Proliferating Pilar Tumors

A Clinicopathologic Study of 76 Cases With a Proposal for Definition of Benign and Malignant Variants

Jay Ye, MD, PhD,[1] Oscar Nappi, MD,[2] Paul E. Swanson, MD,[3] James W. Patterson, MD,[4] and Mark R. Wick, MD[4]

Abstract

We studied proliferating pilar tumors (PPTs) to establish histologic criteria that could predict behavior. We reviewed all cases in our consultation files (1989-2000) and evaluated 76 cases with meaningful follow-up information. Histologic examination involved attention to tumor silhouette, degree of nuclear atypia, mitotic activity, necrosis, and perineurial or angiolymphatic invasion. Tumors were stratified as follows: group 1 PPTs, circumscribed silhouettes with "pushing" margins, modest nuclear atypia, and an absence of pathologic mitoses, necrosis, and invasion of nerves or vessels; group 2 PPTs, similar to group 1 but manifested irregular, locally invasive silhouettes with involvement of the deep dermis and subcutis; group 3, invasive growth patterns, marked nuclear atypia, pathologic mitotic forms, and geographic necrosis, with or without involvement of nerves or vascular structures. Recurrence occurred in none of 48 group 1 PPTs; 3 (15%) of 20 group 2 PPTs had local regrowth; 4 (50%) of 8 of group 3 PPTs recurred and/or metastasized to regional lymph nodes. The differences between groups 1 and 3 and between 2 and 3 were statistically significant (P = .0002, P < .05, respectively). It seems justifiable to regard group 1 PPTs as benign, group 2 as having potential for locally aggressive growth, and group 3 also as having metastatic potential. The latter 2 categories might be equated with low and high grades of malignancy among PPTs of the skin.

The lesion known as *proliferating pilar tumor* (PPT) usually is described in the literature as a well-circumscribed dermal or subcutaneous neoplasm with squamoid cytologic features and trichilemmal-type keratinization.[1] This neoplasm was first recognized by Wilson-Jones[2] in 1966 as an entity that had the histologic capacity to simulate squamous cell carcinoma. A variety of diagnostic terms have been appended during the past 35 years, including proliferating epidermoid cyst, pilar tumor of the scalp, proliferating trichilemmal cyst, proliferating epidermoid cyst, giant hair matrix tumor, hydatidiform keratinous cyst, trichochlamydocarcinoma, and invasive hair matrix tumor,[2-9] reflecting dissimilar interpretations of the biologic nature of the lesion in question. PPTs most commonly occur on the scalp during the fourth to eighth decades of life and have a distinct predilection for women.[10] They typically undergo slow but progressive enlargement over several months to years, yielding lobulated and variably exophytic masses that occasionally might ulcerate.[1]

Although most cases pursue a favorable clinical course and surgical excision is curative, frank malignancy arising in a PPT has been reported.[10-12] High proliferative activity and DNA aneuploidy have been documented in some tumors with malignant transformation.[11,13-16] We undertook the following study to determine whether there were morphologic features that would correlate reproducibly with the biology of PPTs. The validity of the resulting histopathologic construct was tested by analysis of accrued follow-up data on cases included in the series.

Materials and Methods

Cases coded as proliferating pilar neoplasms (or one of the aforementioned diagnostic synonyms) and accessioned January 1989 through December 2000 were retrieved from

Image 1 Clinical photograph of benign proliferating pilar tumor showing a nondescript nodular lesion of the scalp.

our aggregated institutional files. Paraffin-embedded sections were stained with H&E and reviewed in each case. Tumors were segregated histologically into 3 groups based on a combination of the degree of stromal invasion and the level of cytologic atypia, with no knowledge of the clinical evolution of the cases. Group 1 cases showed no infiltration of surrounding tissues and minimal nuclear atypia; group 2 lesions were clearly invasive but had modest cytologic abnormalities; and group 3 tumors were invasive and cytologically anaplastic. Follow-up data were obtained by contacting treating physicians or pathologists from whom consultation materials originated and by reviewing hospital medical records. All necessary documentation had been filed with institutional review boards at our institutions to obtain clearance with respect to procurement of confidential patient information.

The Fisher exact test was used to evaluate statistical differences between diagnostic groups. Computer software (STATA, Computing Resource Center, Santa Monica, CA) was used.

Immunostains on available paraffin blocks of PPT were done with monoclonal antibodies AE13 and AE14, directed at "hard" or pilar-type keratin polypeptides[17] (kindly supplied by T.T. Sun, MD, New York University, New York, NY) at dilutions of 1:150 and 1:200, respectively. Five examples each of well-differentiated, moderately differentiated, and poorly differentiated squamous cell carcinomas of the skin were studied simultaneously for comparison. Heat-mediated (microwave) epitope retrieval[18] was used for all tissue sections, and they were developed with the streptavidin-biotin-peroxidase complex technique. Appropriate positive and negative control sections were included.

Results

Eighty-one cases of PPT were seen collectively during the 12-year study period. However, follow-up could be obtained for only 76 cases, and the other 5, therefore, were not included in the final series of cases.

Clinical Features

Group 1 Tumors

The tumors of 48 patients were classified as PPT. The ages of patients ranged from 23 to 89 years (mean, 65.9 years), and the male/female ratio was 1:5. The lesions were located on the scalp (30 cases) **Image 1**, forehead (10), proximal extremities (3), face (2), neck (2), and trunk (1), and they had been present for 2 months to several years before biopsy was done. The clinical impression was that of a "cyst (not further specified)," or "cylindroma." All patients had complete surgical excisions. No recurrences were reported during follow-up periods of 40 months to 21 years (mean, 8 years).

Group 2 Tumors

Tumors from 20 patients in group 2 were classified as low-grade malignant PPTs (LMPPTs) **Table 1**. Patients' ages ranged from 30 to 87 years (mean, 64.1 years), and the male/female ratio was 1:2. The duration of tumor growth was known in only 6 cases and ranged from 1 month to "several years." The tumors were located on the scalp (11 cases), trunk (3), forehead (2), face (2), and arm and periauricular area (1 each). Clinical diagnoses included keratinous cyst, cyst (not further specified), sebaceous cyst, basal cell carcinoma, squamous cell carcinoma, PPT, and cylindroma. All patients in this group underwent excision of the tumor, and 2 had excision of regional lymph nodes as well. Follow-up information was available for 17 cases, during periods of 26 months to 6 years. Three patients had recurrences of their tumors at 3 months, 9 months, and 2 years after diagnosis. Reexcision apparently was curative in those cases.

Group 3 Tumors

Eight tumors were classified as high-grade malignant PPTs (HMPPTs) in patients ranging in age from 45 to 88 years (mean 64.5 years) **Table 2**. The male/female ratio was 1:2. The tumors were located on the scalp (3 cases) **Image 2**, forehead (1), neck (1), back (1), arm (1), and leg (1), and they had been present for 1 month to "several years." Clinical interpretations included squamous cell carcinoma, angiosarcoma, keratinous cyst, sebaceous cyst, and adnexal tumor. After biopsies were done, surgical excision was accomplished in each case in this group. In addition, 1 patient had a formal regional lymphadenectomy because of palpable occipital and cervical lymphadenopathy, and another patient was given postoperative

■Table 1■
Group 2 Tumors (Low-Grade Malignant Proliferating Pilar Tumors)

Sex/Age (y)	Location	Duration	Size (cm)	Clinical Diagnosis	Treatment	Follow-up
M/41	Scalp	NA	1.0	Lesion	Excision	3 mo, recurred
F/85	Scalp	NA	9.0	Cylindroma	Excision	9 mo, recurred
					LN dissection	36 mo, NED
F/75	Scalp	Several years	1.5	NA	Excision	2 mo, NED
F/44	Scalp	NA	2.1	Keratinous cyst	Excision	6 mo, NED
F/78	Scalp	20 y	6.0	PPT	Excision; LN dissection	12 mo, NED
F/65	Scalp	1 y	3.0	SCC	Excision	15 mo, NED
F/44	Scalp	NA	1.0	Sebaceous cyst	Excision	16 mo, NED
F/57	Scalp	NA	1.0	Cyst	Excision	2 y, NED
F/66	Scalp	NA	3.0	Keratinous cyst	Excision	2 years, NED
M/87	Scalp	1 y	0.6	SCC	Excision	4.5 y, NED
F/65	Scalp	NA	3.0	Lesion	Excision	8.5 y, NED
F/57	Forehead	Several years	1.4	Keratinous cyst	Excision	7 mo, NED
F/52	Eyebrow	1 mo	1.3	BCC	Excision	2 y, recurred
					Reexcision	3 y, NED
M/72	Left temple	NA	0.6	BCC	Excision	3 y, NED
F/75	Periauricular	NA	2.8	NA	Excision	18 mo, NED
M/68	Face	NA	NA	"Lesion"	Excision	36 mo, NED
F/30	Chest	NA	0.7	Cyst	Excision	34 mo, NED
M/64	Arm	NA	1.5	Keratinous cyst	Excision	7 mo, NED
M/84	Abdomen	NA	1.6	Lesion	Excision	6 y, NED
M/73	Trunk	NA	NA	"Cyst"	Excision	22 mo, NED

BCC, basal cell carcinoma; LN, lymph node; NA, not available; NED, no evidence of disease; PPT, proliferating pilar tumors; SCC, squamous cell carcinoma.

■Table 2■
Group 3 Tumors (High-Grade Malignant Proliferating Pilar Tumors)

| Sex/Age (y)	Location	Duration	Size (cm)	Clinical Diagnosis	Treatment	Follow-up
M/66	Scalp	3 mo	2.3	Angiosarcoma	Excision	Regional LN metastases at diagnosis; 5 mo, DOD
F/62	Scalp	1 mo	2.5	Adnexal tumor	Excision	2 mo, died of other causes
F/86	Scalp	6 y	5.0	SCC	Excision; LN dissection	3 y, NED
F/66	Forehead	NA	3.0	SCC	Excision; LN excision	Metastases to salivary gland and LN at diagnosis; 4 y, NED
F/48	Neck	NA	0.6	Sebaceous cyst	Excision	5 y, NED
M/88	Arm	Several years	6.0	SCC	Excision; radiotherapy	5 y, NED
M/45	Back	NA	5.0	Keratinous cyst	Excision	14 mo, recurrence
					Reexcision	42 mo, NED
F/55	Right lower leg	>1 y	4.0	NA	Excision	6 mo, recurrence
					Reexcision	42 mo, NED

DOD, died of disease (tumor); LN, lymph node; NED, no evidence of disease; SCC, squamous cell carcinoma.

radiotherapy. Follow-up information was available for all cases, ranging from 2 months to 5 years. In 1 patient, metastases developed involving the lungs, bones, liver, spleen, and multiple skin sites; the patient died 5 months after diagnosis. Another had secondary spread to the parotid gland and cervical lymph nodes. One additional patient died of a preexisting glioblastoma multiforme shortly after excision of her skin tumor; another 2 had local recurrences after 6 and 14 months but were free of tumor 42 months after reexcisions.

Pathologic Features

Group 1 Tumors

Gross examination showed that the sizes of lesions ranged from 0.3 to 6.5 cm (mean, 2.3 cm). They were multilobulated, flesh-colored masses centered in the dermis with yellowish white cut surfaces ■Image 3■. Histologically, they showed well-demarcated interfaces with the surrounding
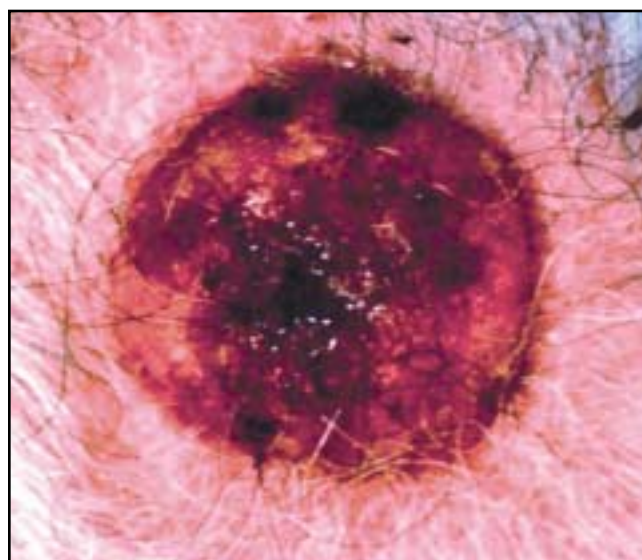
■Image 2■ Clinical photograph of high-grade malignant proliferating pilar tumor demonstrating a nodular, ulcerated, red-pink lesion on the scalp.

Image 3 Gross photograph of resected benign proliferating pilar tumor showing a multinodular tan-pink mass in the dermis with internal foci of hemorrhage and cystification.

dermis and subcutis and were composed of interanastomosing lobules of squamous epithelium **Image 4**. Communications with the overlying epidermis were seen in a minority of cases **Image 5**. The lesional epithelium was devoid of a granular layer, and it was punctuated by areas of "abrupt," glassy, trichilemmal-type keratinization **Image 6**. Focal nuclear atypia and individual cellular dyskeratosis also were apparent. Areas of dystrophic calcification were present in keratinized foci in some cases. The surrounding tissue showed a variably dense mononuclear infiltrate of plasma cells and lymphocytes

with scattered giant cells of the foreign body type. There was no evidence of perineurial or vascular invasion.

Group 2 Tumors

Tumor sizes ranged from 0.6 to 9 cm (mean, 2.3 cm). They were described macroscopically as light tan, firm, dermal nodules with small areas of degeneration.

The microscopic appearance was similar in all cases; the tumors showed continuity with the overlying epidermis in some cases, whereas the others were dermal nodules (or cysts) without direct connections to the surface epithelium. Similar to group 1 PPTs, group 2 tumors were composed of multiple lobulated and bosselated expansive masses of squamous epithelium **Image 7** separated by loose edematous stroma and filled centrally with homogeneous acellular eosinophilic material representing amorphous debris and pilar keratin **Image 8**. In addition, the squamoid tumor cells manifested large, hyperchromatic nuclei with irregular nuclear membranes surrounded by abundant eosinophilic cytoplasm. Foci of single cell necrosis and abrupt keratinization were identified. Cords of atypical squamous epithelium extended into the surrounding dermis **Image 9**, with a desmoplastic stromal response. There was a lack of marked cytologic atypia in group 2 PPTs. A minimal to moderate infiltrate of mononuclear inflammatory cells was identified as well.

Group 3 Tumors

These lesions were described grossly as dermally based, tan-pink, firm masses with central areas of degeneration, hemorrhage, or necrosis. They measured from 2.3 to 6.0 cm in greatest dimension (mean, 3.6 cm).
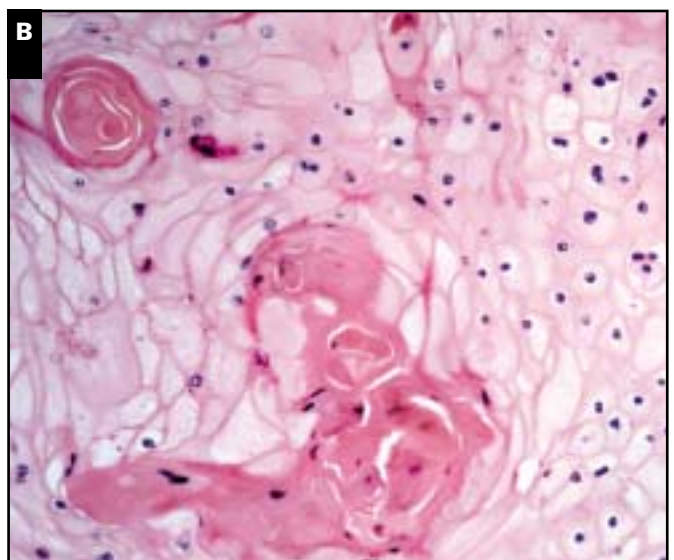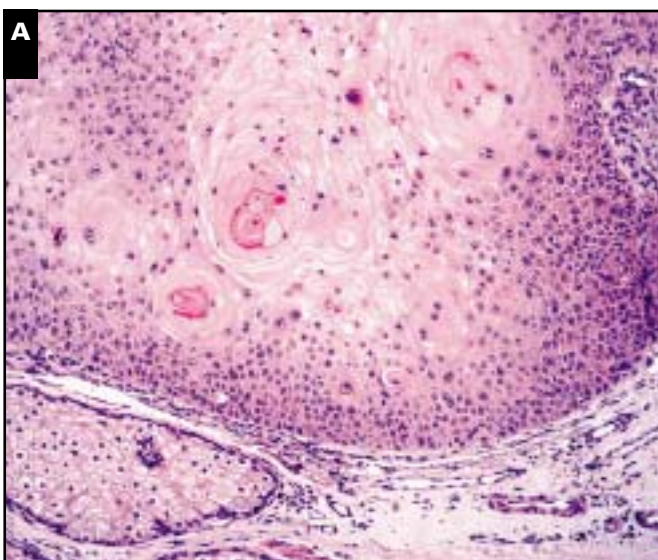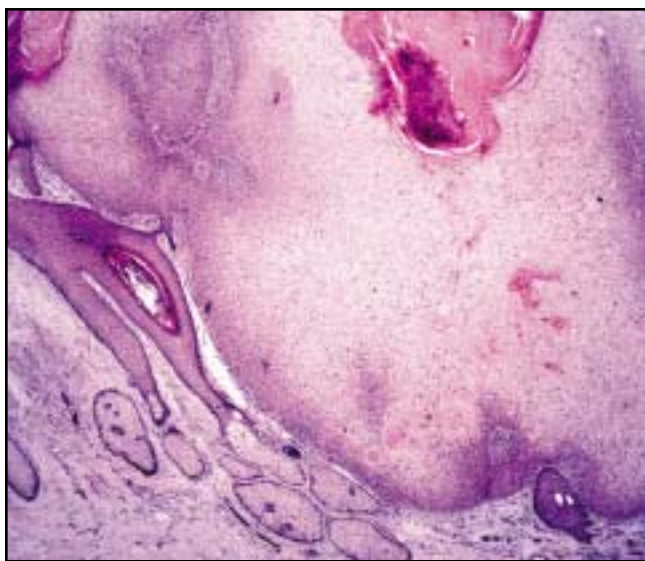
Image 4 **A**, Benign proliferating pilar tumor, showing a "pushing" interface between the squamoid neoplasm and the surrounding dermis. Note internal foci of trichilemmal-type keratinization in the lesion (H&E, ×160). **B**, "Abrupt" pilar-type keratinization is seen in this benign proliferating pilar tumor (H&E, ×250).

Microscopically, all group 3 tumors displayed comparable histologic appearances. They infiltrated the dermis extensively ▮**Image 10**▮, and some involved the overlying epidermis or extended into the subcutis. The tumors in this group were composed of sheets and nests of squamoid cells with multifocal necrosis and abrupt keratinization of the pilar type. The neoplastic cells had large hyperchromatic nuclei and irregular nuclear membranes and a moderate amount of amphophilic cytoplasm. In 1 case, the cytoplasm was clear. Numerous mitoses, many of which were atypical, were identified, averaging 1 per high-power (×400) microscopic field ▮**Image 11**▮.

The central aspects of the tumors often contained homogeneous, eosinophilic, acellular keratin admixed with necrotic debris. The adjacent stroma was desmoplastic. Sparse mononuclear inflammatory cells were dispersed throughout the neoplasms.

Immunohistochemical Results

Paraffin blocks were available from 22 tumors (group 1, 13; group 2, 6; group 3, 3) for immunohistochemical study. Antibody AE13 ▮**Image 12**▮ labeled 13, 5, and 3 of those lesions, respectively, whereas AE14 reacted with 11, 4, and 2

▮**Image 5**▮ This benign proliferating pilar tumor exhibits a connection to the epidermis and protrudes above the adjacent skin surface (H&E, ×40).
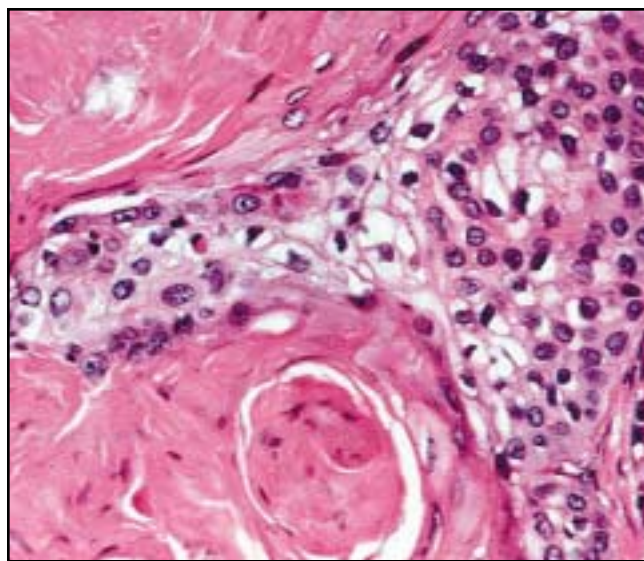
▮**Image 6**▮ A partial clear-cell constituency and pilar-type keratinization are evident in this proliferating pilar tumor (H&E, ×300).
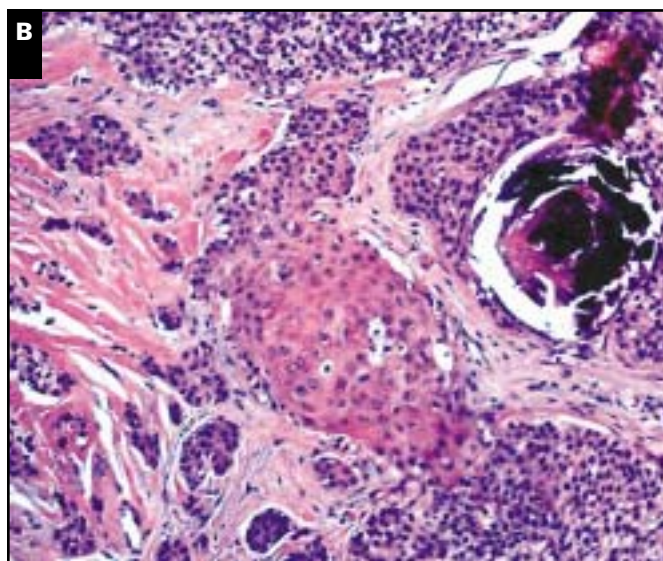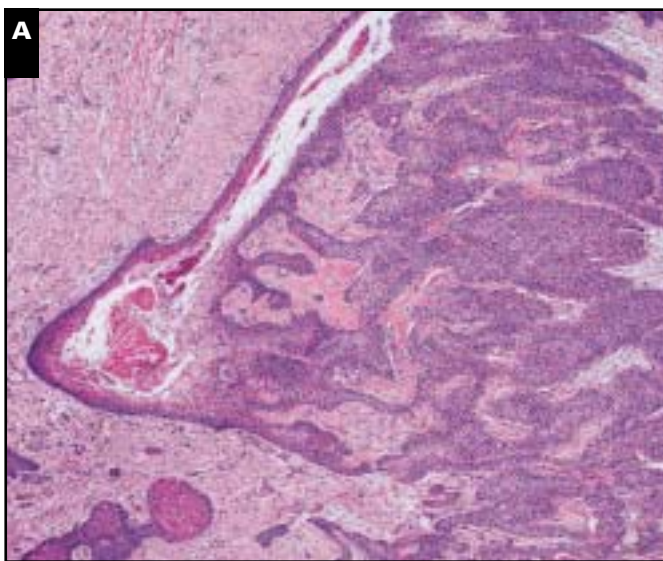
▮**Image 7**▮ **A**, Low-grade malignant proliferating pilar tumor shows irregular infiltration of the dermis by cords of neoplastic squamoid cells (H&E, ×40). **B**, Irregularly permeative cords of tumor cells are seen with foci of dystrophic calcification in low-grade malignant proliferating pilar tumor (H&E, ×160).

of them. None of the squamous cell carcinomas that were included as control sections were positive with AE13 or AE14. Positive and negative control sections stained as expected.

Statistical Comparisons

The major clinical and pathologic features in the 3 groups showed remarkable similarity in age, sex distribution, location, and size of the lesions. The HMPPT group demonstrated slightly higher tumor dimensions and a slightly decreased predilection for the scalp. However, because of the limited number of patients in that cohort, statistical significance of those factors was lacking. Local recurrence in the LMPPT group (3/20 [15%]) was significantly higher than that in patients with group 1 lesions (0/48) (P = .039; Fisher exact probability test). The incidence of adverse outcomes (including recurrence and metastasis) in group 3 patients (4/8 [50%]) was significantly greater than that seen in groups 2 (P = .045) and 1 (P = .0002).

Discussion

PPT arises principally on the scalp of elderly women; it has a clinical resemblance to keratinous or sebaceous cysts
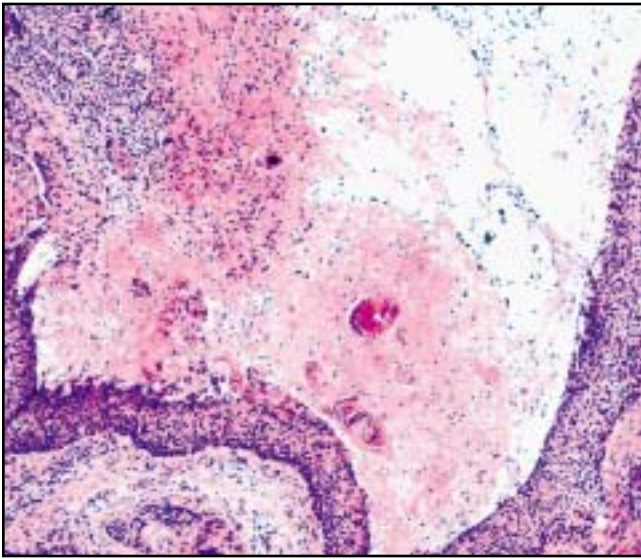

❚Image 8❚ Central cyst formation, with internal amorphous debris and pilar-type keratin, is apparent in this low-grade malignant proliferating pilar tumor (H&E, ×160).
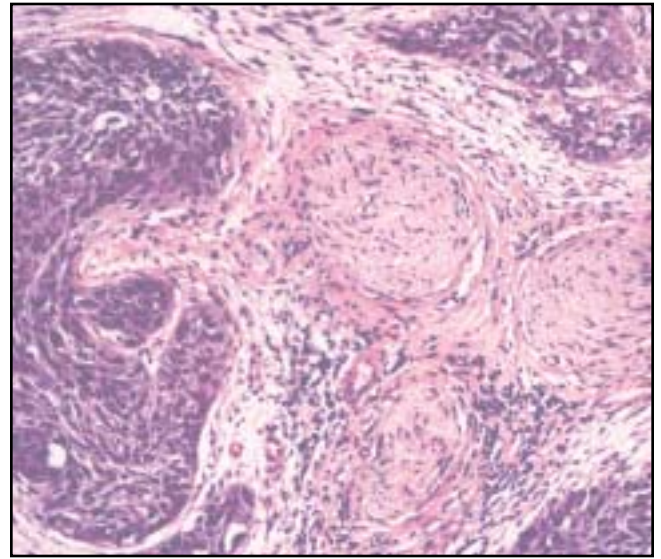
❚Image 9❚ Invasive tongues of tumor surround a nerve bundle in the dermis in this low-grade malignant proliferating pilar tumor (H&E, ×200).
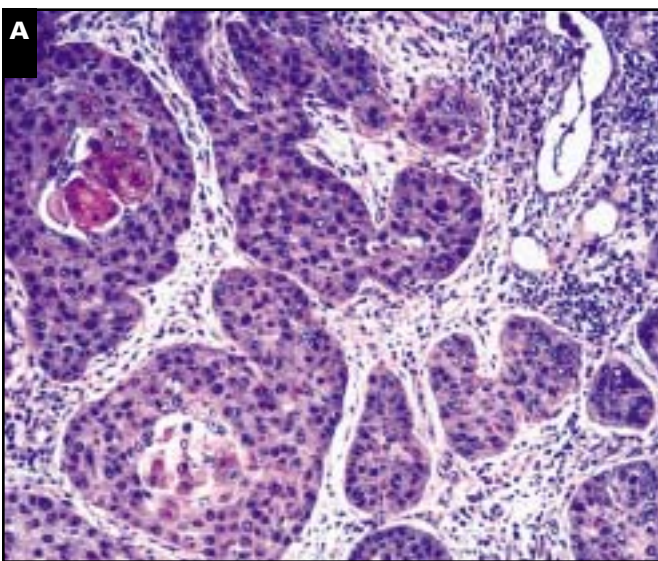
❚Image 10❚ A, Nests and cords of cytologically anaplastic tumor cells are punctuated by pilar-type keratinization in this high-grade malignant proliferating pilar tumor (H&E, ×160). **B**, Striking nuclear atypia and sheet-like cellular growth are apparent in another high-grade malignant proliferating pilar tumor (H&E, ×250).
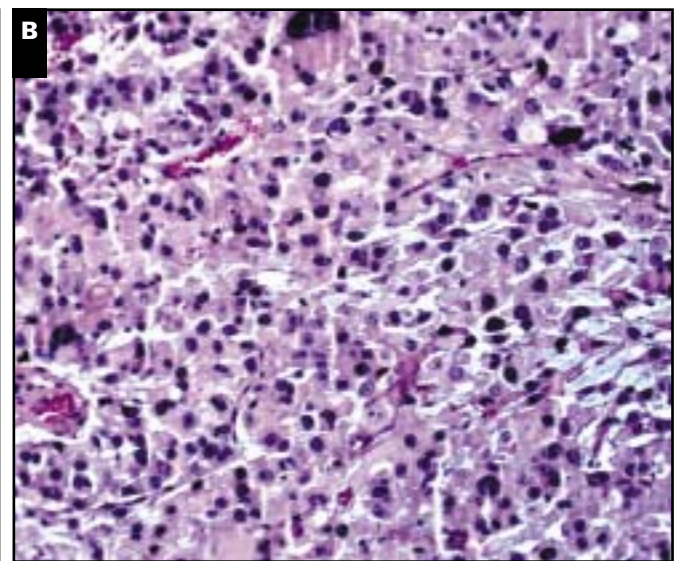
and a microscopic likeness to squamous cell carcinoma.[1-3] Many alternative designations have been used to describe this entity, as listed earlier, in several studies published in the English literature ▮Table 3▮.

A meta-analysis of 185 cases from 8 series[2,3,7-10,19,20] showed that 79.5% of the patients were women and 85.4% of tumors (146 of 171 included) occurred on the scalp. Patient ages ranged from 21 to 88 years, with a mean of 62.4 years, and the tumors measured up to 25 cm in maximum dimension (mean, 3.3 cm). The rates of local recurrence and regional lymph node metastasis were 3.7% and 1.2%, respectively.

Demographic characteristics of the lesions in the present series were comparable; however, they included more tumors that were not on the scalp and higher rates of local recurrence (6.6%) and lymph node involvement (2.6%).

The reasons for the differences are not immediately forthcoming. We speculate that with increased awareness of PPT as a tumor type, more cases are being recognized successfully by pathologists in all body sites and are not being grouped with squamous carcinomas as undoubtedly was true in earlier times. In addition, because follow-up data were not detailed in some previous series, an assumption was made that every
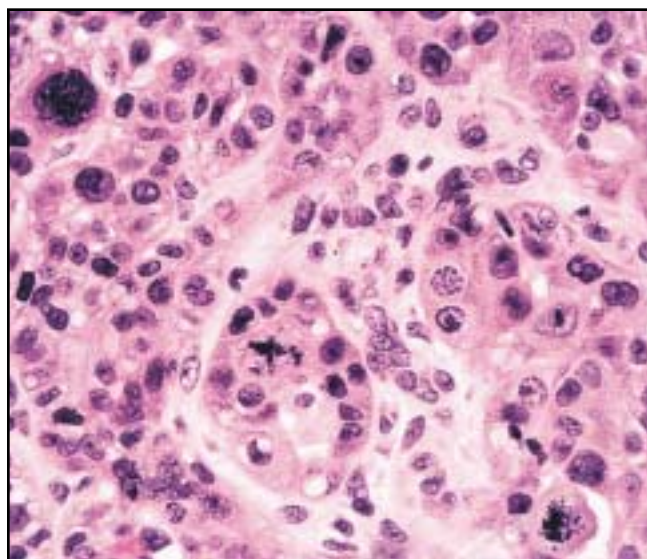
▮Image 11▮ Nuclear pleomorphism and atypical mitotic figures are seen in this high-grade malignant proliferating pilar tumor (H&E, ×300).
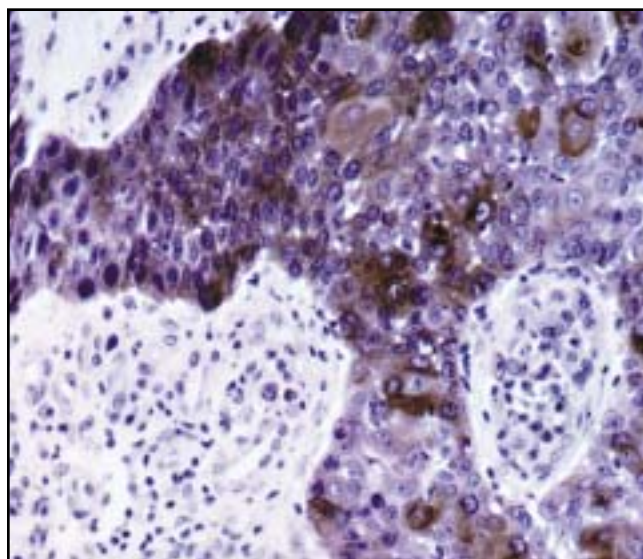
▮Image 12▮ Immunoreactivity with AE13 for pilar-type ("hard") keratin in low-grade malignant proliferating pilar tumor (×250).

▮Table 3▮
Meta-analysis of 8 Reported Series of Proliferating Pilar Tumors

Reference	Nomenclature	No. of Patients	M/F	Age Range (Mean), y	Site	Size Range (Mean), cm	Follow-up
Wilson-Jones[2]	Proliferating epidermoid cyst	9	1/8	50-79 (64)	Scalp, 8; back, 1	NA	1/8 recurred after 3 y
Reed and Lamar[9]	Invasive pilomatrixoma	14	2/12	36-75 (60)	Scalp, 14*	1-10 (3.0)	0/14 recurrences
Holmes[8]	Trichochlamydocarcinoma	7	1/6	65-84 (75)	Scalp, 7	1.5-12 (4.6)	1/6 recurred and spread to LN
Dabska[7]	Giant hair matrix tumor	12	2/10	41-85 (62.7)	Scalp, 10; back, 2	4-25 (8.7)	1/12 recurred
Janitz and Wiedersberg[19]	Trichilemmal pilar tumor	16	1/15	28-88 (63.9)	Scalp, 13†; other sites, 3	0.2-8 (2.8)	NA
Brownstein and Arluk[3]	Proliferating trichilemmal cyst	50	8/42	27-83 (59)	Scalp, 45; other sites, 5	0.4-10 (2)‡	No recurrence§
Baptista et al[20]	Proliferating trichilemmal cyst	14	4/10	40-80 (65.6)	Scalp, 14	3-10 (5.5)‖	1 recurrence§
Sau et al[10]	Proliferating trichilemmal cyst	63	18/45	21-88 (63)	Scalp, 49; other sites, 14	0.4-15 (2.9)	1/59 recurred; 1/59 spread to LN
Totals		185	37/148	21-88 (64.2)	Scalp, 146; other sites, 25	0.2-25 (3.7)	Recurrence, 6/163 (3.7%); LN metastasis, 2/163 (1.2%)

LN, lymph node; NA, not available.
* Excluded from the analysis because authors selected scalp lesions only.
† Nine sites labeled as "head" interpreted as scalp.
‡ Numbers in the parentheses are median but treated as mean in meta-analysis.
§ Number of patients with follow-up information was not stated; meta-analysis was performed assuming every patient was followed up completely.
‖ Information on size was available for only 8 tumors.

patient was followed up when performing the meta-analysis. Consequently, the summarized incidences of recurrence and metastasis are almost certainly underestimates of the actual rates. We did not include case reports in the meta-analysis because patients with adverse outcomes tend to be represented disproportionately in that format. Nevertheless, 12 cases of metastasizing PPT have been reported heretofore.[10,21,22]

The number of patients with PPT who have adverse outcomes is low, but obviously it is not nil. We classified our cases into 3 morphologic groups in an effort to correlate histologic features with tumor behavior. The resulting data indicate that although group 1 lesions (PPTs) behave in a benign manner, group 2 tumors (LMPPTs) have a small risk of local recurrence, and group 3 neoplasms (HMPPTs) have the potential for regional recurrence and metastasis. Irregular infiltration of the surrounding dermis separates group 1 lesions from those in the other 2 strata. Because of that pattern of growth, it is conceivable that discontinuous "skip" foci in the dermis might be missed by attempts at excision and serve as the seeds of subsequent recurrence. The absence of marked anaplasia in LMPPTs seems to indicate that they lack the capacity for embolic metastasis. On the other hand, HMPPT is highly atypical cytologically and possessed that biologic ability; indeed, it is separable morphologically from squamous cell carcinoma only by its demonstration of pilar-type keratinization and reactivity with AE13 and AE14.[17]

Of the metastasizing PPTs reported in the English literature,[8,10,12,21,23-26] all but 1 case[8] showed marked cytologic atypia; several also were said to exhibit infiltrative margins and a desmoplastic stroma. DNA aneuploidy was demonstrated in such histologically anaplastic lesions by Jaworski[27] and Rutty and colleagues.[11] Whether marked cytologic aberrations truly were absent in a metastasizing tumor reported by Holmes[8] is unclear; it is possible that failure to detect them might have reflected sampling error.

Most single case reports of metastasizing PPT were made explicitly because of that behavior, and the real risk of distant spread has been rather unclear. In our series and in that of Sau et al,[10] the combined rate of metastasis was 25% (4/16) for grade 3 lesions. Thus, HMPPT might have a greater risk of untoward evolution than histologically similar squamous cell carcinomas of the skin.[28]

The histologic subclassification of PPT into 3 histologically defined subgroups provides a practical means to estimate the risk of adverse tumor behavior. Benign PPT is curable with simple excision, whereas the more aggressive capabilities of LMPPT and HMPPT might require wider surgical removal and additional therapeutic interventions.

From [1]Dahl-Chase Pathology Associates, Bangor, ME, and the Departments of Pathology, [2]Cardarelli Hospital, Naples, Italy, [3]University of Washington, Seattle, and [4]University of Virginia, Charlottesville.

Address reprint requests to Dr Wick: Division of Surgical Pathology, Room 3882 OMS/Campus Box 800214, University of Virginia Medical Center, 2200 Jefferson Park Ave, Charlottesville, VA 22908-0214.

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