristics of MN associated with the anatomical location in heterogeneous populations to distinguish CM from the vast majority of benign lesions that appear on the genitalia. We believe that the constitutional characteristics of heterogeneous populations are important for several countries due to globalization [11]. Therefore, this study will help raise awareness for pathologists in recognizing

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the clinicopathological characteristics of GMN, particularly AGN versus DMN and CM, to avoid unnecessary large surgical excisions in addition to the possible biopsy of the sentinel lymph node.

The aim of this study was to analyze the clinical and histopathological characteristics of GMN in an ethnically heterogeneous population.

## Materials and Methods

### Materials

This study consisted of a retrospective analysis of human tissue samples from patients from both genders presenting pigmented lesions on the genital area. The samples were fixed in formalin and processed in paraffin blocks. Anatomic pathology reports from between the years 1998 and 2009 of patients with lesions on the genital area (i.e., pubic area, vulva, perineum, penis, and scrotum) with histological diagnosis of lentiginosis, blue nevus, common GMN, AGN, Spitz MN, DMN, and CM were surveyed from the archives of the Pathology Department of the Sao Paulo School of Medicine–Federal University of São Paulo.

### Methods

Clinical data pertaining to genital melanocytic lesions, including the origin of specimens, gender, age, localization, size and recurrence of lesions, were collected for analysis. The original hematoxylin and eosin-stained slides were retrieved from the archive, and the initial diagnoses of the selected cases were reviewed by an experienced dermatopathologist (N.M.), who included the architectural characteristics of melanocytic proliferation [1,2,4,6,8,9], the cytological peculiarities of epidermal and dermal melanocytes [2,6,9,12-16], and the appearance of stroma [2,9] in the analysis.

### Architectural characteristics of the melanocytic proliferation in the dermal-epidermal junction (DEJ)

The following patterns of melanocytic proliferation were noted: (focal or diffuse) lentiginous proliferation and/or nests (defined as three or more cells) and/or (focal or diffuse) pagetoid proliferation and the presence or absence of a lentiginous epidermal component in the adnexa.

Regarding nests, their shape (oval, round, and irregular), localization, and coalescence (bridge formation) were analyzed, along with the presence or loss of cohesion between their component cells. In addition, the proportion of melanocytes that were both isolated and/or forming nests was calculated.

To establish the symmetry or asymmetry of the epidermal and/or dermal components, the definition proposed by the National Institutes of Health (NIH) Consensus Development Conference [17] was used, which classifies any non-round or non-oval lesion as asymmetric.

Whenever the dermal component was present, the presence of shoulders (melanocyte proliferation at the DEJ in three or more rete ridges in addition to the dermal component) was assessed. The regularity and elongation of rete ridges were also analyzed.

### Cytological characteristics of melanocytes in the DEJ and dermis

Although grading atypia involves significant subjectivity and low reproducibility, the degree of atypia in the DEJ and dermis was established according to the literature [12-14] using three categories (mild, moderate, and severe) based on nuclear and cytoplasmic characteristics (Table 1). Mitotic figures and signs of maturation were also analyzed in the dermis.

### Stromal characteristics

The stromal reaction was assessed by noting the presence or absence of different types of fibroplasia (i.e., concentric eosinophilic, diffuse eosinophilic, narrow uniform eosinophilic, and/or lamellar fibroplasias) [2], vascular proliferation, inflammatory infiltrates, and melanophages. Statistical analysis was descriptive and was performed using the Statistical Package for the Social Sciences (SPSS) software version 19.0 for Windows.

## Results

### Clinical characteristics

The sample selected for this study consisted of 111 cases of melanocytic lesions on the genital area. Of these, 101 (91%) were common GMN, exhibiting characteristics similar to MN on non-special sites, two cases were genital melanotic macules (1.8%, one on the vulva and the other on the penis), seven cases were AGN (6.3%), and one case was DMN (0.9%). No cases of genital CM were identified (Table 2).

From the 111 patients with genital melanocytic lesions, 16 (14.4%) were male and 95 (85.6%) were female; the patient ages ranged from 3 to 93 years with a mean age of 34.3 years (Table 3).

The average age of patients with common GMN was 34.7 years old (range of 3 to 93 years old); 65 were located on the vulva (44 on unspecified locations, 14 on the labia majora, five on the labia minora, one on the clitoris, and one on the posterior fourchette), 16 on the pubic region, 10 on the perineum, five on the penis (two on the prepuce, three on the glans, one on the back of the penis, and one on an unspecified location), and one on the scrotum (Table 3).

The age range of the seven patients with AGN was 15 to 39 years (average age of 26.3 years): six females aged 22 to 39 years (average

Characteristic/ degree of atypia	Absent	Mild	Moderate	Severe
Nucleus size	<kn	≥ kn	1- 2x ≥ kn	>2x kn
Nucleus shape	Ovoid or fusiform	Ovoid and/or fusiform and/or irregular	Ovoid and fusiform or irregular	Irregular
Nuclear variability	Minimal	Minimal or moderate	Moderate	Severe
Nucleus chromatin	Homogeneous	Homogeneous or hyperchromatic	Hyperchromatic (irregular nuclear membrane)	Hyperchromatic (irregular nuclear membrane)
Nucleolus	Not evident (absent)	Not evident (absent) or evident (but not prominent-small)	Not evident (absent) or evident (but not prominent-small)	Evident-Prominent (large)
Cytoplasm amount	Scarce	Usually scarce, but sometimes abundant or variable	Usually scarce, but sometimes abundant or variable	Abundant

KN=Keratinocytes; Distribution: Mild atypia- 0-5% of cells; Moderate atypia- 6-10% of cells; Severe atypia- >10% of cells

**Table 1:** Definitions of nuclear atypia for GMN adapted from Weinstock et al. [12], Culpepper et al.[13], and Braun-Falco M et al. [14].

age of 28.2 years) and one 15-year-old male (Table 4). The size range of AGN was 0.2 cm to 1.8 cm (mean=0.71 cm, median=0.5 cm,  $\pm$  0.60). All AGN were removed with surgical margin (mean=0.16 cm, median=0.2 cm,  $\pm$  0.05, range =0.2 cm to 0.1 cm).

The specific location on the vulva for two AGN was not reported, two were on the labia majora, one on the labia minora, one periclitoral, and one on the scrotum (Table 4). Only one case of DMN was identified on the pubic region of a 54-year-old male patient (Tables 2 and Table 4). These lesions were followed up until the present day; none exhibited signs of relapse (average=7.3 years, median=8 years,  $\pm$  3.2 years, range from 1 year to 12 years).

### Morphological characteristics

In this sample, 101 cases (91%) were common GMN exhibiting

characteristics similar to MN on non-special sites (75 dermal, 10 lentiginous compound, 10 lentiginous, five compound, and one junctional nevi). The only case of DMN was a lentiginous compound nevus, where the lentiginous component prevailed in the epidermis and adnexa, and ovoid coalescent nests were observed on the tips of the rete ridges forming bridges. The melanocytes in the epidermal component exhibited a moderate degree of atypia, and those in the dermal component displayed mild atypia. The stroma exhibited concentric eosinophilic and lamellar fibroplasia, diffuse lymphocytic infiltrate, and vascular proliferation.

From the seven cases of AGN, three were compound nevi and located on the vulva (Figure 1, one on an unspecified site, one on the labia majora, and one on the periclitoral area), three were lentiginous compound nevi (Figure 2, one was on the scrotum, and two were on

Type of lesion	Percentage	CI <sup>a</sup> (percentage)
AGN	6.3%	[1.8%; 10.8%]
DMN	0.9%	[0% <sup>b</sup> ; 2.7%]
Genital melanotic macule	1.8%	[0% <sup>b</sup> ; 4.3%]
Common GMN	91.0%	[74.8%; 89.1%]

AGN: Atypical Genital Nevi; DMN: Dysplastic Melanocytic Nevi; GMN: Genital Melanocytic Nevi

**Table 2:** Point and interval distribution of the types of melanocytic lesions on the genital area in the investigated population.

Type of lesion	Gender	N	Mean	Median	Minimum	Maximum	Standard deviation
AGN	Male	1	15.0	15.0	15.0	15.0	-
	Female	6	28.2	26.0	22.0	39.0	6.7
	Total	7	26.3	24.0	15.0	39.0	7.9
DMN	Male	1	54.0	54.0	54.0	54.0	-
	Female	-	-	-	-	-	-
	Total	1	54.0	54.0	54.0	54.0	-
Genital melanotic macule	Male	1	49.0	49.0	49.0	49.0	-
	Female	1	25.0	25.0	25.0	25.0	-
	Total	2	37.0	37.0	25.0	49.0	17.0
Common GMN	Male	13	20.0	15.0	4.0	41.0	13.8
	Female	88	36.6	35.0	3.0	93.0	15.7
	Total	101	34.7	34.5	3.0	93.0	16.3
Total	Male	16	24.1	17.5	4.0	54.0	16.8
	Female	95	35.9	34.5	3.0	93.0	15.4
	Total	111	34.3	33.5	3.0	93.0	16.0

AGN: Atypical Genital Nevi; DMN: Dysplastic Melanocytic Nevi; GMN: Genital Melanocytic Nevi

**Table 3:** Summary of the ages (in years) of the individuals who exhibited one melanocytic lesion on the genital area according to the type of lesion and gender in the investigated population.

	AGN		DMN		Genital melanotic macule		Common GMN		Total	
	n	%	n	%	n	%	n	%	n	%
Scrotum	1	14.3%	-	-	-	-	2	2.0%	3	2.7%
Penis	-	-	-	-	1	50.0%	1	1.0%	2	1.8%
Penis-base	-	-	-	-	-	-	1	1.0%	1	0.9%
Penis-back	-	-	-	-	-	-	1	1.0%	1	0.9%
Penis-glans	-	-	-	-	-	-	3	3.0%	3	2.7%
Penis-prepuce	-	-	-	-	-	-	2	2.0%	2	1.8%
Perineum	-	-	-	-	-	-	10	9.9%	10	9.0%
Pubic area	-	-	1	100.0%	-	-	16	15.8%	17	15.3%
Vulva-non-specified site	2	28.6%	-	-	-	-	44	43.6%	46	41.4%
Vulva-clitoris	-	-	-	-	-	-	1	1.0%	1	0.9%
Vulva-posterior fourchette	-	-	-	-	-	-	1	1.0%	1	0.9%
Vulva-labia majora	2	28.6%	-	-	-	-	14	13.9%	16	14.4%
Vulva-labia minora	1	14.3%	-	-	1	50.0%	5	5.0%	7	6.3%
Vulva-periclitoral	1	14.3%	-	-	-	-	-	-	1	0.9%

**Table 4:** Distribution of melanocytic lesions on the genital area of the investigated population

the vulva-one on an unspecified site and one on the labia minora), and one was a lentiginous nevus (Figure 3) on the labia majora (Table 4).

Most AGN exhibited a prominent and asymmetric junctional epidermal component (71.4%), with a prevalence of melanocytic proliferation in nests (57.1%). The nests were irregular (71.4%) and coalescent (71.4%), exhibited a loss of cellular cohesion (42.9%), and appeared at several sites in the rete ridges (85.7%) (Figure 1a and Figure 2a). Most rete ridges were irregular (57.1%) and non-elongated (85.7%). Shoulder formation was observed in only one case, and the lentiginous epidermal component was present in the adnexa of 71.4% of the cases. The dermal component was asymmetric in 42.9% of the cases (two cases of compound melanocytic nevi [CMN] and one case of lentiginous compound melanocytic nevus [LCMN]). Pagetoid melanocytic proliferation was not observed in most cases (85.7%).

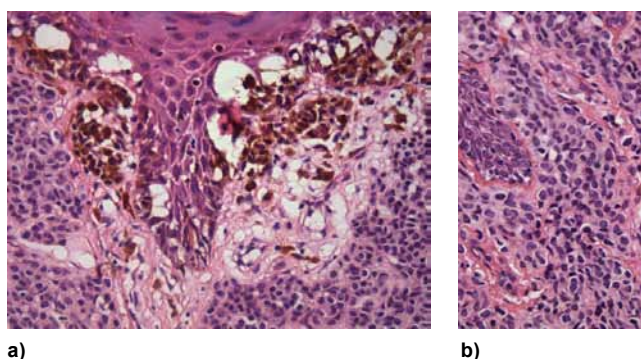
In all cases of AGN, melanocyte maturation (Figure 1b) and melanophages (Figure 2 and Figure 3) were present, and mitotic figures were absent. In the most cases, cytoplasmic pigmentation was present with large coarse melanin granules (Figures 1a, Figure 2b and Figure 3).

The epidermal melanocytes exhibited a moderate degree of atypia in four cases (two LCMN, one lentiginous melanocytic nevus [LMN], and one CMN) and mild atypia in three cases (two CMN and one LCMN); moderate atypia was observed in the melanocytes of the dermal component (LCMN) in only one case.

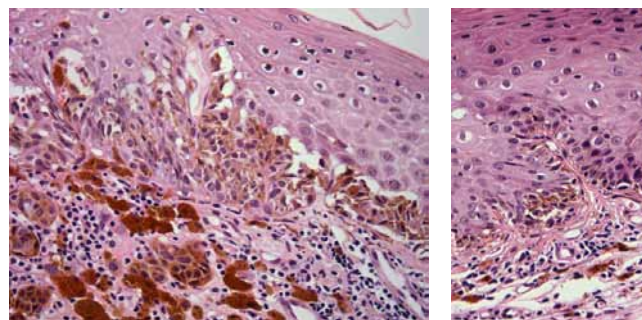
Among the four cases exhibiting fibrosis in the papillary dermis, two were concentric fibrosis (LCMN) (Figure 2b), but only one of them displayed diffuse lymphocytic inflammatory infiltrates. One case exhibited narrow uniform eosinophilic fibroplasia (CMN), and one case of lamellar and concentric fibroplasia (CMN) with focal lymphocytic inflammatory infiltrate and vascular proliferation was noted.

## Discussion

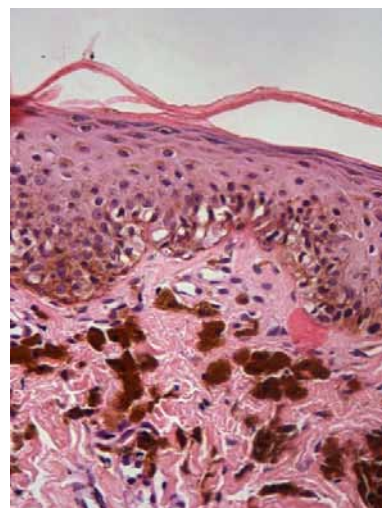
Most melanocytic lesions are classified as either nevi or melanomas [6]. MN exhibits a wide scope of clinical and histological characteristics. Most are diagnosed as benign [6], and some are defined as distinctive entities, such as MN on special sites. The latter are a group of MN exhibiting atypical histological characteristics, which are attributed to their anatomical location and are suggestive of DMN or CM [8,18-20].



**Figure 1: Atypical genital nevus.** a: Asymmetric junctional melanocytic proliferation with mild cytological atypia, composed of coalescent nests exhibiting a loss of cellular cohesion. The nests exhibit a loss of cellular cohesion and vary in size, shape, and position along the rete ridges. Cytoplasmic pigmentation in the junctional and superficial dermal melanocytes. b: Atypia and mitotic figures were not identified in the superficial part of the dermis, but maturation was invariably present (Hematoxylin-eosin stain, 400X).



**Figure 2: Atypical genital nevus.** a: Asymmetric junctional melanocytic proliferation exhibiting nests and focal lentiginous proliferation. The nests of melanocytes are coalescent and exhibit moderate atypia. Coarse melanin pigmentation of the junctional and superficial dermal melanocytes. Diffuse lymphocytic infiltrate and presence of melanophages. b: Presence of concentric eosinophilic fibrosis and melanophages (Hematoxylin-eosin stain, 400X).



**Figure 3: Atypical genital nevus.** Diffuse lentiginous melanocytic proliferation with moderate cytological atypia. Cytoplasmic pigmentation in the junctional melanocytes. Presence of melanophages (Hematoxylin-eosin stain, 400X).

It is believed that MN on special sites does not have the potential for malignant transformation [21], but they can lead to misdiagnosis and possible legal issues [22].

GMN are among the most important nevi found on special sites [8]. The special sites reflect the regional diversity of the skin structure and function, as the skin microanatomy varies in different anatomical regions in terms of thickness of the epidermis, distribution of adnexa, distribution of melanocytes, structure of the dermal-epidermal junction, structure of the dermis, and blood supply [7].

GMN are rare; however, those located on the vulva have been better described than those on male genitalia [3-5]. Most GMN are compound or intradermal; however, other varieties may also occur, including congenital, blue, and Spitz nevi [4,23-25]. In this study, MN comprised 98.2% of the sample (Table 2).

The demographic characteristics of Brazil are interesting due to racial diversity, which we believe might influence the development

of GMN [11]. However, comparing the frequency of different types of melanocytic lesions on female and male genitalia found in this and other studies [3,5] is difficult due to differences in the sample composition of each study.

In our sample, most genital melanocytic lesions were reported in females (85.5%), whereas only 14.4% occurred in males. This gender difference in prevalence is in agreement with other studies [1-5], although the mean age of patients was higher in our sample (mean age of 34.3 years- Table 3).

Of the total number of lesions, 91% were common GMN; most were intradermal (74.3%), followed by compound nevi (14.9%) and AGN (6.1%); only one case of DMN was identified, and no cases of CM were reported (Table 3).

Common GMN on the female genitalia were most often located on the vulva (64.5%), followed by the pubic area (15.8%) and the perineum (9.9%); in males, they were usually located on the penis (8%), followed by the scrotum (2%-Table 4).

In this study, the prevalence of AGN (6.4% of MN cases on the genital area-mean age of 26.3 years, table 3 and table 4) was slightly higher compared to other studies [4,5]; however, the prevalence of AGN has not been fully established in the scientific literature [1,4].

Most of the AGN-affected females (85.7%, mean age of 28.2 years-Table 3) exhibited CMN or LCMN without a preferential location on the vulva (Table 4). Only one case was found in males (14.7% -age of 15 years), which was a lentiginous compound nevus on the scrotum (Table 3 and Table 4).

In agreement with the literature [1-4], the AGN observed in the study population appeared in young females and males; however, the mean age was higher than that reported in the literature, and no cases were diagnosed as CM. In the study by Clark et al. [2], 30% of AGN cases had been previously diagnosed as CM, and the distinction between AGN and CM proved to be extremely difficult in some cases. To facilitate diagnosis of AGN and to distinguish them from CM, the authors [2] described three histological patterns of melanocytic nests at the DEJ: 1) a nested pattern with nests of different sizes, but more typically large, oval, or slightly irregular in shape and perpendicular or parallel to the DEJ; 2) a dyshesive nest pattern (the melanocytes exhibit a lack of cohesion) with oval or round shaped, almost contiguous nests that form a band separating the epidermis from the dermis; and 3) a crowded pattern, where closely apposed single melanocytes and ill-defined nests obscure the DEJ. In the present study, the nested (57.1%) and dyshesive (42.1%) patterns prevailed; (Figure 1a and Figure 2b) the crowded pattern was not observed. Most cases exhibited overlapping of the nested and dyshesive patterns, as also reported in the Gleason et al. Study [9]. In the present study, the adnexa were affected in 71.4% of cases; however, Gleason et al. [9] reported adnexa in only half of the cases.

Different from other studies [1,2,9], most cases in this study exhibited irregular rete ridges and moderate (57.1%) or mild (42.9%) atypia in the epidermal component. Moreover, severe atypia was not observed. Asymmetry of the epidermal and dermal components was observed in 71.4% and 42.9% of cases, respectively; asymmetry does not usually occur in AGN. Furthermore, 85.7% of the AGN cases were associated with dermal nevi (Figure 4), which exhibited mild or moderate atypia on the superficial part of the dermis in 42.9% and 14.3% of cases, respectively.

Despite these difficulties, several characteristics, such as the presence

of melanocyte maturation and cytoplasmatic pigmentation with large coarse melanin granules in epidermal and dermal melanocytes, the absence of mitotic figures in the epidermal component and the common dermal nevi, the absence of pagetoid proliferation in 85.7% of cases, and the absence of regression areas, which are usually not observed in CM [2,26], helped to establish the diagnosis of AGN. Most CM cases are not associated with common dermal nevi [2]. In addition, vulvar melanoma is very rare in young females; it tends to locate on nonglabrous skin and frequently exhibits superficial spreading [26] in contrast to the more nodular appearance of AGN [15]. Despite being comparatively rare in males, diagnosis of melanoma on the penis is more difficult because it is usually nodular and is most commonly located on the glans (82%) and prepuce (10%) areas of elderly men [27], although it may also occur in young men.

Most cases in this study exhibited papillary dermal fibrosis without vascular proliferation (85.7%). The most common pattern of stromal reaction in the AGN cases was concentric fibroplasia (28.6%) (Figure 2b), although at a lower frequency than reported in the literature [1,2,9]. In addition, a few cases of AGN exhibited focal lymphocytic inflammatory infiltrate (28.6%) (Figure 2a). CM generally displays either fibroplasia with lymphocytic infiltrate forming bands or diffuse fibroplasias [2].

Therefore, the stromal pattern of AGN in this case series differed from that of CM. However, it did not differ from that of DMN because we observed one case of AGN with concentric and lamellar fibroplasia. To summarize, AGN is a benign and rare subtype of MN of special sites, occurring on areas not exposed to ultraviolet radiation and most commonly found on the vulvas of young women; its prevalence is not yet precisely known.

It is important to recognize this type of nevus because of the problematic clinical and histological characteristics that can lead to a possible diagnosis of CM and can thus cause social and psychological effects in patients as a result of a wide surgical excision in an anatomically unfavorable location. The biology of this type of lesion needs to be better understood, which might help explain the remarkable difficulty in the histopathological interpretation of atypical melanocytic nevi of the genital area.

This study opens new directions for future research aimed at a better understanding of the molecular pathways and the impact of the physical and hormonal constitutional variables on the development of

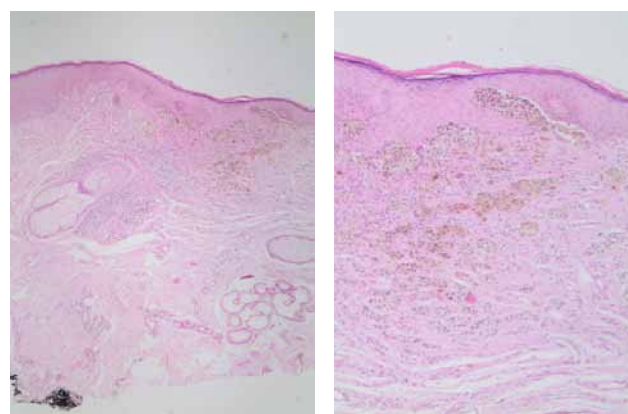


Figure 4: Atypical genital nevus associated with dermal nevi (Hematoxylin-eosin stain, 100X and 200X).

GMN. At this point, the experience of pathologists is of paramount importance for distinguishing between AGN and CM; the subjective judgment and expertise of pathologists are crucial for diagnosis. The identification of molecular markers will likely allow for better reproducibility in the differentiation between GMN and CM.

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