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Original Article

Sex and Self-reported Race: Factors Associated with Anal Mucosal Melanoma and Anal Mucosal Pigmentation?

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Abstract

Background and objectives: Anal canal melanoma (ACM) is a rare, aggressive malignancy with an ominous prognosis. However, its associated factors are largely unknown. Therefore, we investigated potential independent associations of sex and self-reported race with ACM and physiological anal canal pigmentation.

Methods: Two case-control cohorts from a single institution in Miami, Florida, were evaluated. The biopsy cohort comprised 117 sequential patients evaluated prospectively for melanocytic cells/pigment and anal intraepithelial neoplasia (AIN)/squamous intraepithelial lesion (SIL) in anal transitional zone biopsies between January 2021 and August 2022. The melanoma cohort consisted of 28 patients diagnosed with ACM between January 2003 and August 2021 and 116 of the patients in the pigmentation cohort. Multivariable logistic regression analysis was conducted to examine independent factor associations.

Results: In the biopsy cohort, anal transitional melanocytic cells/pigment were identified in 48% (26/54) of Black patients compared to 17% (10/59) of White patients. Multivariable analysis demonstrated that White race was inversely associated with mucosal pigmentation (odds ratio (OR) = 0.19, 95% confidence interval (CI): 0.08–0.48, $P < 0.001$). Conversely, White race was associated with ACM (OR = 6.25, 95% CI: 2.07–18.81, $P = 0.001$). Male sex was also inversely associated with ACM (OR = 0.18, 95% CI: 0.07–0.47, $P < 0.001$). No significant correlations were observed between mucosal pigmentation and AIN/SIL or human immunodeficiency virus status.

Conclusions: Anal transitional zone pigmentation is more prevalent in self-reported Black individuals but is not associated with neoplastic squamous cell precursors. White (versus Black) individuals and female (versus male) individuals both have a significant association with ACM.

Introduction

Melanocytes are derived from the neural crest and are normally found in the anal squamous zone at the anal verge, but a few also populate the anal transitional zone. Their principal function is to produce melanin, which plays a key role in protection against stressors, especially ultraviolet (UV) light in sun-exposed anatomic sites, as well as in antioxidant activity. In addition, melanocytes participate in immune responses through the production of cytokines and toll-like receptors that are important in host defense against infection.[1,2]

Curiously, melanocytes themselves are inconspicuous on standard hematoxylin and eosin (H&E)–stained sections, particularly their nuclei. However, active melanocytes produce melanin and transfer it into squamous cells via cellular processes, where it is stored; these processes are readily identifiable on H&E–stained histologic sections. In skin, the tiny dendrites of a single melanocyte can contact tens of viable keratinocytes to create an epidermal melanin unit.[3] Freshly synthesized melanin

Keywords: Anal mucosal pigmentation; Anal canal melanoma; Anal squamous cell carcinoma; Melanocytes; Sex; Race.
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from the perinuclear region of melanocytes enters melanocyte dendrites, followed by membrane fusion and transfer of melanin-containing vesicles via phagocytosis by squamous cells.[3,4]

Anal canal melanoma (ACM) is rare and behaves aggressively, with an ominous prognosis. Five-year survival had been estimated at 6% to 22%, but a more recent survey reported a median survival of 27.2 months.[5] Because ACM is rare compared to other neoplasms and to melanoma in sun-exposed anatomic sites, much of the literature consists of case reports, as shown by a systematic review of 131 anorectal melanoma cases (110 articles),[6] limiting our understanding of epidemiology, risk factors, and treatment options.

Clinically, ACM presents with nonspecific symptoms that include rectal pain, rectal bleeding, or rectal tenesmus. Its appearance can be confused with that of benign processes, particularly hemorrhoids.[7] ACM is managed according to disease stage, which also governs outcome.[8,9] Localized disease is treated surgically, and advanced disease may require surgery to alleviate bowel obstruction.[5] Although the presence of increased tumor-infiltrating lymphocytes has been associated with improved outcomes, results of immunotherapy have been disappointing to date.[10] Racial disparities in the diagnosis and treatment of melanoma remain.[11] Approximately 20% of mucosal melanomas harbor *KIT* mutations that can be targeted with tyrosine kinase inhibitors.[12-14]

ACM accounts for 0.4% to 1.6% of all melanoma cases and for 1% of all anal malignancies.[7] The incidence increases with age, and ACM is more common in women than in men, with reported ratios of 2.3 to 1.6.[7,15,16] Reported median ages at presentation range from sixty-six to seventy-one years.[6,17] Although Surveillance, Epidemiology, and End Results (SEER) data focused on anal and esophageal melanoma have indicated a predominance in Whites over Blacks in the U.S. population,[17] we suspected that this could be a result of reporting bias and a reflection of the overall demographics of the U.S.; one early study found no association between race and ACM.[18]

We had noted anecdotally that anal transitional mucosal samples from patients self-reported as Black were more likely to display pigment on routine H&E–stained sections than those from patients self-reporting as White. However, it is unclear whether Black patients are more likely to have ACM or pigment in their anal canals than White patients.

In this study, therefore, our primary goals were to examine the potential associations of sex and race with ACM, as well as those with pigment in the anal canal, using two case-control cohorts.

We also aimed to assess the prevalence of melanin in anal transitional mucosa without melanoma, correlating it with patient demographics and comparing it with the demographic distribution of melanoma in our population. We further aimed to investigate the potential association with squamous epithelial neoplasia. This is particularly important in high-risk populations, such as those with human papillomavirus (HPV) infection, human immunodeficiency virus (HIV), or immunosuppression. Anoscopic detection and treatment of anal intraepithelial neoplasia (AIN)/squamous intraepithelial lesions (SILs) has been shown to prevent progression to anal squamous cell carcinoma.[16] Thus, if pigment were associated with AIN/SIL, particularly pigmentation visible on anoscopy, then these regions could be targeted for biopsies.

Materials and methods

We conducted two case-control studies to examine factors associated with pigment in anal canal biopsies and with ACM. The primary factors of interest were race and sex, while other demographics and comorbidities were also considered.

Anal transitional zone biopsy collection and evaluation

Under a local Institutional Review Board-approved protocol (Protocol MOD00052854 of the University of Miami Institutional Review Board, which allowed exemption from specific informed consent for review of slides obtained during the course of clinical care, both prospective and retrospective), we prospectively evaluated anal transitional zone biopsies from sequential patients seen at the University of Miami and Jackson Memorial Health System to determine the prevalence of melanocytic cells in the anal transitional zone. Samples obtained from the anal canal were prospectively and sequentially reviewed by some of the authors (MD, IO, and EAM). The samples were obtained from patients seen at a specialized clinic dedicated to the study of anal HPV and anal cancer prevention, and patient biopsies were reviewed as part of the daily clinical workflow sequentially by the authors over the period between January 2021 and August 2022. Samples were examined and interpreted as "positive for melanocytic cells" or "negative for melanocytic cells" on H&E–stained sections (Figs. 1, 2, 3 and 4). Since the biopsies are typically small (1 mm), any pigmentation was interpreted as positive. The reviewers were blinded to the self-reported race of the patients at the time of review.

Melanocytic processes appear as pigmented, elongated structures that proliferate predominantly in the basal portion of the squamous epithelium and extend into the superficial lamina propria (Fig. 2). Melanin can also be seen within squamous cells or in macrophages in the superficial lamina propria (Fig. 3). No special staining is required to identify melanocytic processes or melanin-containing cells. The authors reviewed the cases together during the daily workflow and recorded whether melanocytic processes were present. No interobserver study was conducted. Other variables recorded included the presence of AIN/SIL, self-reported race, sex, and HIV status of each patient. AIN/SIL was assessed using criteria from the Lower Anogenital Squamous Terminology Project[19]; p16 immunohistochemical staining was added to all lesions believed to conform to AIN2, as this was a criterion for considering ablation. No patient was affected in any way by our review of their slides, which was the justification for exemption from specific consent. Data were de-identified following collection.

Identification of ACM cases

To assess the demographic distribution of ACM in the population served by our hospital system, we queried the pathology database for patients with ACM seen from January 2003 to August 2021 using the terms "anus and melanoma", "anal canal and melanoma", and "rectum and melanoma". Because melanomas are rare, we collected cases over a longer period than those in the separate clinic cohort. We were able to review the initial slides from 15 of the 28 patients identified through computer searches. The remaining slides were no longer available for review, and information was obtained from pathology reports and medical records. No patient was affected in any way by this review, which

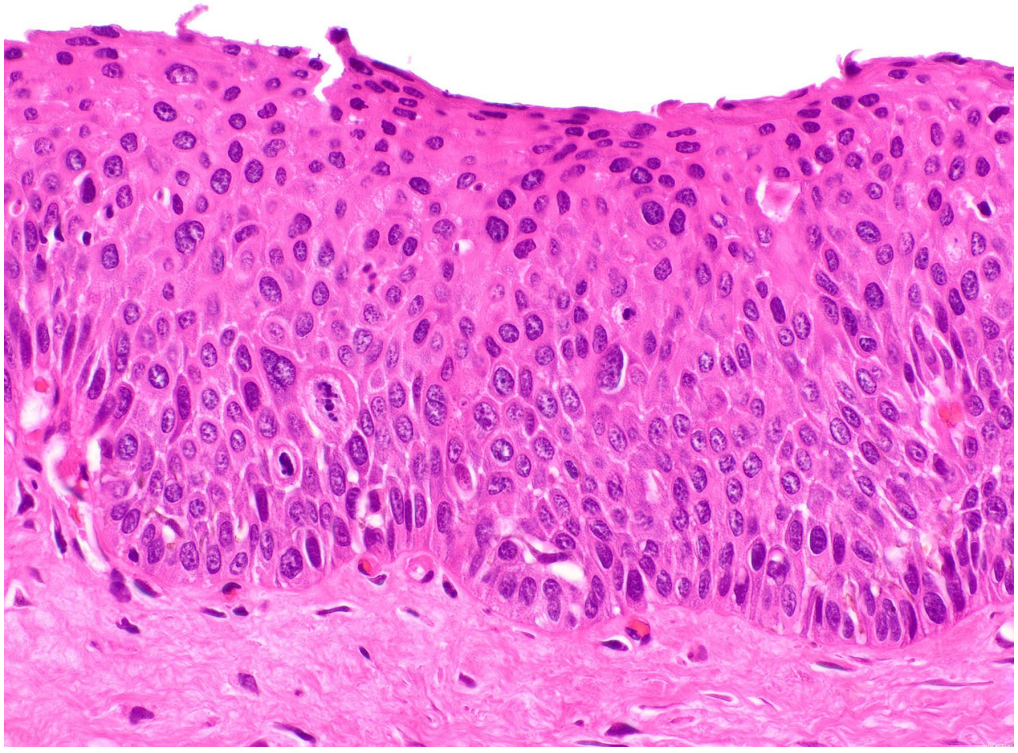

Fig. 1. Anal biopsy without pigment and with HSIL (high-grade squamous intraepithelial lesion, H&E, original magnification 40×). The lesion shows hyperchromatic nuclei and a mitosis well above the basal membrane. A p16 immunohistochemical stain had been performed (not shown) and showed block positivity, supporting the diagnosis. H&E, hematoxylin and eosin.

was the justification for exemption from specific consent. Data were de-identified following collection.

The assessment of the two cohorts is outlined in Figure 5.

Statistical analysis

For the anal canal biopsy cases, Fisher's exact test was used with the following contingencies using SPSS software (IBM, Armonk, New York): AIN & Pigment, AIN & HIV, AIN & Race, AIN & Sex, Pigment & Race, Race & HIV, Pigment & HIV, and Pigment & Sex. Multivariable logistic regression was conducted to examine factor associations using Stata (version 18; StataCorp LLC, College Station, TX). Values of $P < 0.05$ were considered significant. When performing the analyses, self-reported White Hispanic patients were categorized as White. Such patients comprise the majority of self-reported White patients in our catchment area.

Results

Demographic characteristics of anal transitional zone biopsy patients

Anal transitional zone biopsies from 117 patients were analyzed for melanocytic cells/pigmented squamous cells and AIN/SIL (Table 1). There were 54 patients who self-reported as Black (28/54 women, 52%), 3 as Asian (all men), and 59 as White (16/59 women, 27%), among whom 43 self-reported as White Hispanic (11/43 women, 25%). One man declined to provide self-reported race information. His data were excluded from other analyses. Anal transitional melanocytic cells were identified in 37 patients (10 White Hispanic, 26 Black, and 1 Asian). This accounted for 10/59 (17%) of White patients, 26/54 (48%) of Black patients, and 1/3 (33%) of Asian patients.

Associations between pigmentation, demographics, AIN/SIL, and HIV status

There was a statistically significant association between race and anal canal pigmentation ($P = 0.0005$, Supplementary Table. 1), as well as between race and HIV status ($P = 0.0033$); the latter reflected the composition of patients in the clinic. However, there was no statistically significant correlation between pigment and AIN/SIL, race and AIN/SIL, pigment and HIV, or sex and AIN/SIL.

Demographic and clinical features of ACM patients

Twenty-eight patients in our system had ACM, and 11 additional patients had melanomas of the anal verge. The latter 11 were excluded because the anal verge is typically pigmented in all individuals, regardless of reported race. The 28 ACM patients (20 [71%] women and 8 [29%] men) were mostly White (23/28; 82%) (Table 1). All melanoma patients were HIV-negative. Among the 28 patients, 4 had pigmented melanoma (3 White Hispanic and 1

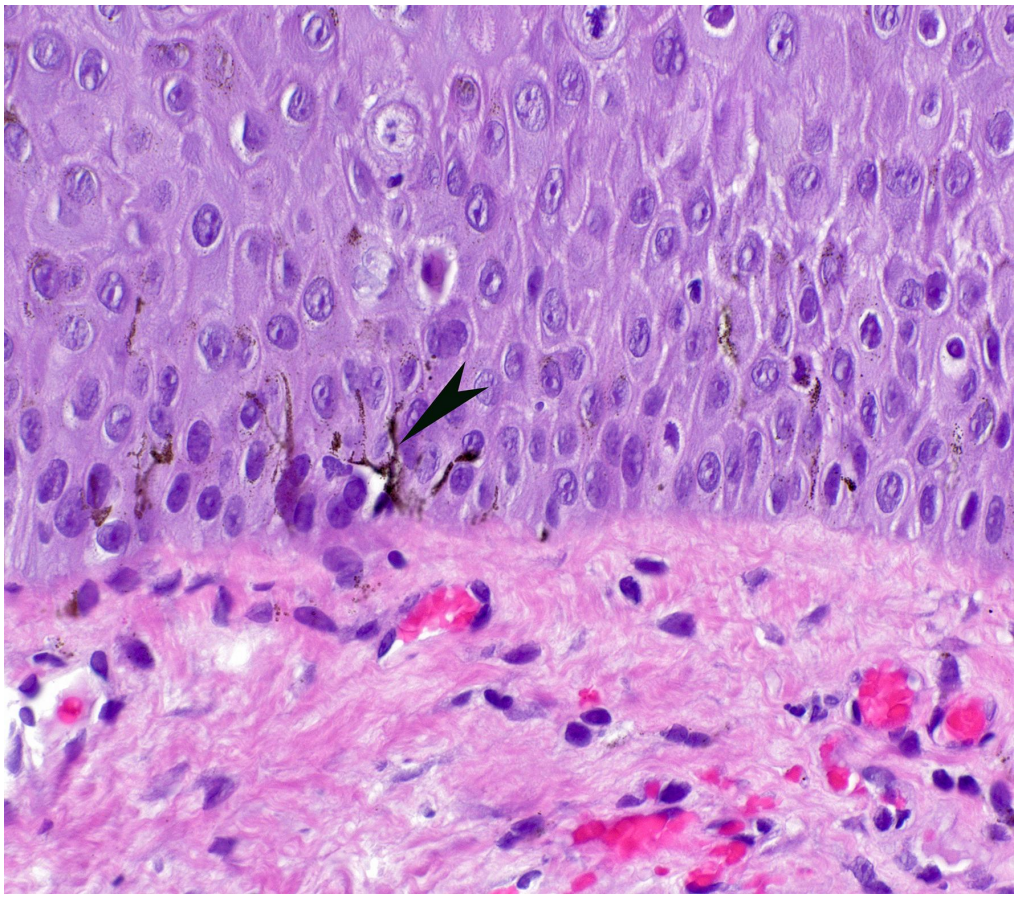

Fig. 2. Anal biopsy with pigment and HSIL (high-grade squamous intraepithelial lesion, H&E, original magnification 40×). The melanocytic processes (arrow) are brown/black and are seen intercalating between squamous cells. H&E, hematoxylin and eosin.

White). *In situ* melanoma was detected in 3 patients, two of whom were White and one Black. We were able to review glass slides for 15 patients; the lesions had "overgrown" the anal transitional zone in these samples such that we were unable to assess the presence of pigment in the adjacent mucosa. Melanoma with and without pigment is shown in Figure 6.

Independent associations of race and sex with anal canal pigmentation or ACM

Given the very small number of Asian patients (n = 3) in these cohorts, they were excluded from the multivariable logistic regression. Multivariable logistic regression was conducted using both sex and race as potential factors. Among patients with anal canal biopsies, White race (versus Black race) was inversely associated with pigmentation in canal biopsies (odds ratio = 0.19, $P < 0.001$, Table 2), but sex was not associated ($P = 0.33$). However, White race (versus Black race) was associated with ACM (odds ratio = 6.25, $P = 0.001$, Table 2) in the combined cohort of patients with ACM and those without known melanoma in anal canal biopsies. Male sex (versus female sex) was also inversely associated with ACM (odds ratio = 0.18, $P < 0.001$).

Comparison of clinic and population demographics

The overall demographic profile of patients in our specialized clinic for anal transitional biopsies differed from that of persons in our institution's catchment area, which, based on census data and other sources (https://www.miamidadematters.org/indicators/index/dashboard?alias=demographics) at the time of our data collection, consisted of: White alone, non-Hispanic: 13.5%; total White: 80.2%; Black or African American: 16.1%; Hispanic or Latino: 70.3%; Other race: 1.9%. However, 18% of ACM patients self-reported as Black, a percentage that closely mirrors the demographics of our patient population.

Discussion

ACM is an uncommon but aggressive disease with unclear risk factors compared with those of cutaneous melanoma. The anal area is the third most common anatomic site for melanoma after the skin and retina. In early studies, it was believed to arise from squamous mucosa unrelated to melanocytes.[20] However, ACM's associated factors are largely unknown. In this study of a large number of ACM cases, we reveal independent associations of sex and race with ACM, yet an inverse association of White race with pigment in the anal canal.

Reviewing cases from a specialized clinic for patients at risk for HPV-associated anal canal neoplasia, we noted anecdotally that anal transitional zone melanin-containing cells were more

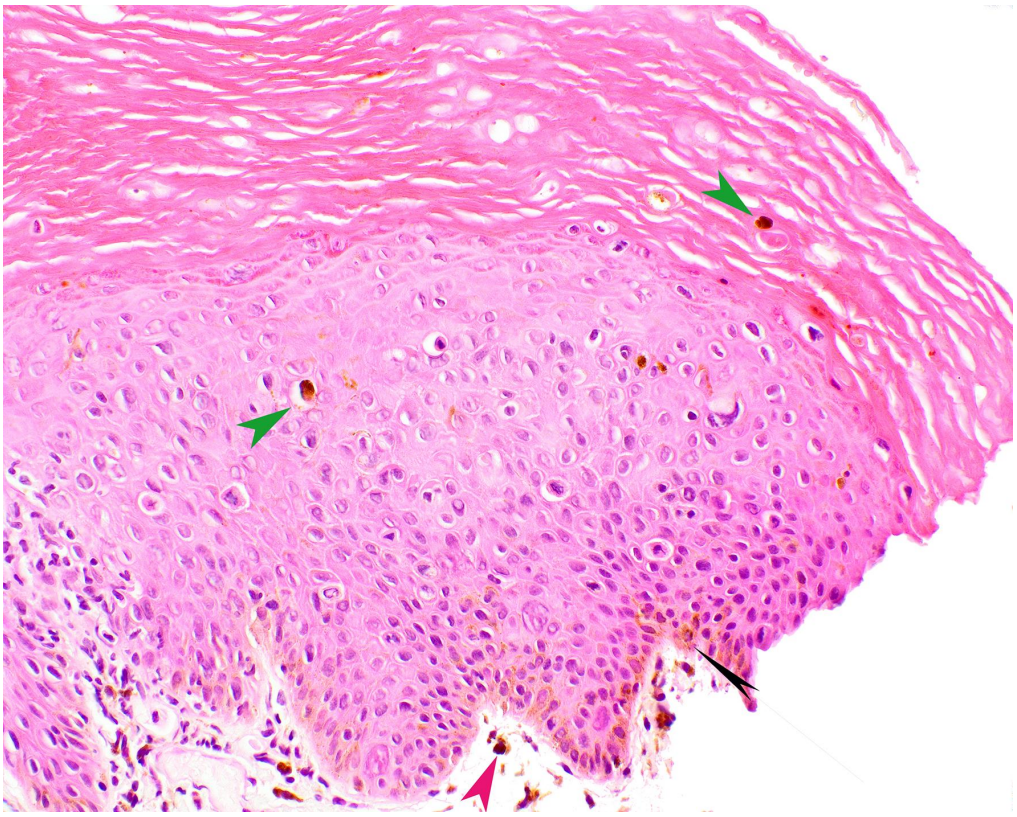

Fig. 3. Anal biopsy with pigment and HSIL (high-grade squamous intraepithelial lesion, H&E, original magnification 40×). Melanin is seen in basal squamous cells (black arrow), a few squamous cells that have migrated higher in the epithelium (green arrows), and in lamina propria macrophages (red arrow). H&E, hematoxylin and eosin.

likely to be present in biopsies from patients who self-reported as Black compared with biopsies from patients who self-reported as White. Based on this observation, we prospectively studied sequential anal transitional zone biopsies to confirm this finding and learned that about one-sixth of White patients have melanin-containing cells in their anal transitional mucosa, whereas nearly half of Black patients have them. Importantly, biopsies taken for screening for squamous lesions do not encompass the entire anal transitional zone, but a limited number of anoscopy colleagues obtain them in a consistent manner such that we believe the likelihood of finding melanin-containing cells is a function of their density in any given patient's anal transitional zone.

Given that about one-third of the patients from our AIN/SIL clinic had pigment, we assessed whether the presence of pigment could correlate with squamous cell carcinoma precursor lesions. This would have obvious benefits for gastroenterologists, as these pigmented lesions are visible on anoscopy and can be targeted for biopsies. However, there was no statistically significant correlation between pigment and AIN/SIL. Rather, pigmentation was much more significantly linked to race.

We also assessed an association between HIV and pigment and/or AIN/SIL, but there was no statistical significance. We would predict that HIV would have some correlation with AIN/SIL, but our sample size may have been insufficient. The role of pigment in melanoma is difficult to interpret, as our sample size was limited to 28 patients with ACM.

According to SEER Program data, ACM arises predominantly in White patients and is also overrepresented in women.[17] Melanomas in sun-exposed skin are a disease predominantly of White individuals (95% of cases), as their skin lacks the protection that melanocytes offer against UV light, whereas protection against UV light is not a factor for ACM. In a SEER-based study of melanoma demographics including 381,035 patients diagnosed between 2000 and 2016, 95.4% of all patients were White and 0.57% were Black.[11] When the data were restricted to 4,615 patients with mucosal melanoma, 3,569 (77.5%) were White and 232 (5%) were Black. Blacks accounted for only 2,286 (0.57%) of all melanomas, and mucosal melanomas comprised 10.1% of melanomas in Black patients.[11] The data were not analyzed by mucosal site and are thus difficult to further interpret.

We postulated that, because of the greater density of melanocytic cells present in self-reported Black patients, Black patients should be more likely than White patients to manifest ACM, in contrast to the reported SEER data. The overall demographic profile of patients in our specialized clinic for anal transitional biopsies differed from that of persons in our institution's catchment area, which, based on local government records, consists of 80.2% White and 16.1% Black individuals, whereas 18% of our ACM patients were Black, suggesting a reflection of the patient population distribution. Unfortunately, our data are not

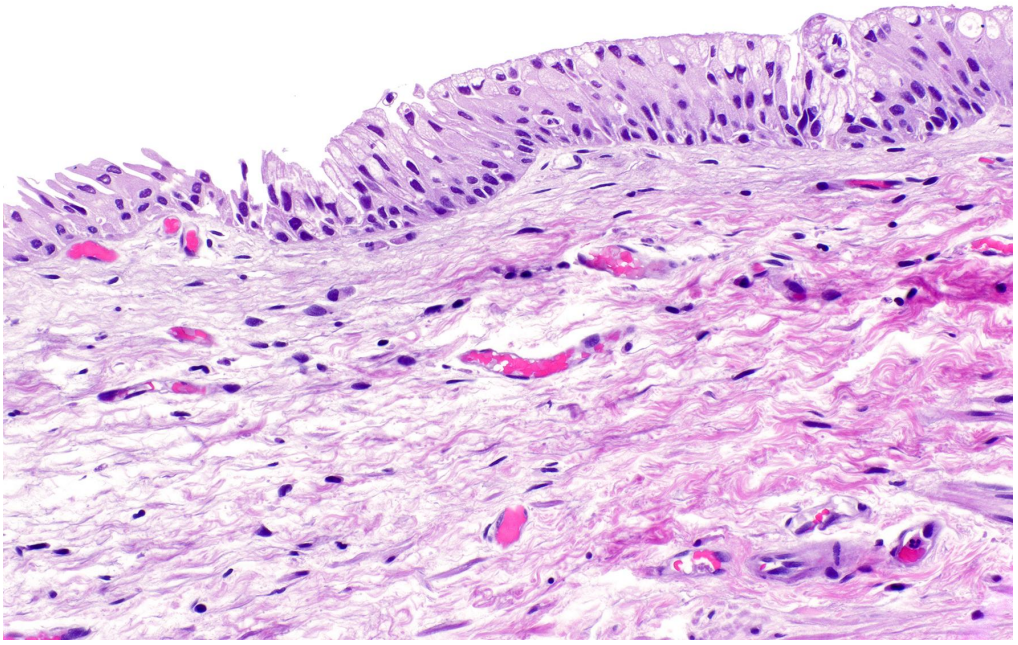

Fig. 4. Anal transitional zone biopsy without pigment (H&E, original magnification 40×). Note that the deeper part of the epithelium appears similar to the squamous basal layer, but there are mucin droplets in cells at the surface. H&E, hematoxylin and eosin.

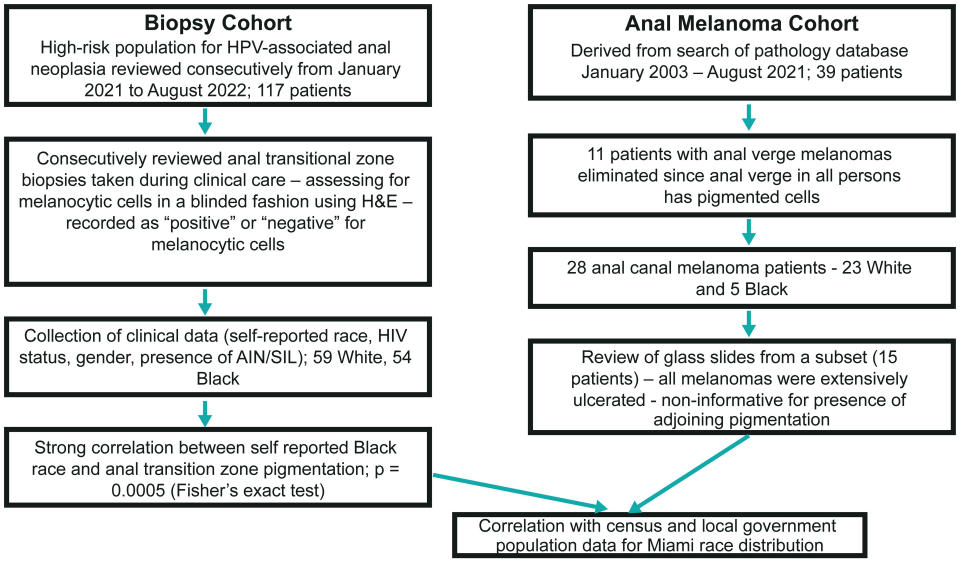

Fig. 5. Flow chart of the biopsy and anal melanoma cohorts. AIN, anal intraepithelial neoplasia; H&E, hematoxylin and eosin; HIV, human immunodeficiency virus; HPV, human papillomavirus; SIL, squamous intraepithelial lesion.

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Table 1. Baseline characteristics of the included patients

	Biopsy cohort			Melanoma cohort		
	Anal transitional zone bx without melanocyte, n (%)	Anal transitional zone bx with melanocyte, n (%)	*P*-value	Anal transitional zone without melanoma, n (%)	Anal canal melanoma, n (%)	*P*-value
Sex						
Male	49 (62%)	23 (62%)	>0.999	72 (62%)	8 (29%)	0.002
Female	30 (38%)	14 (38%)		44 (38%)	20 (71%)	
Race						
White	49 (62%)	10 (27%)	<0.001	59 (51%)	23 (82%)	0.004
Black	28 (35%)	26 (70%)		54 (47%)	5 (18%)	
Asian*	2 (3%)	1 (3%)		3 (2%)	0 (0%)	
Total	79 (100%)	37 (100%)		116 (100%)	28 (100%)	

*Excluded in the analyses due to small sample size; bx, biopsy.

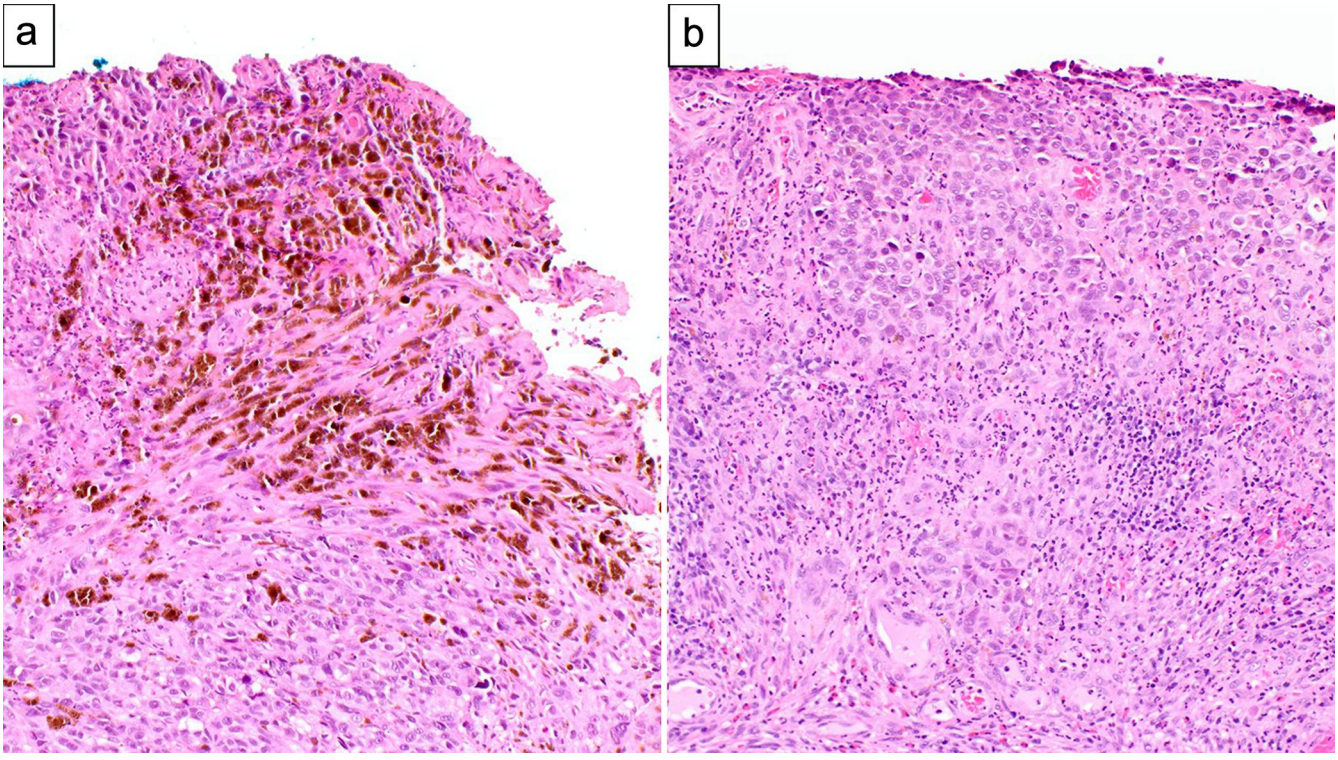

Fig. 6. Anal melanomas. (a) A pigmented melanoma with surface ulceration and abundant dark brown pigmentation (H&E, original magnification 20×). (b) This melanoma lacks pigment and is ulcerated (H&E, original magnification 20×). H&E, hematoxylin and eosin.

conclusive given the small number of ACM cases; the density of anal melanocytes may play a role in the development of ACM, but we are unable to confirm this based on the available data. We are unable to control for the fact that the biopsies assessed to determine melanocyte density were from a different subset of our population than the population with ACM. Additionally, Miami has a large Hispanic population. Unfortunately, defining Hispanic can be difficult. The Merriam-Webster dictionary offers the following definition: "of, relating to, or being a person of Latin American descent and especially of Cuban, Mexican, or Puerto Rican origin living in the U.S." (https://www.merriam-webster.com/dictionary/Hispanic). People meeting these criteria can have a variety of ancestries and appearances, and current medical documentation of race/ethnicity is based on self-identification. Most self-reported Hispanic individuals in Miami also identify as White.

Although some observers have suggested a role for HIV in the development of ACM, the available data are weak.[21] Skin

Table 2. Independent associations of sex and race with pigmentation and melanoma in the anal canal

	Odds ratio	95% CI	*P*-value
Biopsy cohort			
Male (vs. Female)	1.57	(0.64-3.87)	0.328
White (vs. Black)	0.19	(0.08-0.48)	<0.001
Melanoma cohort			
Male (vs. Female)	0.18	(0.07-0.47)	<0.001
White (vs. Black)	6.25	(2.07-18.81)	0.001

CI, confidence interval; vs, versus.

melanomas are reportedly overrepresented in HIV-positive patients, but there are few data for ACM in HIV-positive patients.[22,23] None of our patients with ACM were HIV-positive.

A provocative issue arises with cutaneous melanomas affecting the palms and soles (acral lentiginous melanoma (ALM), subungual melanoma), the subtype most likely to affect Black individuals.[24] These account for 15.5% to 36.6% of melanomas that arise in Black patients and 0.5% to 1% of those detected in White patients.[24-26] ALM is therefore either equally represented or overrepresented in Black patients.[24] Based on data compiled between 1986 and 2005, the overall 5- and 10-year survival rates for Black and White patients with ALM were 77.2% and 71.5% versus 82.6% and 69.4%, respectively.[25]

This subtype of melanoma, akin to ACM, is unrelated to chronic sun exposure and has been attributed by some to trauma or predisposition to nevi,[24,26,27] although associated nevi can be identified in only about 10% of cases.[28] In contrast to UV radiation–induced melanomas, ALMs have a low mutational burden and thus are unlikely to respond to immunotherapy,[29,30] a feature shared with mucosal melanomas.[31] They also harbor targetable mutations (*BRAF, KIT*) and *CDK4* amplification, additional features shared with mucosal melanomas, of which ACM is a key example.[31] Similarly, all types of acral melanocytic lesions (nevi, pigmented areas on dermoscopy) are overrepresented in Black patients,[32] and an early study showed increased melanocyte density in acral (palmar) skin of Black individuals compared with White individuals.[33]

Limitations

Our data are limited by several factors. We reviewed material from patients at a single institution, making our observations preliminary. Additionally, the racial distribution of patients in the specialized clinic was inconsistent with that of the regional population. We were also limited by small sample sizes (117 biopsy patients and 28 ACM patients), although this represents one of the larger ACM cohorts reported. We were thus unable to confirm an association between pigmentation and ACM. Furthermore, in our population, there are no clear distinctions between race and ethnicity. Our ACM cases and biopsy patients were in different cohorts, and the pigment status of the adjacent mucosa in ACM patients could not be evaluated because the lesions were ulcerated, and we were only able to review a subset of lesions, making it impossible to directly correlate melanocyte density with tumor development. Future multicenter studies could include larger numbers of patients and review early mucosal melanomas that are not ulcerated to determine whether adjacent non-neoplastic melanocytic cells are present. Finally, age was not included in the multivariable analysis and may therefore represent a residual confounder. Previous studies have reported median ages of approximately sixty-six to seventy-one years among patients with anorectal melanoma.[6,17] Large multicenter studies are required to further examine our findings.

Conclusions

There is an increased presence of anal transitional zone melanocytic cells in patients who self-reported as Black compared with those who self-reported as White, without sex predominance. Our multivariable regression across two case-control cohorts shows that female sex and White race (versus Black race) are independently associated with ACM, while White race (versus Black race) is inversely associated with pigment in anal canal biopsies. ACM shares several characteristics with ALM, which is overrepresented in Black individuals. Pigmentation was unrelated to squamous cell carcinoma precursor lesions.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTP.2025.00041.

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None.

Conflict of interest

The authors have declared that there is no conflict of interest.

Author contributions

Data collection (DSL, MD, IO, JCP, EAM), data analysis (DSL, DHW, EAM), writing, revising and proofreading (DSL, DHW, MD, EAM). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study was approved by the University of Miami Institutional Review Board under a local Institutional Review Board-approved protocol (Protocol MOD00052854). The requirement for specific informed consent was waived because the study involved the review of pathology slides obtained during routine clinical care, both prospectively and retrospectively, and the data were de-identified after collection. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

Data sharing statement

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

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