PRIMARY ACQUIRED MELANOSIS OF THE CONJUNCTIVA: EXPERIENCE WITH 311 EYES

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ABSTRACT

Purpose: To evaluate clinical features and risks for transformation of conjunctival primary acquired melanosis (PAM) into melanoma.

Methods: Retrospective chart review and Kaplan-Meier estimates of times to PAM enlargement, recurrence, and transformation into melanoma. Main outcome measures: PAM enlargement, recurrence, and transformation into melanoma.

Results: The mean patient age at diagnosis of PAM was 56 years; 62% were female and 96% Caucasian. The conjunctival quadrant(s) affected by PAM and its extent in clock hours were recorded. Initial management included observation in 62%, biopsy combined with cryotherapy in 34%, and other methods in 4%. Of PAM that was observed, Kaplan-Meier estimates at 10 years revealed PAM enlargement in 35% and transformation into melanoma in 12%. Of those that underwent incisional or excisional biopsy, 10-year estimates of PAM recurrence and transformation into melanoma were 58% and 11%, respectively. Progression to melanoma occurred in 0% of PAM without atypia, 0% of PAM with mild atypia, and 13% of PAM with severe atypia. Multivariable analysis revealed that the most significant factor for both PAM recurrence and progression to melanoma was extent of PAM in clock hours.

Conclusion: PAM without atypia or with mild atypia shows 0% progression into melanoma, whereas PAM with severe atypia shows progression into melanoma in 13%. The greater the extent of PAM in clock hours, the greater the risk for transformation into melanoma.

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INTRODUCTION

Primary acquired melanosis of the conjunctiva (PAM) is a potentially serious melanocytic lesion that can lead to the development of melanoma.[1-29] In a practice of ocular oncology, PAM accounted for 11% of all conjunctival tumors and 21% of melanocytic lesions.[2] There has been controversy regarding the terminology, incidence, clinical and histopathologic criteria for diagnosis, frequency of progression to melanoma, and management of PAM.[4,8,13,14]

It has been estimated that approximately 75% of conjunctival melanomas arise in association with PAM.[4,10-12] Most studies regarding PAM have emphasized its relationship to melanoma, and less attention has been given to the clinical features of PAM or clinical factors of PAM that are predictive of progression to melanoma. In this study, an analysis of PAM was performed in a tertiary referral setting to determine demographic features, clinical characteristics, management, and frequency of PAM enlargement, recurrence, and progression to melanoma. Clinical features predictive of PAM transformation to melanoma were assessed.

METHODS

The charts of patients with the diagnosis of PAM on the Ocular Oncology Service of Wills Eye Institute (WEI) were reviewed. Institutional review board approval was obtained for this retrospective study. Patients with PAM only were included in this analysis. Patients with PAM and melanoma at presentation were excluded. PAM was defined clinically as 1 or more patches of acquired asymmetric, flat, discrete, conjunctival and/or corneal brown pigmentation of at least 1 mm in diameter.

We defined PAM histopathologically using a slight modification of the criteria employed in previous reports from the Armed Forces Institute of Pathology (AFIP).[7] PAM without atypia was defined as pigmentation of the conjunctival epithelium with or without benign melanocytic hyperplasia. PAM with atypia was characterized by the presence of atypical melanocytic hyperplasia. PAM with mild atypia was defined as atypical melanocytes confined to the basal layer of the epithelium. PAM with severe atypia was defined as atypical melanocytic hyperplasia that extended into the more superficial nonbasal portion of the epithelium in a pagetoid fashion and/or contained epithelioid cells.

Data were collected regarding patient and ocular features, including age at presentation, gender, race, and iris color. Ocular symptoms, tumor laterality, number of lesions per eye, and anatomic and quadrantic location of PAM were determined. The tumor extent was measured in millimeters and by clock hour involvement. The initial tumor management was recorded, and cases that had undergone biopsy were assessed for the presence and degree of cytologic atypia.

Outcomes of PAM were separately evaluated for cases initially managed with observation and those initially managed with incisional or excisional biopsy and cryotherapy. For those cases managed by observation, a series of univariate Cox proportional

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hazards regressions assessed the degree of relationship of all of the variables to rates of PAM enlargement and progression into melanoma. For cases that underwent biopsy, a series of univariate Cox proportional hazards regressions assessed the degree of relationship of all of the variables to rates of PAM recurrence and progression to melanoma. All of the variables were analyzed as discrete variables except for patient age at presentation, PAM basal dimension in millimeters, and number of clock hours of PAM, which were evaluated as continuous variables. Subsequent multivariate models included variables that were significant on a univariate level ($P < .05$) to identify the combination of factors best related to the outcomes. Kaplan-Meier survival estimates calculated for the observed group included time to PAM enlargement and time to melanoma development. Kaplan-Meier survival estimates calculated for the biopsied group included time to PAM recurrence and time to melanoma development.

RESULTS

There were 311 eyes with PAM included in this analysis. Patient demographic data are shown in Table 1. The mean patient age at diagnosis was 56 years (range, 15-90 years), 62% were female, 96% were Caucasian, and 58% had brown irides. The clinical features of PAM are shown in Table 2. The quadrant(s) of the conjunctiva affected were temporal (57%), inferior (45%), nasal (42%), and superior (37%). The anatomic location was bulbar conjunctiva (91%), limbal conjunctiva (55%), cornea (23%), forniceal conjunctiva (13%), palpebral conjunctiva (12%), and caruncle (11%). PAM involved a mean of 3 clock hours of conjunctiva (range, up to 12 clock hours).

TABLE 1. CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) IN 311 EYES OF 276 PATIENTS: DEMOGRAPHIC FEATURES*

FEATURE	ALL PATIENTS N = 276 PATIENTS, 311 EYES	PAM OBSERVED n = 165 PATIENTS, 194 EYES	PAM BIOPSIED n = 107 PATIENTS, 107 EYES
Age, yr			
mean [median, range]	56 [56, 15-90]	55 [56, 16-90]	56 [57, 15-89]
Gender			
Male	105 (38%)	73 (44%)	30 (28%)
Female	171 (62%)	92 (56%)	77 (72%)
Race			
Caucasian	265 (96%)	163 (99%)	97 (91%)
African American	4 (1%)	1 (<1%)	4 (4%)
Hispanic	6 (2%)	0 (0%)	6 (6%)
Asian	1 (<1%)	1 (<1%)	0 (0%)
Laterality			
Unilateral	241 (87%)	130 (79%)	102 (95%)
Bilateral	35 (13%)	35 (21%)	5 (5%)
Eye color			
Brown	181 (58%)	118 (61%)	60 (56%)
Blue	110 (35%)	62 (32%)	43 (40%)
Green	16 (5%)	10 (5%)	4 (4%)
Unknown	4 (1%)	4 (2%)	0 (0%)

*Ten eyes were treated by methods other than excision (topical chemotherapy or cryotherapy alone) and are not included in the calculations for this table. Therefore the total number of eyes for the observed group and the excised group was 301 (194+107).

Initial PAM management is listed in Table 3. Of the 311 affected eyes, initial management was observation in 194 (62%), incisional or excisional biopsy combined with cryotherapy in 107 (34%), and topical chemotherapy and/or cryotherapy without biopsy in 6 (3%). Eyes managed with observation showed smaller PAM size (median, 4 mm) as compared to eyes managed with biopsy and cryotherapy (median, 8 mm) (Table 2).

Of those eyes managed with observation and with at least 3-year follow-up, PAM enlargement was detected in 16% and progression to melanoma in 5%. The mean interval to melanoma development was 56 months (Table 4). Of those eyes managed with biopsy and cryotherapy and with at least 3 years follow-up, PAM recurrence was detected in 27% and progression to melanoma in 3%. The mean interval to melanoma development was 39 months (Table 5).

Of the 112 eyes with biopsy (initial or follow-up) and histopathologic assessment of PAM with at least 3 years of follow-up, PAM recurrence was found in 11% of those without atypia, 26% with mild atypia, and 50% with severe atypia. None of the cases in the biopsied group with no cytologic atypia or mild atypia progressed to melanoma. In contrast, progression to melanoma occurred in

13% of those with PAM with severe atypia (Table 6). A comparison of the findings from the AFIP[4,7,8] with our results from WEI is shown in Table 7. In biopsied eyes with cytologic atypia, overall progression was remarkably lower in the WEI series as compared to the AFIP series.

TABLE 2. CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) IN 311 EYES: TUMOR CHARACTERISTICS AT INITIAL EXAMINATION

TUMOR FEATURES	ALL EYES N = 311 EYES	PAM OBSERVED n = 194 EYES	PAM BIOPSIED n = 107 EYES
Symptoms			
None	170 (55%)	129 (66%)	36 (34%)
Spot	138 (44%)	64 (33%)	70 (65%)
Stable	89 (29%)	46 (24%)	42 (39%)
Growing	49 (16%)	18 (9%)	28 (26%)
Redness	3 (1%)	1 (<1%)	1 (1%)
No. of lesions per eye			
mean [median, range]	2 [1,1-7]	2 [1, 1-7]	2 [1, 1-7]
Quadrantic location*			
Superior	116 (37%)	69 (36%)	42 (39%)
Temporal	178 (57%)	108 (56%)	64 (60%)
Inferior	139 (45%)	80 (41%)	52 (49%)
Nasal	131 (42%)	79 (41%)	47 (44%)
Conjunctival anatomic location*			
Cornea	70 (23%)	25 (13%)	42 (39%)
Limbal conjunctiva	172 (55%)	94 (48%)	70 (65%)
Bulbar conjunctiva	284 (91%)	180 (93%)	96 (90%)
Forniceal conjunctiva	39 (13%)	13 (7%)	23 (21%)
Palpebral conjunctiva	35 (12%)	10 (5%)	21 (20%)
Caruncle	34 (11%)	17 (9%)	16 (15%)
Extent of PAM (No. of clock hours)			
mean [median, range]	3 [2,1-12]	2 [2, 1-12]	3 [3, 1-12]
Extent of PAM			
Focal (≤3 clock hours)	238 (76%)	166 (86%)	67 (63%)
Diffuse (>3 clock hours)	70 (23%)	25 (13%)	40 (37%)
Unknown	3 (1%)	3 (1%)	0 (0%)
Size of largest PAM, mm			
mean [median, range]	8 [5,1-36]	6 [4, 1-36]	11 [8, 1-35]

*Totals are greater than 100% because in some eyes more than 1 quadrant or radial location of conjunctiva was involved by PAM.

TABLE 3. INITIAL MANAGEMENT OF CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) IN 311 EYES

INITIAL MANAGEMENT	ALL EYES N = 311 EYES	PAM OBSERVED n = 194 EYES	PAM BIOPSIED n = 107 EYES
Observation	194 (62%)	194 (100%)	…
Incisional/excisional biopsy	107 (34%)	…	107 (100%)
Mitomycin C only	4 (1%)	…	…
Cryotherapy only	1 (<1%)	…	…
Mitomycin C and cryotherapy	1 (<1%)	…	…
No information	4 (1%)	…	…

In our series, Kaplan-Meier estimates at 10 and 15 years for progression to melanoma in the initially observed group were 12% and 21%, whereas in the initially biopsied group the estimates were 11% and 11% (Table 8). The only multivariable factor predictive of progression to melanoma in the observed group was extent of PAM in clock hours ($P < .0001$) (Table 9). There were no factors on the multivariable level predictive of melanoma development in the biopsied group, but the most important factor predictive of PAM recurrence in this group was extent of PAM in clock hours ($P < .0001$) (Table 10).

TABLE 4. ENLARGEMENT WITH AND WITHOUT DEVELOPMENT OF MELANOMA IN 131 EYES WITH CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) IN WHICH PAM WAS INITIALLY OBSERVED WITH FOLLOW-UP OF AT LEAST 3 YEARS

TUMOR OUTCOME	PAM OBSERVED WITH ≥3-YEAR FOLLOW-UP n = 131 EYES
PAM enlargement	
Without development of melanoma	21 (16%)
With development of melanoma	6 (5%)
Time* to PAM enlargement without development of melanoma, mo mean [median, range]	32 [25, 3-126]
Time* to PAM enlargement with development melanoma, mo mean [median, range]	56 [47, 25-126]

*Time from date of first visit on the Ocular Oncology Service, Wills Eye Institute.

TABLE 5. RECURRENCE AND PROGRESSION TO MELANOMA IN 98 EYES WITH CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) IN WHICH PAM WAS INITIALLY MANAGED WITH EXCISION AND CRYOTHERAPY WITH FOLLOW-UP OF AT LEAST 3 YEARS

TUMOR OUTCOME	PAM BIOPSIED WITH ≥3-YEAR FOLLOW-UP n = 98 eyes
PAM recurrence	
Without development of melanoma	26 (27%)
With development of melanoma	3 (3%)
Time* to PAM recurrence without development of melanoma, mo mean [median, range]	19 [15, 2-70]
Time* to PAM recurrence with development melanoma, mo mean [median, range]	39 [41, 13-62]

*Time from date of first visit on the Ocular Oncology Service, Wills Eye Institute.

TABLE 6. OUTCOME ACCORDING TO DEGREE OF ATYPIA IN 112 EYES WITH CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) THAT ULTIMATELY WERE MANAGED WITH EXCISION AND CRYOTHERAPY WITH FOLLOW-UP OF AT LEAST 3 YEARS

GRADE OF ATYPIA	OUTCOME		
	NO PAM RECURRENCE (n = 80 EYES)	PAM RECURRENCE WITHOUT DEVELOPMENT OF MELANOMA (n = 29 EYES)	PAM RECURRENCE WITH DEVELOPMENT OF MELANOMA (n = 3 EYES)
None (n = 44)	39 (89%)	5 (11%)	0 (0%)
Mild (n = 44)	32 (73%)	12 (26%)	0 (0%)
Severe (n = 24)	9 (38%)	12 (50%)	3 (13%)

TABLE 7. COMPARISON OF THE RATE OF PROGRESSION OF CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) TO MELANOMA IN THE ARMED FORCES INSTITUTE OF PATHOLOGY (AFIP) SERIES AND THE WILLS EYE INSTITUTE (WEI) SERIES

DEVELOPMENT OF MELANOMA	AFIP[4,7,8] n = 41 eyes	WEI (current series) n = 233 eyes
Inclusive all cases with and without biopsy	**NA**	**n = 233**
Progression to melanoma	NA	4%
Inclusive cases with biopsy	**n = 41**	**n = 112**
Overall progression to melanoma	32%	3%
If no atypia	0%	0%
If any atypia (overall)	46%	3%
If mild atypia	NA	0%
If severe atypia	75%-90%	13%

NA, not addressed.

TABLE 8. SUMMARY OF OUTCOMES IN 311 EYES WITH CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) USING KAPLAN-MEIER ESTIMATES

OUTCOMES	KAPLAN-MEIER ESTIMATES			
	2 yr	5 yr	10 yr	15 yr
Initially observed group (n = 194 eyes)				
PAM enlargement without development of melanoma	9%	26%	35%	43%
PAM enlargement with development of melanoma	0	8%	12%	21%
Initially biopsied group (n = 107 eyes)				
PAM recurrence without development of melanoma	38%	52%	58%	58%
PAM recurrence with development of melanoma	2%	5%	11%	11%

TABLE 9. FACTORS PREDICTIVE OF CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) PAM ENLARGEMENT WITH AND WITHOUT DEVELOPMENT OF MELANOMA IN INITIALLY OBSERVED GROUP (N = 194) USING MULTIVARIABLE ANALYSIS

MULTIVARIABLE ANALYSIS	*P* VALUE	RR	95% CI
PAM enlargement without development of melanoma (n = 21)			
Previous excision elsewhere (present vs absent*)	.001	5.63	1.20-15.87
PAM enlargement with development of melanoma (n = 6)	<.0001	1.70†	1.29-2.23
Extent of PAM (No. of clock hours)			

CI, confidence interval; RR, relative risk.
*Reference variable.
†Per 1-hour increase.

TABLE 10. FACTORS PREDICTIVE OF CONJUNCTIVAL PRIMARY ACQUIRED MELANOSIS (PAM) ENLARGEMENT WITH AND WITHOUT DEVELOPMENT OF MELANOMA IN INITIALLY BIOPSIED GROUP (N = 107) USING MULTIVARIABLE ANALYSIS

MULTIVARIABLE ANALYSIS	*P* VALUE	RR	95% CI
PAM recurrence without development of melanoma (n = 26)			
PAM involvement of caruncle (present vs absent*)	.006	3.53	1.44-8,68
Extent of PAM (No. of clock hours)	<.0001	1.43†	1.22-1.69
PAM recurrence with development of melanoma (n = 3)			
No significant variables	…	…	…

CI, confidence interval; RR, relative risk.
*Reference variables.
†Per 1-hour increase.
‡There were no variables significant on the multivariable level. The only significant univariable factor was the presence of skin cancer (*P* = .013, RR = 34.70, 95% CI, 2.14-563.67).

DISCUSSION

Primary acquired melanosis of the conjunctiva has been the subject of changing concepts and controversy with regard to demographics, terminology, clinical definition, histopathologic definition, incidence, natural course, and management.[1-29] This study was designed to address some of these issues.

Concerning demographics, PAM is mainly a condition of adult Caucasians, with a median age at diagnosis of 56 years (Table 1). However, in this series, classic PAM was seen in patients as young as 15 years of age. We have no explanation for the slight preponderance of females (62%). PAM does not occur exclusively in Caucasians. Of our 276 patients, 4% were non-Caucasian. In dark-skinned individuals, PAM must be differentiated from racial melanosis, which is usually bilateral and symmetrical.[1] We have treated several African American patients who presented with aggressive conjunctival melanoma that had clearly arisen from PAM (unpublished observations). PAM is generally considered to be a unilateral disease. The finding that 13% of cases in this series were bilateral could partly be related to the fact that patients underwent a meticulous examination of both eyes, and small foci of PAM in the fellow eye were detected, recorded, and coded.

The terminology related to PAM has been controversial. Historically, Reese[5] called the condition *precancerous* melanosis. Zimmerman[6] objected to that term, since many cases had benign clinical and histopathologic features. He called it *acquired* melanosis and divided it into stage I (benign acquired melanosis) and stage II (cancerous acquired melanosis). The World Health Organization subsequently adopted the term *primary acquired melanosis* (PAM).[4,7] Folberg and associates[4,8-12] used that term in several publications and established histopathologic criteria to predict which cases are more likely to progress to melanoma. Ackerman,[13] a dermatopathologist, has challenged this terminology and believes that PAM should be called *melanoma-in-situ*, similar to lentigo maligna of the skin. The term *melanoma-in-situ* could possibly apply to PAM with severe atypia, which comprises 21% of biopsied lesions (Table 6) and 8% of all cases of PAM seen in a clinical practice (Tables 1 and 6), but certainly not to all cases of PAM. We believe that the term *melanoma-in-situ* could unnecessarily alarm both clinicians and patients, particularly since many PAM lesions have little propensity to evolve into melanoma. The term *PAM* seems acceptable, since the condition is primary, acquired, and generally pigmented.

To date, there has not been a clear clinical definition of PAM. In this study, we chose to be inclusive and define PAM clinically as any acquired flat, noncystic pigmented lesion of the conjunctiva, cornea, or caruncle (Figures 1 through 4) that lacks the typical features of localized nevus or racial melanosis.[1] Although the differentiation of these 2 conditions from PAM is straightforward in most instances, there are occasional cases where this distinction is challenging both clinically and histopathologically. The histopathologic definition of PAM is provided in the "Methods" section and is derived from the AFIP definitions.[7-12] In some instances it may be extremely difficult to determine histopathologically if low-grade melanocytic hyperplasia is present or whether conjunctival pigmentation reflects melanin pigment within squamous epithelial cells. Immunohistochemical stains for melanocytic and epithelial markers can help to make this distinction in challenging cases. On the other hand, the results of this study suggest that this distinction actually is of little significance clinically because neither PAM without atypia nor PAM with mild atypia progresses to melanoma.

The reported incidence of PAM varies greatly in different clinical settings. Motivated by the AFIP reports that recommended biopsy for most cases, Gloor and Alexandrakis[14] attempted to establish the true incidence by screening all Caucasian patients over age 10 years who were referred to a cornea clinic for unrelated conditions. Using minimally stringent criteria for diagnosis, they concluded

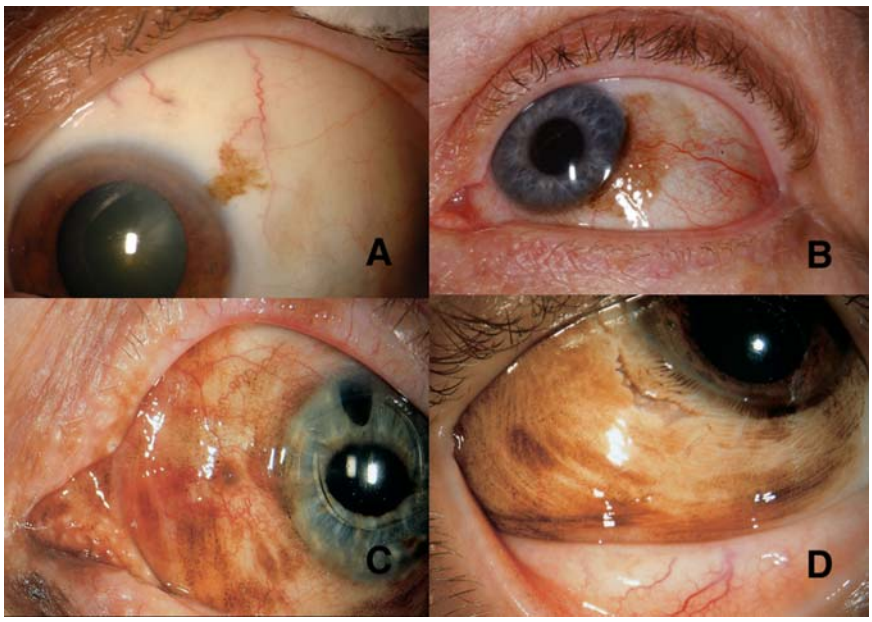

FIGURE 1

Primary acquired melanosis (PAM) with varying extent of involvement. A, PAM involving less than 1 clock hour of bulbar conjunctiva. B, PAM involving 4 clock hours of conjunctiva with slight corneal extension. C, PAM involving more than 6 clock hours of bulbar conjunctiva with extension into the cornea. D, PAM involving entire bulbar conjunctiva (12 clock hours).

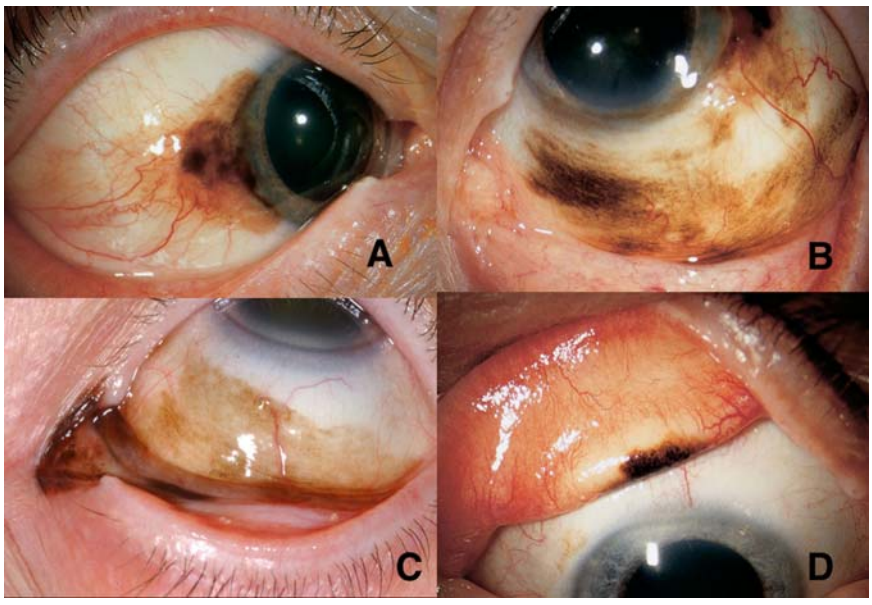

FIGURE 2

Appearance of primary acquired melanosis (PAM) at various sites. A, PAM involving bulbar conjunctiva and adjacent cornea. B, Extensive multifocal PAM involving broad areas of bulbar conjunctiva and cornea. C, PAM involving bulbar and forniceal conjunctiva and caruncle. D, PAM confined to tarsal conjunctiva as seen with eyelid everted.

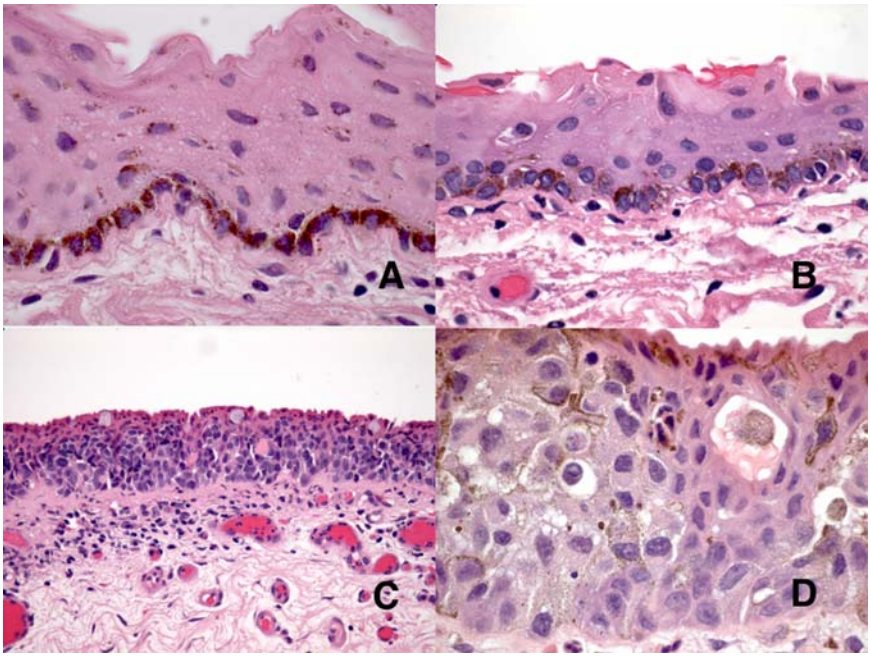

FIGURE 3

Histopathology grading of primary acquired melanosis (PAM). A, PAM without atypia (hematoxylin-eosin, ×100). B, PAM with mild atypia (hematoxylin-eosin, ×100). C, PAM with severe atypia (hematoxylin-eosin, ×50). D, PAM with very severe atypia (hematoxylin-eosin, ×200).

that PAM was present in 36% of adult Caucasians. They emphasized that many PAM lesions were small and did not require surgical biopsy, since the vast majority were not destined to transform into melanoma. In a report of 1643 conjunctival lesions from an ocular oncology practice, PAM comprised 11% of all conjunctival tumors and pseudotumors and 21% of pigmented conjunctival lesions.[2] Nevus and melanoma were more common than PAM, reflecting referral bias for these more obvious and more suspicious conditions. Based on our experience and review of the literature, we believe the incidence of PAM actually is much higher than generally believed, because many lesions that meet the diagnostic criteria for PAM never come to clinical attention and may even be ignored by the patient and the physician.

The clinical features of PAM were elucidated in this study (Table 2). Most patients were asymptomatic or noticed only the patch of pigment. The extent of PAM was 3 clock hours or less in 76% and more than 3 clock hours in 23%. Corneal involvement with PAM was noted in 23%. The extent of PAM is best determined by making large detailed drawings during meticulous preoperative slit-lamp examination. Careful preoperative assessment is important because the precise extent of PAM is often less obvious in photographs or during intraoperative examination with the operating microscope. Accurate information concerning the extent of the lesion is critical in planning therapeutic strategies.

The natural course of PAM with regard to progression, recurrence, and evolution to melanoma has not been previously elucidated. In the frequently cited histopathologic series from the AFIP, the investigators reported that 32% of 41 eyes with PAM progressed to melanoma. If the PAM showed microscopic evidence of atypia, progression to melanoma occurred in 46%, but if there was no atypia, the chances were nil.[8-11] The study included mainly cases that were referred to the AFIP for histopathologic diagnosis. Hence, they generally were larger lesions with more bothersome histopathologic features. The investigators concluded that biopsy or removal of all PAM lesions was warranted. However, that study did not include potential cases in the general population that were not subjected to biopsy.

Neither the studies of Folberg and associates[7-11] nor the study of Gloor and Alexandrakis[14] addressed the natural course of PAM following the initial clinical diagnosis. In this study, we attempted to address that question. All patients in our series had a lesion that appeared sufficiently suspicious to the referring ophthalmologist to prompt consultation at our ocular oncology center. Hence, this study presumably provides a somewhat more reliable estimate of the true risk of the progression of PAM to melanoma. However, this study also has selection bias, because lesions that are more suspicious clinically are more likely to be directed to a tertiary referral center.

The majority of PAM lesions in this series were small, allowing for observation (62%), and only 21% of these observed lesions showed enlargement during the course of follow-up (Tables 3 and 4). Hence, it appears that many small, bland lesions can cautiously be followed and are likely to remain stable and require no treatment.

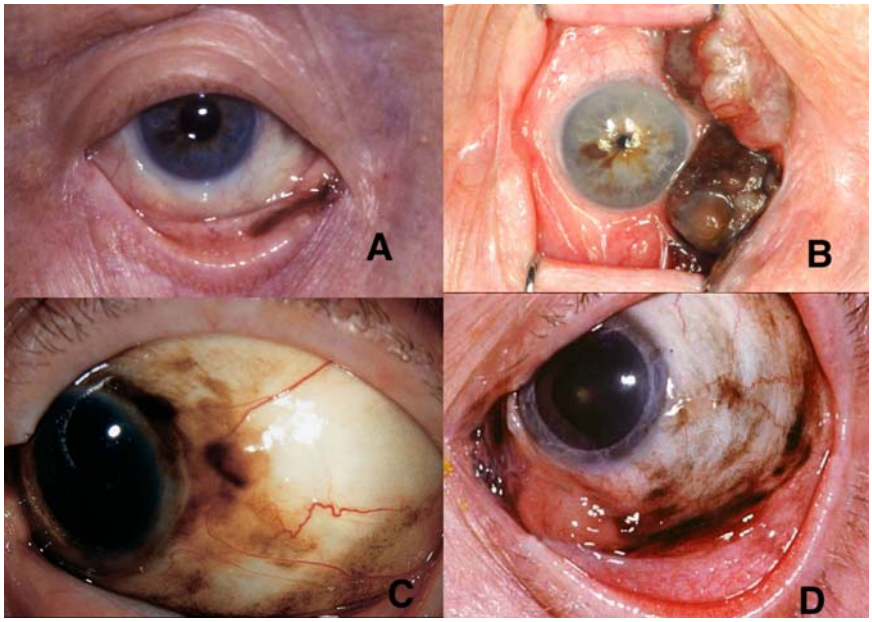

FIGURE 4

Transformation of primary acquired melanosis (PAM) into melanoma. A, At initial presentation, flat PAM was detected on the bulbar and forniceal conjunctiva. The lesion was removed and cryotherapy performed. It proved to be PAM with atypia. B, The patient did not return for follow-up, and 5 years later a large conjunctival melanoma invading into the caruncle, orbit, and eyelids was found and managed by complete surgical excision, canthoplasty, and postexcision cyberknife radiotherapy. C, PAM with early transformation into melanoma. The elevated darker areas suggest foci of evolving melanoma. D, PAM giving rise to nodule of amelanotic melanoma. The melanoma that arises from pigmented PAM is often nonpigmented clinically.

Of the larger lesions that were managed by initial biopsy and cryotherapy (Table 5), 27% recurred and 3% eventually evolved to melanoma. The mean interval from initial surgery to recurrence was 19 months, and the mean interval to development of melanoma was 39 months. The latter observations stress the need for periodic long-term follow-up of all patients who have had observation or excision of PAM, particularly if histopathologic studies reveal atypia.

Some differences were found in the AFIP series and the WEI series with regard to PAM progression to melanoma (Table 7). In the WEI series that included all cases (observed and biopsied), the incidence of progression to melanoma was 4%. In comparing only cases with available histopathology, overall progression to melanoma was 32% in the AFIP series and 3% in the WEI series. Both studies found no progression to melanoma if there was no cytologic atypia.

With regard to the assessment of the effect of the degree of cellular atypia and progression to melanoma, the current WEI series attempted to use the same criteria for atypia and severe atypia that were used in the AFIP series. The lower incidence of progression to melanoma in the WEI series probably reflects a variety of factors, including the probable referral of cases with more severe histopathologic features to the AFIP in contradistinction to cases with no atypia or mild atypia. Furthermore, patients in the WEI clinical series were followed up periodically by the same group of experienced ocular oncologists, and residual or recurrent PAM was treated promptly before it progressed to a more advanced stage.

In the WEI series, Kaplan-Meier estimates showed that the rate of PAM enlargement in the initially observed group was 26% at 5 years, 35% at 10 years, and 43% at 15 years. The estimates for evolution into melanoma were 8% at 5 years, 12% at 10 years, and 21% at 15 years (Table 8). These findings show the slow but potentially malignant progression of PAM. In the initially biopsied group, Kaplan-Meier estimates showed that the rate of PAM recurrence was 52% at 5 years and 58% at 10 and 15 years, and the rate of melanoma development was 5% at 5 years and 11% at 10 and 15 years. Despite apparent resolution of PAM on clinical inspection after meticulous treatment by excisional or incisional biopsy followed by cryotherapy, patients should be followed closely, because PAM recurrence with melanoma development can pose a serious threat.

The greater the extent of PAM on the surface of the globe, the greater the risk for PAM recurrence following biopsy and the greater the risk for melanoma (RR 1.70) development (Tables 9 and 10). For example, in patients who were observed, PAM involving 4 clock hours carried a 6.8 times greater risk for melanoma development than PAM of only 1 clock hour. If PAM involved 12 clock hours, the risk for melanoma development was 20.4 times greater than with a 1-clock-hour lesion.

Our philosophy for PAM management is based on long-term clinical experience and the results of this study. All patients with PAM (or any conjunctival tumor) should have a large detailed drawing performed in the office using slit-lamp biomicroscopy. The surgical plan is made on the basis of this drawing. If PAM is confined to the bulbar conjunctiva and is less than 1 clock hour in extent, we generally recommend observation once or twice a year unless the patient requests excision. In this analysis, 62% of cases were managed with observation, the majority of which were small lesions (Tables 3 and 4). If PAM is 1 to 2 clock hours in extent, the patient is counseled and offered the options of observation or treatment with the advice that excision is probably preferable. If the lesion is greater than 2 clock hours in extent, we generally recommend complete surgical excision and cryotherapy for those up to 5 clock hours and wide incisional biopsy plus cryotherapy for larger lesions.

For more diffuse PAM, our approach is to perform small conjunctival map biopsies in each quadrant and double freeze thaw cryotherapy to all remaining areas of pigment.[1,18-20] When extensive conjunctival tissue is removed and primary closure is difficult, amniotic membrane or buccal mucosal graft is employed.[25,26] Corneal PAM is managed with either alcohol epitheliectomy or topical mitomycin C. Depending on subsequent clinical and histopathologic findings, supplemental treatment for residual or recurrent PAM might include in-office cryotherapy or topical chemotherapy using mitomycin C.[20-22] Plaque brachytherapy can be used in selected instances.[1]

In conclusion, PAM appears to be more common than generally believed. Small foci of PAM (<1 clock hour) generally remain stable, but larger lesions carry greater potential for evolution into invasive melanoma. PAM without atypia and PAM with mild atypia carry almost no risk for progression into melanoma, whereas PAM with severe atypia shows 13% transformation to melanoma. Cautious, long-term follow-up is advised for all patients with PAM.

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PEER DISCUSSION

DR HANS E. GROSSNIKLAUS: In this study, Dr. Jerry Shields and coauthors evaluated their extensive experience in 311 eyes of 276 patients with a clinical diagnosis of primary acquired melanosis (PAM). The most significant clinical risk factor for progression was size in clock hours, with a 1.7 relative risk for enlargement per clock hour of conjunctival involvement. The authors provide practical treatment recommendations based on number of clock hours involved. In a purely clinical study, Gloor and Alexandrakis[1] found PAM in 36% of adult Caucasians. In a partly clinical and partly pathologic study, Dr Carol Shields and coworkers[2] found that PAM accounted for 11% of all conjunctival tumors and 21% of all melanocytic conjunctival tumors. In a purely pathologic study, PAM accounted for 6.6% of pigmented conjunctival lesions.[3] Therefore, even though PAM is fairly common, it is likely clinically overdiagnosed, as secondary melanosis and other lesions may clinically mimic PAM. Additionally, it is clinically impossible to distinguish between PAM without and PAM with atypia.

Of the 311 eyes in this series, 107 (34.4%) underwent biopsy as part of the initial management and 112 (36%) were ultimately biopsied. Of those 112 cases, 44 (39.3%) were histologically diagnosed as PAM without atypia, 44 (39.3%) as PAM with mild atypia, and 24 (21.4%) as PAM with severe atypia. Recurrence rates were 11%, 26%, and 50%, respectively, among those 3 groups, and melanoma developed in only 3 patients (13%), all of whom had PAM with severe atypia. Whereas the current series estimated a 13% progression of PAM to melanoma, the AFIP purely pathology series found a 32% progression of any type of PAM to melanoma.[4,5] This discrepancy is likely due to clinically overdiagnosed PAM, the referral nature of the AFIP series, and other factors. Importantly, both the current study and the AFIP series demonstrate that there are pathologic risk factors, such as degree of atypia, that correspond to disease progression. This has recently been shown by another group.[6]

There has been some controversy regarding the nomenclature of PAM. Some have advocated for the term *melanoma-in-situ*. Shields and coauthors believe that the term *melanoma-in-situ* may unnecessarily alarm clinicians and patients. I agree that PAM is the best term for this condition,[7] especially since ophthalmologists understand the implications of this diagnosis. Shields and coauthors use mild and severe atypia in their histopathologic classification scheme for PAM, yet there is no moderate category, as proposed by others.[8] This study found that clinical size in clock hours correlated with disease progression. Did the authors evaluate for nodularity, thickening, or change in color? The authors advocate for map biopsies for diffuse PAM (>5 clock hours). In some instances, it is quite difficult to discern the extent of the PAM at the slit lamp. Are there any clinical clues that may help distinguish the extent of nonpigmented PAM, the so-called PAM sine pigmento[9]? The authors used topical mitomycin C in some instances. This should be used judiciously and only by experienced ophthalmic oncologists for PAM, as the PAM may become depigmented after treatment, thus masking underlying invasive melanoma. I wish to congratulate the authors on their extensive work and for bringing this important topic to our attention.

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DR. ALLAN J. FLACH: No conflicts. When you chose your suspicious lesions and performed biopsies of them, was there any change in growth or behavior after those biopsies? How did you select which ones were suspicious, and not more likely malignant, without the results of your present study?

DR. JOSE S. PULIDO: No conflict of interest. I really would like to thank both Dr. Shields for their wonderful presentation and their ability to bring forward clinical science. They both gave presentations that showed important valid interest to clinicians. My question for Dr. Shields relates to the patients who had the progressive enlargement in association with prior biopsy. What did the biopsy show? Was there a relationship between having had the biopsy and being referred? Was there a confounding effect from that?

DR. BALAMURALI AMBATI: What is the role of interferon alpha 2, mitomycin-C (MMC), and 5-fluourouracil (5-FU) for intralesional or topical chemotherapeutic of PAM or melanoma either as single agent applications or given in combination?

DR. JERRY A. SHIELDS: I would like to thank everyone for their comments. They are all very constructive. First, with regard to Dr. Grossniklaus and his point about the possible over-diagnosis of PAM based on the clinical features. In our series we adhered strictly to the definition that I provided. The lesions were primary, acquired, melanotic, and flat. Was there a rare case of some other condition like an atypical nevus? It might have occurred, but we were pretty strict in our diagnostic approach, and I do not think there were any errors due to over-diagnosis.Dr. Grossniklaus mentioned melanoma in situ. He has written a magnificent article on this in response to Dr. Bernie Ackerman, a dermatopathologist, who claims that all PAM should be called melanoma in situ and that ophthalmic pathologists use the wrong terminology. Opposition to that claim was presented by Dr. Grossniklaus in the journal Modern Pathology. I believe that we are going to continue to call it PAM in ophthalmology. With regard to the question regarding mild, moderate, and severe classification, our pathologist, Ralph Eagle, generally preferred to use the categories of mild and severe. Many are histological borderline cases. and are - difficult interpretations for pathologist.. Regarding nodularity and vascularity that Dr. Grossniklaus has mentioned, if there was nodularity or vascularity we generally excised the lesion and if they proved to be melanoma initially, they were excluded from this study of PAM. I think that answers that question. That also answers the question regarding amelanotic PAM. I think if you have PAM and you follow the patient and you see amelanotic thickening starting anywhere, you must assume that PAM is evolving into a melanoma. .Regarding question of Dr. Flach about change after biopsy, there many different cases here and indeed, some of them did change after biopsy and showed progression. Many of those were from patients who had undergone biopsy elsewhere before being referred to us. These were much more extensive lesions and we could not remove them entirely. Therefore, we performed the biopsy and applied cryotherapy so that the entire pigmented area was treated. Using that approach, recurrence is not common. Regarding how we select treatment, when a patient presents with 1 o'clock of PAM we generally advise observation. However, there are several factors you must consider, such as the age and general health of the patient, a personal history of cancer, family history of cancer,, and others. All of these findings are taken into account when making a therapeutic decision The last question was about chemotherapy and other topical agents. Topical mitomycin-C is effective for mild cases of PAM. It is less effective for more extensive cases, particularly if there is deeper stromal involvement. Mitomycin C is more squamous cell carcinoma in situ. I appreciate the attention of the audience and the comments of Dr. Grossniklaus and others.