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A Retrospective Study of the Clinicopathological Characteristics of Approximately 1,600 Pilomatricomas Treated at a Single Institution

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Background: First reported by Malherbe in 1880, pilomatricoma is a common benign skin tumor generally believed to occur mainly in children and adolescents. We conducted this study to better define the characteristics of pilomatricoma and compare our findings with current knowledge.

Methods: Patients diagnosed pathologically with pilomatricoma from 2016 through 2020 at Nippon Medical School Musashi Kosugi Hospital were included (1,559 patients, 1,590 tumors). Clinicopathological characteristics were analyzed.

Results: The male to female ratio was 1:1.6, and the most common tumor site was the upper limbs (33.7%). Preoperative diagnosis was correct in 48.5% of the patients, and their average age at resection was 33.5 years. Resection was carried out in 70% of the patients within 1 year, but time to resection was more than 1 year in the other 30%. Pathologically, squamous stratifying keratinocytes were observed in 41.7% of the patients, cells with a large pale pink cytoplasm in 38.9%, hair papilla-like structures in 33.9%, ossification in 15.7%, trichohyalin granules in 11.9%, and aggregations of follicular germinative cells in 7.8%. Of the chronological and morphological stages proposed by Kaddu (stage 1: early, stage 2: fully developed, stage 3: early regressive, stage 4: late regressive), stage 3 was the most common (70.6%).

Conclusion: Pilomatricoma is more common in females, regardless of ethnicity or age, but the tumor location in the upper limbs commonly observed in Japanese patients may indicate ethnic differences. Pathologically, the fact that cells linked to follicular differentiation are observed suggests that pilomatricoma is a complex panfollicular neoplasm. Time to resection appears to correlate with Kaddu stages. Factors such as age, location, sex, depth, and stage may affect the pathological features of this tumor.

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Key words: pilomatricoma, female, upper limbs, Japanese, panfollicular

Introduction

Pilomatricoma is a common benign skin tumor generally believed to occur mainly in children and adolescents. First reported by Malherbe[1] in 1880, it is a firm, asymptomatic, slow-growing dermal or subcutaneous nodule with a female predilection, most commonly occurring in the head and neck[1]. However, in our daily outpatient clinics, patients with pilomatricoma are not limited to young people, and sites vary, with tumors also found in the trunk and limbs. The aim of this study was to better define the clinical and pathological characteristics of pilomatricoma and compare them with current knowledge. No other retrospective study of pilomatricoma including more than 1,000 cases from a single institution has been reported in the literature. Using pathological reports from our dermatopathology division, we also examined the relationships between the clinical and pathological characteristics of pilomatricoma in a search for factors related to its pathogenesis.

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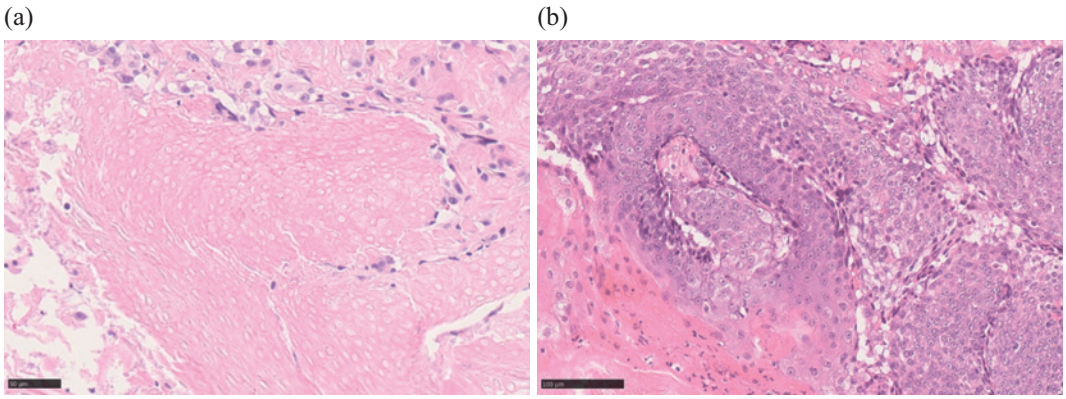

Fig. 1 Shadow cells (a) and basaloid cells (b) on HE slides
(a) Shadow cells (female, 12 years old, upper limbs)
(b) Basaloid cells (male, 67 years old, face)

Materials and Methods

This retrospective cross-sectional study was conducted at Nippon Medical School Musashi Kosugi Hospital, Kawasaki, Kanagawa, Japan. The research adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of Nippon Medical School Musashi Kosugi Hospital (approved ID: 638-3-33). All patients who had been histologically diagnosed with pilomatricoma by dermatopathologists and had undergone surgical resection from 2016 through 2020 were identified by reviewing the medical database of the hospital's dermatopathology division. This database contains digital whole-slide images of all surgically resected specimens fixed in formalin, processed, embedded in paraffin, and stained with hematoxylin and eosin (HE) by routine procedures. A NanoZoomer S210 Digital Slide Scanner C13239-01®, and NDP.view2 Image viewing software U12388-01® (Hamamatsu Photonics, Hamamatsu, Shizuoka, Japan) were used for digital imaging. Patient and clinical details (age at resection, sex, lesion location, presurgical clinical diagnosis, and time to resection) were also collected and stored in an anonymous dataset. A total of 1,559 patients and 1,590 tumors (1,561 tumors with actual slides) were included in this study. Histopathological diagnosis of pilomatricoma was made when an admixture of islands of enucleated shadow (ghost) cells surrounded by nucleated basaloid cells was identified, with the shadow cells having a distinct border and a central unstained area representing loss of nuclear detail (**Fig. 1a**)[2]. Most of the tumors consisted of shadow cells and basaloid cells (**Fig. 1b**), but we also included tumors consisting of shadow cells alone, without basaloid cells. Basaloid cells are packed and have round pale staining and finely stippled nuclei with prominent nucleoli[3].

We collected clinical data on 1,561 tumors, including age of the patient at resection, sex, tumor location, clinical diagnosis, and time to resection. Age at resection was divided into 4 groups by age range: 0-10 years old, 11-19 years old, 20-49 years old, and ≥50 years old. The tumor locations were the scalp, neck, face, trunk, and limbs (upper and lower). Time to resection ranged from days to years but was calculated in days (1 week=7 days, 1 month=30 days, 1 year=365 days), and the cases were categorized as <1 month, 1-3 months, 4-6 months, 7 months-1 year, or >1 year. Average time to resection for each age range was calculated. Data on time to resection were available for 430 cases. The clinical diagnoses and surgical excisions were made either at Nippon Medical School Musashi Kosugi Hospital or at hospitals that referred patients to us for histopathological diagnosis. All histopathological analyses were performed in the dermatopathology division of Nippon Medical School Musashi Kosugi Hospital.

We investigated the detailed pathological characteristics of the 1,561 tumors diagnosed as pilomatricoma: depth, the presence of hair papilla-like structures, trichohyalin granules, aggregations of follicular germinative cells, ossification, squamous stratifying keratinocytes, cells with a large pale pink cytoplasm, and the morphological stages proposed by Kaddu[4] (stage 1: early, stage 2: fully developed, stage 3: early regressive, stage 4: late regressive) (**Fig. 2, 3**). Depth was defined according to where >50% of the tumor resided (subcutaneously or dermally) when there was enough surrounding tissue to determine its depth. Trichohyalin granules are bright red granules in the cytoplasm of cells in the inner root sheath of the hair (**Fig. 3a**)[5]. Hair papilla-like structures consist of basaloid aggregations with sharp circumscription and

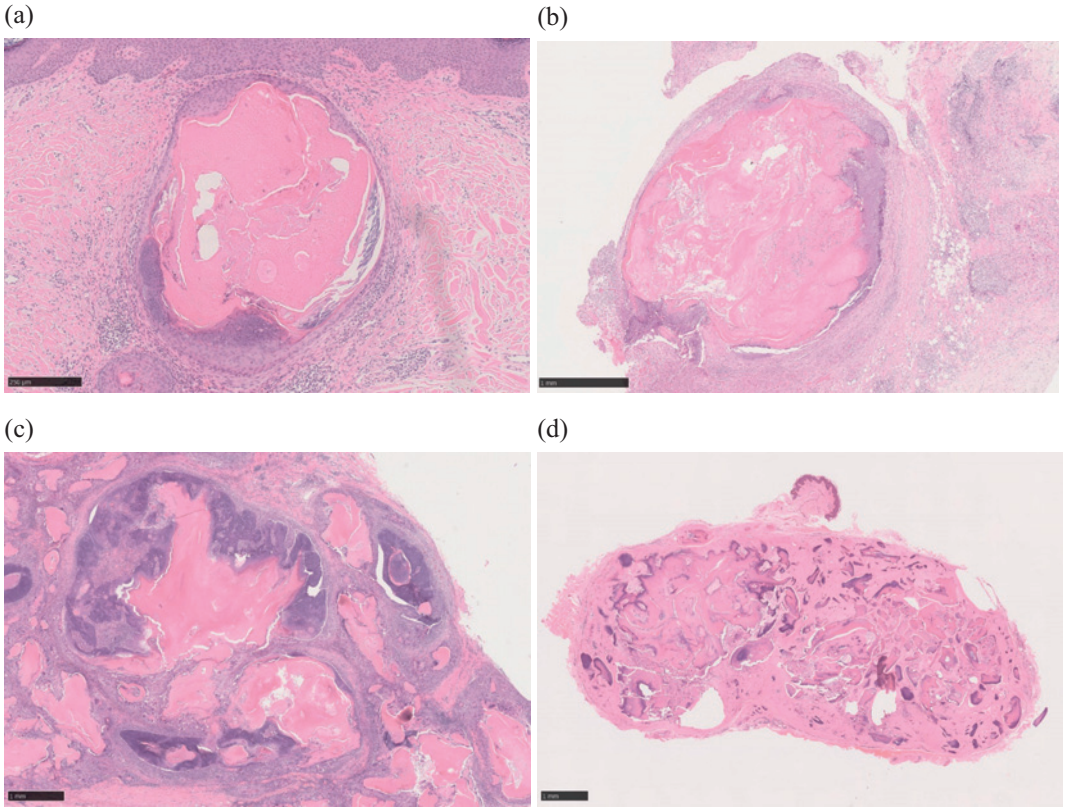

Fig. 2 The 4 stages of Kaddu
(a) Stage 1: early (female, 74 years old, head)
(b) Stage 2: fully developed (male, 67 years old, face)
(c) Stage 3: early regressive (female, 22 years old, face)
(d) Stage 4: late regressive (male, 27 years old, upper limbs)

smooth borders, with peripheral alignment surrounded by compressed fibrous tissues, and dermal protrusion (**Fig. 3b**)[5,6]. Follicular germinative cells are palisading cells with oval nuclei, like those in the follicular bulge (**Fig. 3 c**); they have thin, oval, dark-staining nuclei without discernable nucleoli or a distinct chromatin pattern[7]. Squamous stratifying keratinocytes consist of flat homogenous multiple-layered cells with a bright cytoplasm with or without a nucleus, and are similar to the keratinocytes found in the squamous cell layer of the epidermis (**Fig. 3d**)[5]. Cells with a large pale pink cytoplasm have an eosinophilic cytoplasm and an oval nucleus; their glassy appearance is similar to that of keratinocytes in the outer root sheath of the isthmus (**Fig. 3e**)[5,8].

Kaddu[4] categorized pilomatricoma lesions chronologically into 4 morphological stages and proposed that these reflect the "life" of a pilomatricoma. Lesions begin as infundibular matrix cysts and end up as calcified and ossified nodules with no visible epithelial components. The details of the 4 stages proposed by Kaddu[4] in 1996, are 1. early stage (stage 1): small cystic structures lined by squamoid and basaloid epithelium containing keratin filaments and shadow cells (**Fig. 2a**); 2. fully developed stage (stage 2): large neoplasms lined with basaloid epithelium at their periphery, and composed within of irregularly shaped, densely packed zones of cornified masses containing shadow cells (**Fig. 2b**); 3. early regressive stage (stage 3): no apparent epithelial lining but with basaloid cell foci at the periphery, and composed within of pink hair matrix material with shadow cells surrounded by granulation tissue with inflammatory infiltrate and multinucleated histiocytic giant cells (**Fig. 2c**); 4. late regressive stage (stage 4): no epithelial component and composed of irregularly shaped, partially confluent masses of faulty hair material, and calcified (sometimes metaplastically ossified) shadow cells embedded in a desmoplastic stroma, with little or no inflammatory infiltrate (**Fig. 2d**)[4,9]. We classified the tumors included in this study accordingly.

The time to resection for each Kaddu stage did not show a normal distribution on the Shapiro-Wilk test ($p < 0.05$). The Kruskal-Wallis test and Steel-Dwaas test were used to assess the relationships between time to resection and Kaddu stage. The relationships between the patho-

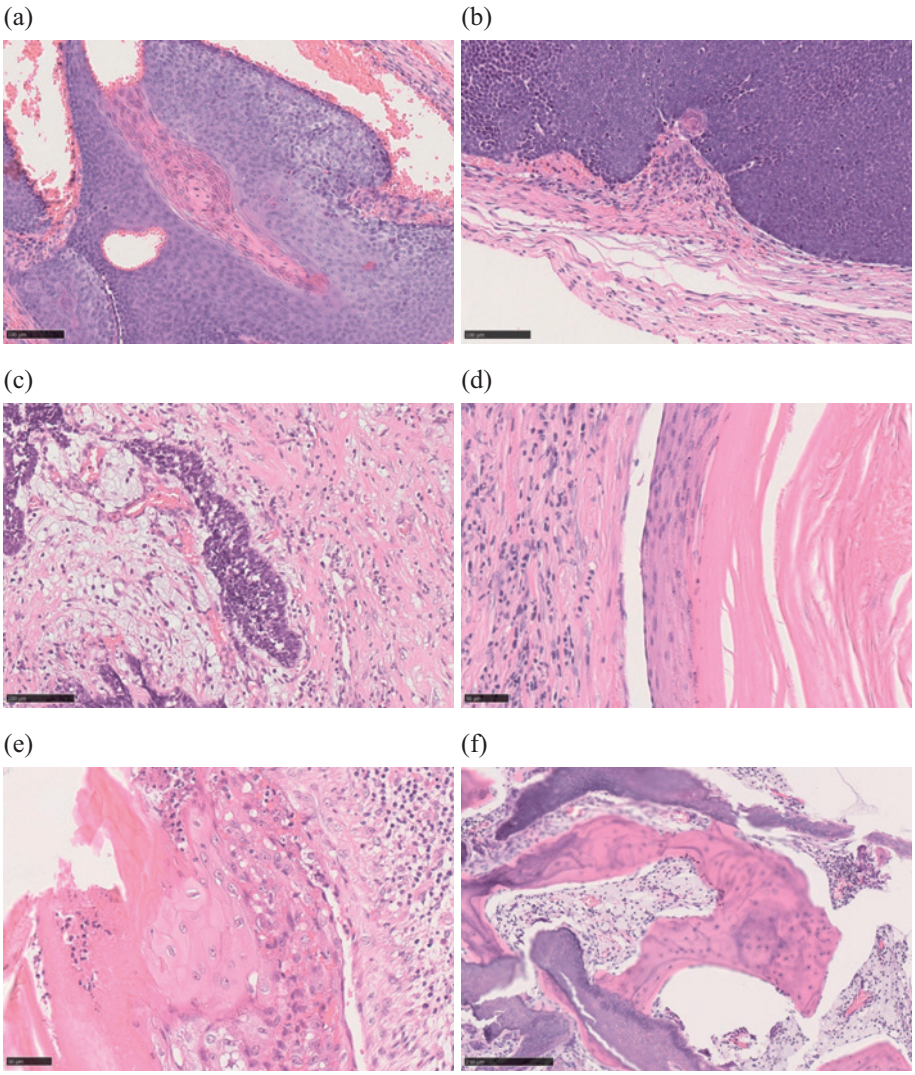

Fig. 3 Pathological characteristics of pilomatricoma found on HE slides
(a) trichohyalin granules (male, 37 years old, neck)
(b) hair papilla-like structure (female, 18 years old, upper limbs)
(c) follicular germinative cells (male, 68 years old, face)
(d) squamous stratifying keratinocytes (male, 14 years old, face)
(e) cells with a large pale pink cytoplasm (male, 67 years old, face)
(f) ossification (female, 30 years old, trunk)

logical characteristics and age, location, sex, depth, and Kaddu type were assessed with the X^2 test of independence for contingency tables, and on the basis of analysis of the residuals. Statistical significance was set at $p<0.05$, and results of $p<0.05$ on the X^2 test of independence were deemed to represent a correlation, with the strength of correlation indicated by the value of Cramer's V: the closer the value was to 1, the stronger the correlation. Adjusted residuals were calculated by analysis of the residuals. Adjusted residuals ≥ 1.96 ($p<0.05$) indicated a positive correlation, and adjusted residuals ≤ -1.96 ($p<0.05$) indicated a negative correlation. All calculations and statistical analyses were performed with Microsoft Excel® and Bell Curve for Excel®.

Results

a. Clinical Findings

Clinical findings are shown in **Table 1**. We found 1,590 pilomatricomas in 1,553 patients aged from 0 to 95 years (average age: 33.5 ± 19.0 years, median age: 29.5 ± 19.0 years). When classified according to age, patients aged 20-49 years predominated, representing nearly half of the cases (48.6%). The ratio of males to females was 1:1.6, and the female ratio was higher in all age ranges. The most common tumor site was the upper limbs (33.7%). Presurgical clinical diagnosis was correct in 48.5% of the

Table 1 Case numbers, incidence rate, clinical characteristics, and average time to resection in each age range

Clinical Characteristics	Age	All	0-10 years old	11-19 years old	20-49 years old	≥50 years old
		Cases (%)				
		1,553	139 (9.0)	359 (23.1)	754 (48.6)	301 (19.4)
Sex	Male	608	55	117	296	140
	Female	943	84	241	457	161
	Ratio	1:1.6	1:1.5	1:2.1	1:1.5	1:1.2
	Total cases	1,551	139	359	754	301
Location	Scalp	94 (6.0)	7 (5.1)	10 (2.8)	29 (3.9)	41 (13.8)
	Neck	193 (12.4)	55 (40.1)	100 (28.1)	227 (30.2)	110 (36.9)
	Face	500 (32.2)	18 (13.1)	51 (14.3)	91 (12.1)	39 (13.1)
	Trunk	147 (9.5)	10 (7.3)	46 (12.9)	71 (9.4)	21 (7.0)
	Upper limbs	524 (33.7)	42 (30.7)	16 (4.5)	278 (37.0)	68 (22.8)
	Lower limbs	93 (6.0)	5 (3.6)	13 (3.7)	56 (7.4)	19 (6.4)
	Total cases	1,555	137	356	752	298
Clinical Diagnosis	Calcifying epithelioma or pilomatricoma	754 (48.5)	89 (64.0)	210 (58.8)	373 (49.6)	105 (34.9)
	Atheroma	316 (20.3)	13 (9.4)	57 (16.0)	180 (23.9)	70 (23.3)
	Skin tumor	133 (8.6)	13 (9.4)	24 (6.7)	55 (7.3)	47 (15.6)
	Subcutaneous	132 (8.5)	16 (11.5)	37 (10.4)	78 (10.4)	31 (10.3)
	Others	219 (14.1)	8 (5.8)	29 (8.1)	66 (8.8)	48 (15.9)
	Total cases	1,554	139	357	752	301
Time to resection	<1 month	10 (2.3)	0	0	6 (3.5)	4 (4.4)
	1-3 months	118 (27.4)	16 (27.1)	33 (31.4)	32 (18.8)	35 (38.5)
	4-6 months	77 (17.9)	10 (16.9)	16 (15.2)	26 (15.3)	25 (27.5)
	7 months-1 year	98 (22.8)	19 (32.2)	35 (33.3)	29 (17.1)	13 (14.3)
	>1 year	127 (29.5)	14 (23.7)	21 (20.0)	77 (45.3)	14 (15.4)
	Total cases	430	59	105	170	91
	Average ± SD (days)	821 ± 2,269.2	409 ± 710.0	443 ± 710.0	1,480 ± 3,458.1	408.1 ± 981.2
Multiple lesions	2 lesions	25	2	8	4	1
	3 lesions	3	0	0	2	1
	Total cases	28	2	8	6	2

patients. The most common clinical diagnosis was calcifying epithelioma or pilomatricoma in all age groups (35-64%). Among the 430 cases for whom we knew the time to resection, the average time was 821.3 ± 2,269.2 days (about 2 years), with 29.5% of them falling into the >1 year group, the largest of the time to resection groups. However, about 70% of the tumors were resected within 1 year of being identified. The median time to resection was 240 ± 2,269.2 days. There were 28 cases (1.8%) of multiple lesions.

b. Pathological Findings

Pathological findings are shown in **Table 2**. Squamous stratifying keratinocytes were the most common (41.7%), followed by cells with a large pale pink cytoplasm (38.9%), hair papilla-like structures (33.9%), ossification (15.7%), trichohyalin granules (11.9%), and aggregations of follicular germinative cells (7.8%). Of the four Kaddu stages, stage 3 (70.6%) was the most common, with stages 1, 2, and 4 accounting for 0.9%, 11.8%, and 16.7%, respectively.

We evaluated the relationships between ossification, follicular germinative cells, hair papilla-like structures, squamous stratifying keratinocytes, cells with a large pale pink cytoplasm, and trichohyalin granules and the following factors: age at resection, location, sex, depth, and Kaddu stage. The X^2 test of independence showed the following results: for age, $X^2(27)=170.99$, $V=0.12$, $p<0.05$; for location, $X^2(45)=119.02$, $V=0.07$, $p<0.05$; for sex, $X^2(12)=25.05$, $V=0.01$, $p<0.05$; for depth $X^2(9)=203.53$, $V=0.26$, $p<0.05$; and for stage $X^2(27)=1,520.87$, $V=0.34$, $p<0.05$. Statistically positive and negative correlations are summarized in **Table 3**.

Ossification was positively correlated with age 20-49 years, tumor located in the upper limbs or subcutaneously, and Kaddu stage 4. Hair papilla-like structures were positively correlated with age ≥50 years, being male, and Kaddu stages 2 and 3. Squamous stratifying keratinocytes had a positive correlation with age of 20-49

Table 2 Incidence of pathological characteristics in relation to age at resection, location, sex, depth and Kaddu stage

Pathological Characteristics	Clinical and Pathological Characteristics																		
		Age				Location						Sex		Depth		Kaddu stage			
		0-10 years old	11-19 years old	20-49 years old	≥50 years old	Scalp	Neck	Face	Trunk	Upper limbs	Lower limbs	M	F	Dermal	Subcutaneous	1	2	3	4
	139	359	754	301	94	193	500	147	524	93	608	943	201	870	14	184	1,102	261	
	Cases (%)																		
Ossification	245 (15.7)	14 (10.1)	35 (9.7)	163 (21.6)	29 (9.6)	7 (7.4)	39 (20.2)	54 (10.8)	24 (16.3)	98 (18.7)	18 (19.4)	96 (15.8)	148 (15.7)	15 (7.5)	142 (16.3)	0	1 (0.5)	40 (3.6)	204 (78.2)
Follicular germinative cells	122 (7.8)	8 (5.8)	31 (8.6)	59 (7.8)	22 (7.3)	6 (6.4)	20 (10.4)	31 (6.2)	13 (8.8)	50 (9.5)	2 (2.2)	50 (8.2)	72 (7.6)	14 (7.0)	69 (7.9)	1 (7.1)	16 (8.7)	105 (9.5)	0
Hair papilla-like structure	529 (33.9)	43 (30.9)	123 (34.3)	224 (29.7)	133 (44.2)	39 (41.5)	76 (39.4)	159 (31.8)	43 (29.3)	184 (35.1)	25 (26.9)	235 (38.7)	290 (30.8)	98 (48.8)	348 (40.0)	1 (7.1)	97 (52.7)	430 (39.0)	1 (0.4)
Squamous stratifiying keratinocytes	651 (41.7)	61 (43.9)	176 (49.0)	262 (34.7)	146 (48.5)	42 (44.7)	80 (41.5)	217 (43.4)	60 (40.8)	220 (42.0)	26 (28.0)	249 (41.0)	398 (42.2)	121 (60.2)	372 (42.8)	8 (57.1)	119 (64.7)	518 (47.0)	6 (2.3)
Cells with a large pale pink cytoplasm	608 (38.9)	50 (36.0)	157 (43.7)	240 (31.8)	156 (51.8)	45 (47.9)	80 (41.5)	198 (39.6)	21 (14.3)	210 (40.1)	25 (26.9)	244 (40.1)	361 (38.3)	112 (55.7)	259 (56.7)	6 (42.9)	104 (56.5)	497 (45.1)	1 (0.4)
Trichohyalin granules	185 (11.9)	12 (8.6)	55 (15.3)	66 (8.8)	50 (16.6)	14 (14.9)	35 (18.1)	57 (11.4)	11 (7.5)	62 (11.8)	5 (5.4)	77 (12.7)	107 (11.3)	33 (16.4)	111 (16.4)	2 (14.3)	34 (18.5)	144 (13.1)	1 (0.4)

Table 3 Summary of correlations between pathological features and age at resection, location, sex, depth, and stage

Pathological features	Clinical and Pathological features									
	Age at resection (years old)		Location		Sex		Depth		Kaddu stage	
	Correlation									
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Ossification	20-49	11-19, ≥50	Upper limbs	Face, scalp			Subcutaneous	Dermis	4	2, 3
Follicular germinative cells										
Hair papilla-like structures	≥50				Male	Female			2, 3	4
Squamous stratifying keratinocytes		20-49							2, 3	4
Cells with a large pale pink cytoplasm	≥50	20-49	Scalp	Trunk			Dermis	Subcutaneous	2, 3	4
Trichohyalin granules	≥50	20-49	Neck						3	4

Table 4 Time to resection in relation to stage

Stage	Average ± SD (days)
1	158.8 ± 126.4
2	389 ± 736.2
3	649.0 ± 427.5
4	2,924.9 ± 4,907.9

years and Kaddu stages 2 and 3. Cells with a large pale pink cytoplasm had a positive correlation with age ≥50 years, tumor location in the scalp or dermis, and Kaddu stages 2 and 3. And trichohyalin granules were positively correlated with age ≥50 years, tumor location in the neck, and Kaddu stage 3.

Ossification had a negative correlation with age 11-19 years or ≥50 years, tumor location in the face, scalp, or dermis, and Kaddu stages 2 and 3. Hair papilla-like structures had a negative correlation with being female. Cells with a large pale pink cytoplasm had a negative correlation with age 20-49 years, tumor located in the trunk or subcutaneously, and Kaddu stage 4. Trichohyalin granules had a negative correlation with age 20-49 years, and Kaddu stage 4.

The relationships between time to resection and Kaddu stage are shown in **Table 4**. Average time increased in order from stages 1 to 4 ($X^2(3)=94.91$, $p<0.05$), with significant differences between stages 1 and 2, 2 and 4, and 3 and 4 (Steel-Dwaas, $p<0.05$). Time to resection for stage 4 was significantly longer than for the others.

Discussion

This retrospective study was larger in scale than any other previously reported in the literature: it presents both clinical and pathological data on pilomatricoma diagnosed pathologically in 1,559 patients with 1,590 tumors from 2016 through 2020 at a single institution. A comparison with past studies is shown in **Table 5**.

Unlike in other studies, where age was reported at clinical diagnosis, on examination or presentation, or not specified, we report age at resection[10–22]. Although methods varied slightly, the average age in other studies, both international and domestic, was lower than in ours (33.5 years), and median age was not mentioned in other reports. The most common age range overall was 11-20 years old, which again was lower than in our study[16,19–22]. One possible explanation is that because pilomatricoma is commonly thought of as a condition affecting the young, it is more likely to be diagnosed in them. Also, because our study included the largest population of patients with pilomatricoma (1,559) visiting a single center, the concentration of cases might have led to a more diverse age range. But pilomatricoma was certainly not limited to the young in our study.

As for tumor location, the most common site reported in 5 previous Japanese studies was the upper limbs[15,17,19,20,22]. This was also the most common location in our study and, in fact, the percentage of tumors in the upper limbs was higher in our study than in the other 5. Neither our study nor any of the other 5 mentioned the ethnicity of the patients, but they can be assumed to have been predominantly Japanese. By contrast, the most

Table 5 Comparison of clinical findings overseas and in Japan

	Year	Cases	Country	Average age	Most Common Age Range	M:F	Most Common Tumor Location	Clinical Accuracy	Multiple Lesions	Time to resection
Moehlenbeck[10]	1973	1,569	Various			1:1.5	Scalp			
Julian and Bowers[11]	1998	209	UK			1:1.5	Scalp 52%	21%	1.9%	1 week to 30 years
Pirouzmanesh et al.[12]	2002	336	USA			1:1.8		26%		
Guinot-Moya et al.[13]	2011	205	Spain	27	≤20 years old 46.4%	1:1.1	Scalp 35%		2.4%	
Hernandez-Nunez et al.[14]	2014	239	Spain	26.4		1:2.4	Scalp and neck 50%	54%		
Matsui et al.[15]	1985	152	Japan	22.5	≤20 years old 50.7%	1:2.4	Upper limbs 31%		4.6%	Few days to 40 years
Noguchi et al.[16]	1994	355	Japan	21.3	11-20 years old 32.2%	1:2.2	Face 42%		9.3%	
Kawakami et al.[21]	1996	156	Japan		11-20 years old 33%	1:2	Face 35%		2.0%	
Iwasaki et al.[20]	1997	52	Japan	23.7	11-20 years old 26.9%	1:1.6	Upper limbs 30%		1.9%	1 week to 10+ years
Takata et al.[22]	1997	37	Japan	17.4	11-20 years old 40.5%	1:1.5	Upper limbs 25%		8.0%	1 day to 60 years
Iizuka et al.[19]	1998	71	Japan	26.5	11-20 years old 35.2%	1:1.6	Upper limbs, Shoulders 45%		4.2%	
Akabane et al.[18]	2004	301	Japan		≤10 years old 38.9%	1:1.7	Face 41%		8.3%	
Fukuda[17]	2004	35	Japan	29.4	20-29 years old 37.14%	1:1.5	Upper limbs 50%	53%	2.9%	1 week to 29 years
Our data	2022	1,590	Japan	33.5	20-39 years old 34.1%	1:1.6	Upper Limbs 34%	49%	1.8%	

common location reported in previous overseas studies was the scalp[10–14]. Tumor location may differ by ethnicity, and the predominance of the head and neck in previous reports may be due to the fact that the patient populations tended to be Caucasian. As far as sex is concerned, however, ethnicity does not seem to be a factor, with all of the reported studies, including ours, showing a higher female occurrence of pilomatricoma.

Thanks to the increased use of techniques such as ultrasound and radiographic imaging, diagnostic accuracy has increased recently, with accuracy ranging from 21% to 54.4% in the reported studies[10,11,14,17]. Two had accuracy rates of around 50%, similar to our 49%[14,17]. As in our study, reported time to resection varied from days to years. The presence of multiple lesions ranged from 1.9% to 9.3%[11,13,15,17–22].

Few studies have analyzed the percentages of the Kaddu stages or described their characteristics. However, Kaddu stages 3 and 4 were the most common stages in our study and two others[4,23]. The original paper by Kaddu et al.[4] reported on a total of 118 lesions from 116 patients. There were 8 cases (6.8%) of early lesions (stage 1), 27 (22.9%) of fully developed lesions (stage 2), 37 (31.4%) of early regressive lesions (stage 3), and 42 (35.6%) of late regressive lesions (stage 4). Ishige et al.[23] studied 16 lesions and found only stage 3 and stage 4 lesions (11 [68.8%] and 5 [31.2%], respectively). In our study, stage 3 accounted for the highest percentage of cases (70.6%). A possible explanation is that the later the stage, the larger the size of the tumor, with pain caused by inflammation making the lesions more noticeable.

Time to resection in past studies ranged from 1 day to

Table 6 Comparison of percentage of pathological features observed overseas and in Japan

Pathological features	Our study (n=1,561)	Simi et al.[3] (2010, n=20)
	Percentage (%)	
Ossification	15.7	10
Infundibular keratinization		55
Isthmic keratinization		15
Trichohyalin granules	11.9	20
Follicular germinative cells	7.8	
Hair papilla-like structure	33.9	
Squamous stratifying keratinocytes	41.7	
Cells with pale pink cytoplasm	38.9	
Outer root sheath differentiation		40

40 years[11,15,17,20,22]. In our study, average time increased from Kaddu stage 1 to 4, supporting Kaddu's suggestion that pilomatricoma progresses from stage 1 to 4 (**Table 4**). Time to resection for stage 4 was significantly longer than for the other types.

Few studies have assessed the detailed microscopic features seen in pilomatricoma[3,8,15], but a comparison of the microscopic features reported by Simi et al.[3] is presented in **Table 6**. Our study looked at pathological features linked with follicular differentiation, including several unrecognized in other studies (perhaps because ours included a much higher number of cases than previous studies): neither hair papilla-like structures nor squamous stratifying keratinocytes, for example, have been reported in past studies[3,8,15]. Simi et al. reported infundibular keratinization, isthmic keratinization, outer root sheath differentiation, and sebocytes[3], and Nishie et al.[7] reported aggregations of follicular germinative cells. In general, pilomatricoma has been thought of as a tumor with differentiation towards cortical cells of the normal hair shaft[5]. However, the microscopic features seen in our study (squamous stratifying keratinocytes, cells with large pale pink cytoplasm, presence of a hair papilla-like structure, trichohyalin granules, and aggregation of follicular germinative cells) and previous studies, suggest follicular differentiation besides the hair shaft and variety in the stages of development of the hair follicle[3,7,8,15]. Due to follicular differentiation, the following features besides the hair shaft are found in a normal hair follicle. Squamous stratifying keratinocytes are found in the follicular infundibulum. Cells with pale pink cytoplasm are found in the follicular isthmus. Trichohyalin granules are found in the inner root sheath. Hair papilla-like structures develop in relation with the hair bulb consisting of matrical cells[5]. Follicular germinative cells are similar to normal germinative cells such as embryonic follicular germ cells or follicular stem cells in the follicular bulge, which are seen in earlier stages of the development of the hair follicle, before follicular differentiation occurs[5,7]. Some reports have suggested pilomatricoma can differentiate towards the hair matrix, hair cortex, follicular infundibulum, outer root sheath, and hair bulge[7,24]. Nishie et al.[7] suggested that the neoplastic cells of pilomatricoma had a pluripotent faculty of differentiation towards all parts of the hair follicle-like follicular stem cells, and the follicular germinative cells may be precursors cells of pilomatricoma. The features observed in our study and others suggest that pilomatricoma could be a complex panfollicular neoplasm[3,7,8,15].

Although previous studies have not analyzed the relationships between the pathological and clinical features of pilomatricoma[3,8,15], our results show notable relationships with age at resection, location, sex, depth, and Kaddu stage (**Table 3**). We found, for example, that ossification had a positive correlation with age 20-49 years, tumor location in the upper limbs, subcutaneous location, and Kaddu stage 4. The fact that ossification was most common in patients aged 20-49 years old may be due to age-related increased cell activity. Foreign body reaction-induced macrophages have been suggested to induce calcification and ossification in pilomatricoma[25]. Foreign body reaction may also induce inflammation that results in a deeper location of the tumor in the subcutaneous tissue. The positive correlation with stage 4 is due to categorizing according to the definition of the Kaddu stage. The positive correlation between ossification and tumor location in the upper limbs with may be due to this site being more subject to external stimuli than the face and scalp. Subcutaneous and intramuscular injections such as vaccinations may be possible stimuli[26–30].

Hair papilla-like structures had a positive correlation with age ≥50 years, being male, and Kaddu stages 2 and 3; they were negatively correlated with being female and Kaddu stage 4. We can suggest no plausible explanations for these correlations. Squamous stratifying keratinocytes had a positive correlation with age 20-49 years and Kaddu stages 2 and 3. This age group had the longest average time to resection, which may have allowed pilomatricoma to become more advanced with more follicular differentiation, leading to the presence of squamous stratifying keratinocytes. But again, we cannot currently offer any plausible explanation for the correlation with the Kaddu stages. Cells with a large pale pink cytoplasm were positively correlated with age ≥50 years, location in the scalp and dermis, and Kaddu stages 2 and 3; they were negatively correlated with age 20-49 years, tumor location in the trunk and subcutaneous tissue, and Kaddu stage 4. The positive correlation with the scalp location may be due to isthmic keratinization, a type of hair differentiation more likely to occur in the scalp, where there are abundant hair follicles. But we cannot yet explain the correlation with age, depth, and Kaddu stage. Trichohyalin granules had a positive correlation with age ≥50 years, tumor location in the neck, and Kaddu stage 3, but we are unable to explain why.

To conclude, our study was the first to look at the details of the clinical features of pilomatricoma in Japanese patients, and to investigate the factors involved in its pathological features. Female predisposition seems to be a clinical feature of pilomatricoma, regardless of ethnicity or age, but the tumor location in the upper limbs commonly observed in Japanese patients may indicate ethnic differences. Pathologically, the fact that cells linked to follicular differentiation are observed suggests that pilomatricoma is a complex panfollicular neoplasm, and time to resection correlates with Kaddu stages. The pathological features of pilomatricoma may be affected by certain factors such as age at resection, sex, tumor location and depth, and Kaddu stage. Although no definitive relationships have been established as yet, further accumulation of knowledge should clarify the pathogenesis of pilomatricoma as well.

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References

1. Kang S, Amagai M, Bruckner AL, et al. Fitzpatrick's dermatology. 9th ed. New York (NY): McGraw-Hill Education; 2019.
2. Hassan SF, Stephens E, Fallon SC, et al. Characterizing pilomatricomas in children: a single institution experience. J Pediatr Surg [Internet]. 2013 Jul;48(7):1551–6. Available from: https://www.jpedsurg.org/article/S0022-3468(12)00642-2/fulltext
3. Simi CM, Rajalakshmi T, Correa M. Pilomatricoma: a tumor with hidden depths. Indian J Dermatol Venereol Leprol [Internet]. 2010 Sep-Oct;76(5):543–6. Available from: http://www.ijdvl.com/article.asp?issn=0378-6323;year=2010;volume=76;issue=5;spage=543;epage=546;aulast=Simi
4. Kaddu S, Soyer HP, Hodl S, Kerl H. Morphological stages of pilomatricoma. Am J Dermatopathol. 1996 Aug;18(4):333–8.
5. Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, Xu G. Lever's histopathology of the skin. 10th ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009. 1257 p.
6. Kaddu S, Soyer HP, Wolf IH, Kerl H. Proliferating pilomatricoma. A histopathologic simulator of matrical carcinoma. J Cutan Pathol [Internet]. 1997 Apr;24(4):228–34. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0560.1997.tb01586.x?sid=nlm%3Apubmed
7. Nishie W, Kimura T. Follicular germinative cells in pilomatricoma. Am J Dermatopathol. 2006 Dec;28(6):510–3.
8. Fukuda H. Sekkaikajohishu no hasshobochi ni kansuru kenkyu (2) byorisoshikigakuteki narabini menekisoshikikagakuteki kento [The development site of calcifying epithelioma: II. histopathological and immunohistochemical examination of calcifying epithelioma]. J Med Soc Toho [Internet]. 2004 Sep;51(5):271–80. Available from: http://search.jamas.or.jp/link/ui/2005175137. Japanese.
9. Oh YW, Suh HS, Choi YS. Optimal timing of surgical excision in pediatric pilomatricoma: association between clinicopathological features and cosmetic outcomes. Ann Dermatol. 2020 Apr;32(2):93–100.
10. Moehlenbeck FW. Pilomatrixoma (calcifying epithelioma). A statistical study. Arch Dermatol [Internet]. 1973 Oct;108(4):532–4. Available from: https://jamanetwork.com/journals/jamadermatology/article-abstract/533468
11. Julian CG, Bowers PW. A clinical review of 209 pilomatricomas. J Am Acad Dermatol [Internet]. 1998 Aug;39(2 Pt 1):191–5. Available from: https://www.jaad.org/article/S0190-9622(98)70073-8/fulltext
12. Pirouzmanesh A, Reinisch JF, Gonzalez-Gomez I, Smith EM, Meara JG. Pilomatrixoma: a review of 346 cases. Plast Reconstr Surg. 2003 Dec;112(7):1784–9.
13. Guinot-Moya R, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Pilomatrixoma. Review of 205 cases. Med Oral Patol Oral Cir Bucal. 2011 Jul 1;16(4):e552–5.
14. Hernandez-Nunez A, Najera Botello L, Romero Mate A, et al. Retrospective study of pilomatricoma: 261 tumors in 239 patients. Actas Dermosifiliogr [Internet]. 2014 Sep;105(7):699–705. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0001731014000337?via%3Dihub. English, Spanish.
15. Matsui K, Sakihama S, Nakama K, et al. Okinawaken ni okeru moboshu ni kansuru rinshobyorigakuteki kenkyu [Clinicopathological study of pilomatricoma (calcifying epithelioma) in Okinawa Prefecture]. Pathol Clinical Med.

1985 Feb;3(2):197–203. Japanese.
16. Noguchi H, Hayashibara T, Ono T. A statistical study of calcifying epithelioma, focusing on the sites of origin. J Dermatol. 1995 Jan;22(1):24–7.
17. Fukuda H. Sekkaikajohishu no hasshobochi ni kansuru kenkyu (1) Sekkaikajohishu no rinshoteki kento [The development site of calcifying epithelioma: I. clinical study of calcifying epithelioma]. J Med Soc Toho [Internet]. 2004 Sep;51(5):265–70. Available from: http://search.jamas.or.jp/link/ui/2005175136. Japanese.
18. Akabane N, Himi Y, Ikeno Y. Sekkaikajohishu 301rei no kento to kazokunaihasseirei [A study of 301 cases of Calcifying Epithelioma and a case of familial occurence]. J Jpn Soc Plast Reconstr Surg [Internet]. 2004 Feb;24(2):90–4. Available from: https://cir.nii.ac.jp/crid/1571417125089474816. Japanese.
19. Iizuka M, Okuda T, Ooi T, Saga M. Sekkaikajohishu no tokeiteki kansatsu saikin 11nenkan no jikenrei narabini honpo hokoku tahatsu rei ni tsuite [A statistical study of calcifying epithelioma including multiple occurence cases in Japan and experienced cases in the past 11 years]. Rinsho Derma [Internet]. 1998 Oct;40(11):1747–50. Available from: http://search.jamas.or.jp/link/ui/1999064284. Japanese.
20. Iwasaki Y, Yashiro K, Sakai N. Toka ni okeru sekkaikajohishu no tokei [Statistics of calcifying epithelioma in our department]. Rinsho Derma (Tokyo) [Internet]. 1997 Feb;39(2):302–3. Available from: http://search.jamas.or.jp/link/ui/1997180027. Japanese.
21. Kawakami Y, Yamamoto O, Maruyama T, Suenaga Y, Asahi S. Sangyoikadaigaku hifuka ni okeru sekkaikajohishu no tokeigakuteki kento [Statistical surveys on calcifying epithelioma at the Department of Dermatology, University of Occupational and Environmental Health, Japan]. Nishinihon J Dermatol [Internet]. 1996;58(6):1000–2. Available from: https://cir.nii.ac.jp/crid/1390001204298615168. Japanese.
22. Takata Y, Kusaba Y, Dekio S, Jidoi J. Shimaneikadaigaku fuzoku byoin hifuka ni okeru sekkaikajohishu no tokeiteki kansatsu - shuyo hassei no yoin ni tsuite no kosatsu [A statistical study of calcifying epithelioma at the Department of Dermatology, Shimane Medical University: discussion on the factors to develop the tumors]. Jpn J Clin Dermatol [Internet]. 1997 Dec;51(13):1087–9. Available from: http://search.jamas.or.jp/link/ui/1998099818. Japanese.
23. Ishige T, Kikuchi K, Miyazaki Y, et al. Differentiation and apoptosis in pilomatrixoma. Am J Dermatopathol. 2011 Feb;33(1):60–4.
24. Kurokawa I, Yamanaka K, Senba Y, et al. Pilomatricoma can differentiate not only towards hair matrix and hair cortex, but also follicular infundibulum, outer root sheath and hair bulge. Exp Dermatol [Internet]. 2009 Aug;18(8):734–7. Available from: https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/j.1600-0625.2008.00835.x?download=true
25. Sung KY, Lee S, Jeong Y, Lee SY. Ossifying pilomatricoma and a novel hypothesis for its pathogenesis: A case report and comprehensive literature review. Medicine (Baltimore). 2022 Feb 11;101(6):e28753.
26. Aquilina S, Gatt P, Boffa MJ. Pilomatricoma arising at a BCG vaccination site. Clin Exp Dermatol [Internet]. 2006 Mar;31(2):296–7. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2230.2005.02016.x
27. Jeon H, Jeong SH, Dhong ES, Han SK. Pilomatricoma arising at an influenza vaccination site. Arch Plast Surg [Internet]. 2014 Nov;41(6):775–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4228226/pdf/aps-41-775.pdf
28. Tas B, Tas E, Sar M. A Bullous pilomatricoma developed after hepatitis A vaccination. West Indian Med J [Internet]. 2015 Mar;64(2):166–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4696645/pdf/wimj-64-0166.pdf
29. Zhang H, Jin J, Chen X, Cai L, Zhang J, Wen G. Bullous pilomatricoma after influenza vaccination. Clin Cosmet Investig Dermatol. 2022 Apr 13;15:657–60.
30. Alvarez-Rubio FJ, Martinez-Ortega JI, Fernandez-Reyna I. Correction: bullous pilomatrixoma after COVID-19 vaccination. Cureus. 2023 Jan 23;15(1):c97.

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