Clinical spectrum of cutaneous melanoma morphology

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Background: Melanoma can mimic other cutaneous lesions, but the full spectrum and prevalence of these morphologic variants remain largely unknown.

Objective: To classify nonacral cutaneous melanomas into distinct morphologic clusters and characterize clusters' clinicopathologic features.

Methods: All pathologic melanoma diagnoses (occurring during 2011-2016) were reviewed for routine prebiopsy digital photographs (n = 400). Six dermatologists independently assigned lesions into 1 of 14 diagnostic classes on the basis of morphology. Image consensus clusters were generated by K-means; clinicopathologic features were compared with analysis of variance and χ^2.

Results: Five morphologic clusters were identified: typical (n = 136), nevus-like (n = 81), amelanotic/nonmelanoma skin cancer (NMSC)—like (n = 70), seborrheic keratosis (SK)—like (n = 68), and lentigo/lentigo maligna (LM)—like (n = 45) melanomas. Nevus-like melanomas were found in younger patients. Nevus-like and lentigo/LM-like melanomas tended to be thinner and more likely identified on routine dermatologic examinations. NMSC-like melanomas were tender, thicker, more mitotically active, and associated with prior NMSC. Typical and SK-like melanomas had similar clinicopathologic features.

Limitations: Cluster subdivision yielded diminished sample sizes. Visual assignment was performed without clinical context.

Conclusion: When primary cutaneous melanomas were assigned into diagnostic groups and subjected to novel consensus clustering, recurrent morphologic patterns emerged. The spectrum of these morphologies was unexpectedly diverse, which might have implications for visual training and possibly clinical diagnosis. (J Am Acad Dermatol 2019;80:178-88.)

Key words: diagnostic accuracy; early diagnosis; education; melanoma; melanoma appearance; melanoma mimics; morphology; nevi; pigmented lesions; unusual-appearing melanoma.

Melanoma is a prevalent and potentially fatal malignancy, with >90,000 estimated new cases and 9000 new deaths in 2018 in the United States.[1] Although surgical excision is often curative for localized disease, advanced metastatic melanoma carries a poor prognosis. Increased time to diagnosis is associated with increased stage, thickness, and likelihood of distant metastasis.[2] Some studies ascribe delayed diagnosis to patient-related issues,[3-6] such as inability to identify early melanoma features[7] or lack of concern or knowledge,[8,9] and some ascribe it to physician delay.[10-12]

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Patients identify most melanomas,[13,14] but melanomas identified by dermatologists are associated with thinner and more curable tumors.[4,6,15-19] Thus, early patient and clinician melanoma detection is crucial for improving outcomes.[20] The ABCDE (asymmetry, border, color, diameter, evolution) system[21,22] and ugly duckling sign[23] are currently taught as easily-accessible rules to guide examination of potential cutaneous malignancies.[24]

Textbook images of melanoma are self-reinforcing, considering that classic-appearing lesions are more often photographed as exemplars. However, unusual-appearing melanomas are often not photographically documented because the unexpected diagnosis occurs much later. Melanomas with unusual morphologies are of particular interest, as they represent a rarely studied visual spectrum and are often difficult to diagnose a priori. Melanoma lesions can mimic other skin lesions (eg, NMSC[25] and SK[26-30]), delaying their proper diagnosis. Melanoma more frequently mimics benign skin lesions in pediatric populations; these mimics are often thicker and of higher stage.[31] The characteristics of patients who develop unusual-appearing melanomas have not been systematically described. In this study, we aimed to portray melanoma morphologic subgroupings on the basis of consensus clustering with emphasis on unusual-appearing lesions and to identify associated factors that might assist in their diagnosis.

CAPSULE SUMMARY

- Melanoma can mimic many cutaneous lesions, impairing correct diagnosis. By clustering of diagnostic assignments, 5 common melanoma morphologic groupings were identified: typical, nevus-like, amelanotic/nonmelanoma skin cancer—like, seborrheic keratosis—like, and lentigo/lentigo maligna—like.
- Awareness of the diversity of melanoma appearances and their associated clinical factors might help dermatologists improve their diagnostic accuracy.

METHODS

Study subjects

Electronic medical record review was approved by the Partners HealthCare Institutional Review Board. All patients were from Massachusetts General Hospital. For purposes of site identification during routine care, prospectively ascertained pre-biopsy images were often (during 2011-2013) or always (2013 and thereafter) documented by a quick-grab image in the clinic. All consecutive histologically proven melanoma cases during 2011-2016 were initially identified through pathology record searches. Clinical information extraction and image-pathologic record pairing were performed during electronic medical record review. Of 443 preliminary cases, 400 remained after excluding 34 for reasons related to their digital images and 9 for their lack of clinical information (Supplemental Fig 1; available at http://www.jaad.org).

Image classification

Because all lesions reviewed were histologically diagnosed as melanomas, this exercise was not an issue of diagnostic accuracy. We aimed to identify recurrent morphologic groupings as independently adjudicated by 6 board-certified dermatologists practicing in the Massachusetts General Hospital Melanoma and Pigmented Lesion Clinic. Digital images were randomized and presented to the panel. Without any clinical information, each dermatologist was asked to select the best diagnostic assignment from these choices: actinic keratosis (AK), basal cell carcinoma (BCC), compound nevus, dermal nevus, dysplastic nevus, eczema, lentigo maligna (LM), melanoma (amelanotic), melanoma (pigmented), seborrheic keratosis (SK), squamous cell carcinoma (SCC), solar lentigo, or wart. Free text input (other) was recoded. SCC included invasive SCCs, and SK included inflamed SK. Vascular lesions included hemorrhage, trauma, hemangioma, and ecchymoses. Pigmented nevus included Reed, Spitz, and combined nevi, and angiomas included angiosarcoma, angiokeratoma, thrombosed angioma, and cherry angioma. Categories with fewer than the median assignments were aggregated to other. Data was normalized to assignment percentage.

Statistical methods

R version 3.4.4,[32] irr,[33] ggpubr,[34] superheat,[35] and factoextra[36] packages were used for analysis. Consensus clustering was performed by using Hartigan-Wong unsupervised K-means algorithm[37] on image assignment data (n = 400) with 100 random starts. Unsupervised hierarchical clustering with Ward algorithm[38] on Manhattan distances was used to visualize relationships between individual morphologic assignments and to independently validate cluster choice by the K-means algorithm (Fig 1). Fleiss kappa[39] was used to assess concordance among the 6 dermatologists. Clinical and pathologic factors were then compared between clusters. Continuous means were compared by

Abbreviations used:

AK:	actinic keratosis
BCC:	basal cell carcinoma
CL:	cluster
LM:	lentigo maligna
NMSC:	nonmelanoma skin cancer
SCC:	squamous cell carcinoma
SK:	seborrheic keratosis

Kruskal-Wallis 1-way analysis of variance (ANOVA, linear ANOVA residuals were not normally distributed by Shapiro-Wilk test). Post hoc analyses were performed by paired-Wilcoxon tests with Bonferroni correction. Categorical variables were analyzed by χ^2.

RESULTS

Five consensus clusters represent common melanoma appearance groupings

Total cluster number was determined empirically. Statistical simulations with 1-10 centroids and individual review of 4-6 centroid algorithms revealed a 5-centroid algorithm provided optimal resolution (Supplemental Figs 2 and 3, *A-C*; available at http://www.jaad.org).

Cluster 1 (CL1) (n = 136) represented images most frequently assigned pigmented melanoma (70%), followed by dysplastic nevus (8%) or SK (7%). Cluster 2 (CL2) (n = 81) images were predominately assigned dysplastic nevus (54%), followed by pigmented melanoma (16%) and compound nevus (14%). Cluster 3 (CL3) (n = 70) images were assigned BCC (26%), SCC (19%), AK (12%), amelanotic melanoma (12%), or other (7%). Cluster 4 (CL4) (n = 68) were assigned SK (47%), then pigmented melanoma (30%). Last, cluster 5 (CL5) (n = 45) contained lesions most often assigned LM (30%) and solar lentigo (30%), followed by SK (16%) (Supplemental Fig 3, *A*). Representative cluster member images are shown (Fig 2). In aggregate, the concordance among the 6 raters was k = 0.308.

Hierarchical morphologic group clustering (Fig 1) revealed close relationships between solar lentigo and LM; among dermal nevus, amelanotic melanoma, AK, SCC, BCC, compound nevus, and other; and between SK and dysplastic nevus. Pigmented melanoma represented a unique branch. Taken together, the results of K-means and hierarchic clustering support 5 morphologic clusters: a typical pigmented melanoma cluster (CL1), a nevus-like melanoma cluster (CL2), an amelanotic/NMSC-like melanoma cluster (CL3), an SK-like melanoma cluster (CL4), and a lentigo/LM-like melanoma cluster (CL5).

Clinical features of individual clusters

No significant sex differences among clusters were observed (Table I). Approximately 40%-50% of patients were female. Mean and median age at diagnosis, with exception of CL2, was 60-70 years.

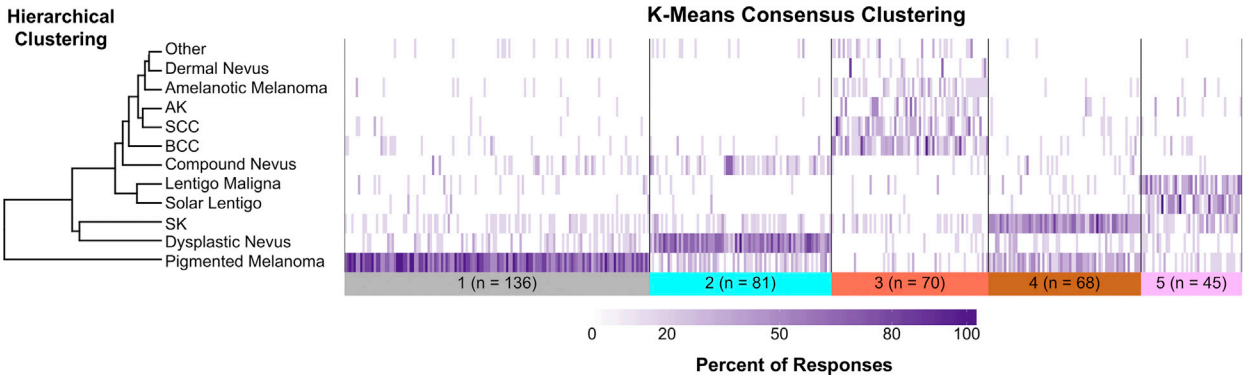

Fig 1. Distribution of morphologic assignments of 400 digital images by 6 board-certified dermatologists. Five morphologic clusters (typical, nevus-like, amelanotic/nonmelanoma skin cancer—like, SK-like, and lentigo/lentigo maligna—like) were derived by using an unsupervised K-means clustering algorithm. Depth of color corresponds to assignment percentage. A dendrogram representation of relationships among individual assignments was produced by unsupervised hierarchical clustering by using Ward algorithm with Manhattan distances. This analysis revealed close relationships between solar lentigo and lentigo maligna; among dermal nevus, amelanotic melanoma, AK, SCC, BCC, compound nevus, and other; and between SK and dysplastic nevus. Pigmented melanoma represented a unique dendrogram branch. *AK*, Actinic keratosis; *BCC*, basal cell carcinoma; *SCC*, squamous cell carcinoma; *SK*, seborrheic keratosis.

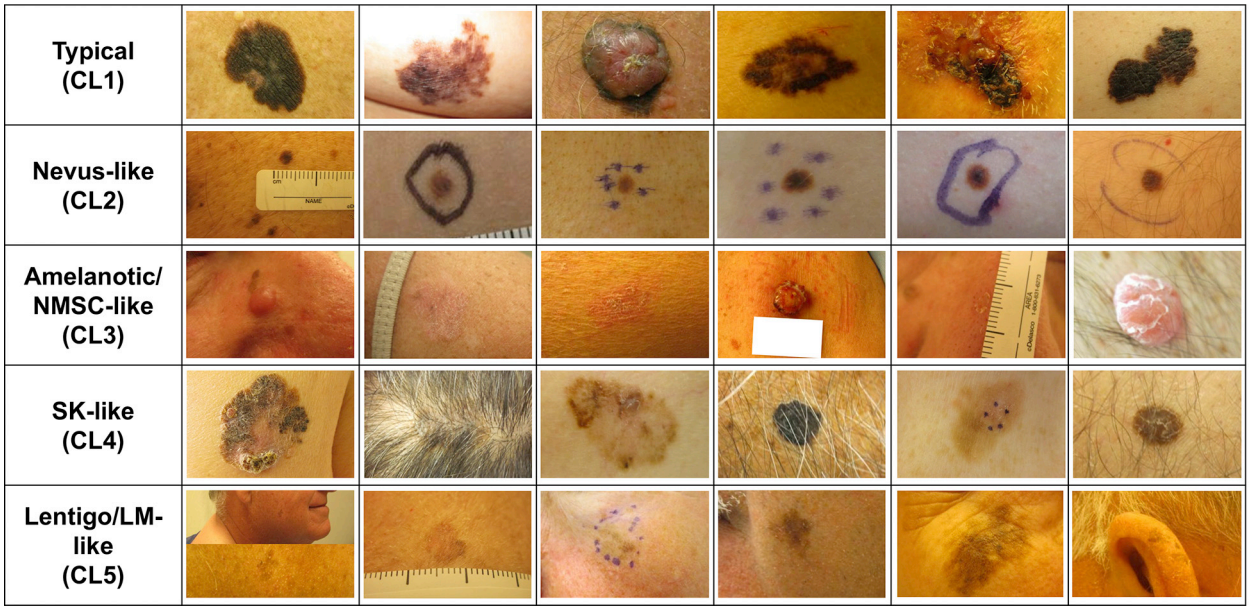

Fig 2. Malignant melanoma. Representative images are included to illustrate the 5 distinct melanoma morphologic clusters identified by consensus clustering. *CL*, Cluster; *LM*, lentigo maligna; *NMSC*, nonmelanoma skin cancer; *SK*, seborrheic keratosis.

Patients with nevus-like melanomas were significantly younger (mean 52.8 years, median 53.6 years) than other clusters ($P < .001$) (Fig 3, *A*). Typical and amelanotic/NMSC-like melanomas were most likely initially noted by the patient or a family member. In contrast, nevus-like and lentigo/LM-like melanomas were most likely to be first identified by a dermatologist on routine examination (Fig 3, *B*). Amelanotic/NMSC-like melanomas (74%, $P < .001$) followed by lentigo/LM-like melanomas (64%) were most likely to arise in patients with personal histories of NMSC. Amelanotic/NMSC-like melanomas (36%) and lentigo/LM-like melanomas (31%) were more likely to occur in patients with a history of melanoma ($P < .001$). Differences in family history of melanoma and personal history of sunburns or tanning bed use were not significant. Fitzpatrick skin types were similar among clusters, with most patients (54%-65%) having skin types II or II-III. More than 50% of patients in each cluster had low nevi density. Amelanotic/NMSC-like and lentigo/LM-like melanomas were most often found in the setting of severe dermatoheliosis.

Comparisons of morphologic features and symptoms reported in the medical record

There were no significant differences in lesion laterality between clusters (Table II). Typical, nevus-like, and SK-like melanomas favored the trunk, amelanotic/NMSC-like melanomas favored the upper limbs, and lentigo/LM-like melanomas favored the head and neck (Fig 3, *C*). Amelanotic/NMSC-like melanomas were the most likely to cause pain or irritation (17%, $P = .001$). Typical melanomas were growing in 35% of cases, followed by lentigo/LM-like melanomas (31%) and SK-like melanomas (28%). In contrast, nevus-like melanomas were growing in significantly fewer cases (10%, $P = .01$). Amelanotic/NMSC-like melanomas were the most likely to be reported as a new lesion (11%); however, differences were not statistically significant. Bleeding or itching were rarely reported, regardless of lesion type. Lesion colors documented at initial examination varied significantly. Amelanotic/NMSC-like melanomas (29%) were less likely than other clusters (≥80%, $P < .001$) to be described as brown and were more often reported as pink and erythematous (88%, $P < .001$). Typical melanomas (29%) were more often than other clusters (≤11%, $P < .001$) to be described as black. Color and border irregularity were noted in 285 (71%) and 79 (20%) cases, respectively. Irregular color was less frequent among amelanotic/NMSC-like lesions versus other clusters (73% vs ≥84%, $P = .03$). Border irregularity revealed no significant variation. Amelanotic/NMSC-like melanomas most commonly presented as raised lesions (81%, $P < .001$). Lentigo/LM-like melanomas were more commonly flat.

Pathologic profiles of melanoma morphologic clusters

Although all diagnoses were primary cutaneous melanomas, final pathologic features displayed significant variation (Table III; Fig 4, *A*). CL1-4

Table I. Patient demographics and clinical factors by cluster

Factor	Cluster 1	2	3	4	5	*P* value*
Demographic variables, N = 400						
n†	136	81	70	68	45	
Female sex, n (%)	56 (41)	42 (52)	30 (43)	29 (43)	18 (40)	.59
Age, y, mean ± SD*	63.6 ± 17.1	52.8 ± 16.9	63.7 ± 15.6	61.7 ± 13.2	66.6 ± 10.2	**<.001**
Age, y, median	65.7	53.6	66.4	61.7	69.1	
First identified by, N = 400,* n (%)						**<.001**
n†	136	81	70	68	45	
Patient or family	70 (51)	23 (28)	35 (50)	30 (44)	19 (42)	
Dermatologist	41 (30)	53 (65)	28 (40)	30 (44)	25 (55)	
Nondermatology professional‡	25 (18)	5 (6)	7 (10)	8 (12)	1 (2)	
Personal history of NMSC, N = 374*						
n†	126	73	66	67	42	
Yes, n (%)	42 (33)	19 (26)	49 (74)	27 (40)	27 (64)	**<.001**
Personal history of melanoma, N = 394*						
n†	132	80	69	68	45	
Yes, n (%)	12 (9)	21 (26)	25 (36)	12 (18)	14 (31)	**<.001**
Family history of melanoma, N = 352						
n†	125	69	59	63	36	
Yes, n (%)	25 (20)	26 (38)	13 (22)	17 (27)	13 (36)	.052
Personal history of sunburns, N = 146						
n†	50	26	25	32	13	
Yes, n (%)	42 (84)	19 (73)	23 (92)	30 (94)	13 (100)	.07
Personal history of tanning bed use, N = 196						
n†	86	35	25	42	8	
Yes, n (%)	17 (20)	12 (34)	10 (40)	10 (24)	3 (38)	.19
Fitzpatrick skin type,§ N = 250, n (%)						.56
n†	97	37	40	50	26	
I+	19 (20)	9 (24)	13 (32)	14 (28)	7 (28)	
II+	55 (57)	24 (65)	23 (57)	27 (54)	17 (65)	
III+	19 (20)	4 (11)	4 (10)	8 (16)	2 (8)	
IV	4 (4)	0 (0)	0 (0)	1 (2)	0 (0)	
Density of nevi,¶ N = 165, n (%)						.22
n†	67	32	27	29	10	
Low	41 (61)	18 (56)	21 (78)	17 (59)	8 (80)	
Moderate	15 (22)	4 (12)	4 (15)	6 (21)	2 (20)	
High	11 (16)	10 (31)	2 (7)	6 (21)	0 (0)	
Dermatoheliosis,‖ N = 296,* n (%)						**.012**
n†	103	60	51	53	29	
Mild	14 (14)	15 (25)	13 (25)	11 (21)	0 (0)	
Moderate	62 (60)	37 (62)	21 (41)	32 (60)	19 (66)	
Severe	27 (26)	8 (13)	17 (33)	10 (19)	10 (34)	

Bolded values are statistically significant.

NMSC, Nonmelanoma skin cancer; *SD*, standard deviation.

*Calculated by Kruskal-Wallis 1-way analysis of variance for continuous variables and by χ^2 testing for categorical variables.

†Number of patients for whom information on group of variables was available.

‡Nondermatologist professionals included primary care physicians, nondermatologist MDs, and hair dressers.

§I+ includes I and I-II, II+ includes II and II-III, III+ includes III and III-IV.

¶Low includes none and very low; moderate includes low-moderate; high includes very high.

‖Mild includes none and mild-moderate; moderate includes moderate-severe and present.

melanomas were most commonly superficial spreading melanomas, and lentigo/LM-like melanoma was often confirmed LM melanoma. Amelanotic/NMSC-like melanomas were least likely diagnosed as malignant melanoma in situ but the most likely diagnosed as nodular or another subtype (including 2 desmoplastic, 3 nevoid, and 1 spindle cell). Most nevus-like and lentigo/LM-like

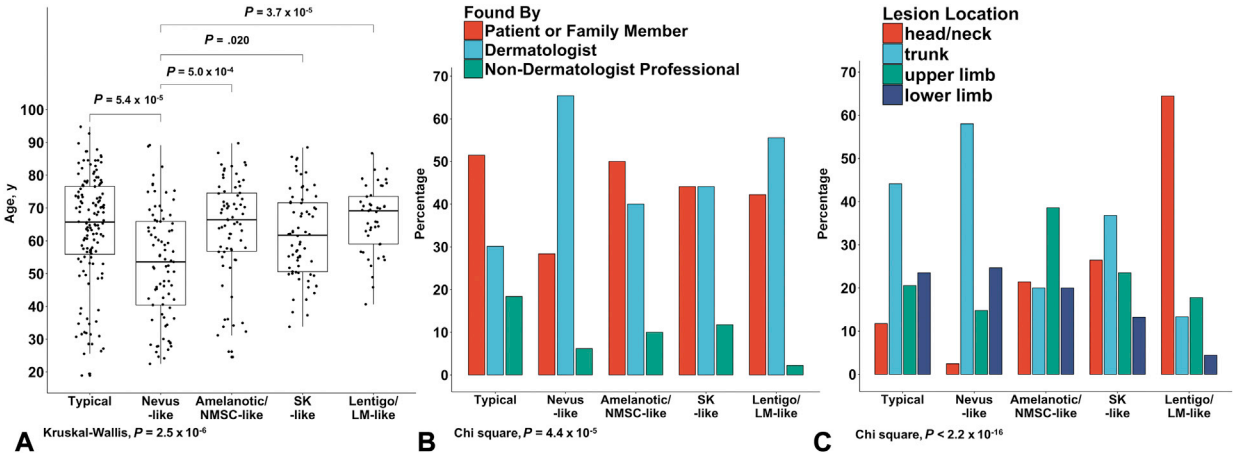

Fig 3. Clinical comparisons of melanoma morphologic clusters. **A**, Nevus-like melanomas (cluster [CL] 2) were diagnosed at a significantly younger age than melanomas of other morphologies. **B**, Nevus-like (CL2) and lentigo/LM-like (CL5) melanomas were more likely to be initially noted by a dermatologist, and typical and amelanotic/NMSC melanomas (which might be erythematous and keratotic) were often initially noted by the patient or a family member. **C**, Typical and nevus-like melanomas were most often located on the trunk, amelanotic/NMSC-like melanomas favored the upper limb, and lentigo/LM-like melanomas favored the head and neck. *LM*, Lentigo maligna; *NMSC*, nonmelanoma skin cancer; *SK*, seborrheic keratosis.

melanomas were anatomic level II or II-III, and most amelanotic/NMSC-like melanomas were anatomic level IV+ (Fig 4, *B*). Typical and amelanotic/NMSC-like had significantly greater thickness than nevus-like and lentigo-like melanomas ($P < .001$) (Fig 4, *C*). Amelanotic/NMSC-like melanomas displayed the highest mitotic activity ($P < .001$) (Fig 4, *D*), were least likely (75%) to display a radial growth phase, and most likely to display vertical growth phase (86%).

DISCUSSION

To increase diagnostic accuracy and decrease diagnostic delay, it is important to understand the clinical spectrum of melanoma and the factors associated with melanoma morphologic types. A classification of melanomas on the basis of their morphologic features was determined with an unsupervised algorithm. The results suggest 5 distinct clusters with discriminating clinical factors that could aid in melanoma recognition.

There is perhaps unappreciated diversity in the appearance of cutaneous melanomas. Because images were captured prebiopsy for routine clinical care, it is untethered to diagnostic impression; this offers a morphologic spectrum that is likely to be less biased than a teaching set of melanoma images. For instance, a keratotic surface response in melanomas (CL4) was surprisingly common in our set, yet rarely shown in textbook images. There are case-reports of verrucous-keratotic melanomas.[40-42] Similarly, there appears to be a group (CL3) of early ill-defined, erythematous, scaly melanomas resembling AKs or possibly eczematous patches (Fig 2). We developed consensus clustering to empirically collapse a larger number of diagnostic classes into clinically-plausible morphologic groups. For instance, pink and erythematous plaques and nodules with variable degrees of scaling characterize amelanotic melanomas and BCC; thus, these 2 diagnostic classes logically co-cluster (CL3).

The data also indicate that nevus-like melanomas occur more frequently in younger adult patients. New nevi occur more frequently in younger patients, peaking at age 30 years and continuing into the fifth decade.[2,43] The propensity of nevogenesis with younger age mostly likely underpins the mimicry between benign and dysplastic nevi and melanoma. Many of the thin melanomas among young patients appear to be morphologically identical to banal or clinically atypical moles (Fig 2). The true clinical false-negative rate might, thus, be underestimated considering these lesions are unlikely to draw any attention during a routine skin examination.

In patients with history of NMSC presenting with a pink and erythematous, raised, painful or irritated lesion, clinicians may consider including melanoma on the differential along with BCC or SCC (CL3 melanomas comprised 18% of our cohort). We found higher frequency of nodular melanoma, which

Table II. Morphologic factors by cluster

Morphologic factor	Cluster 1	2	3	4	5	*P* value*
Left and right location, N = 341, n (%)						.24
n†	112	69	63	58	39	
Left	64 (57)	32 (46)	37 (59)	29 (50)	22 (56)	
Right	47 (42)	33 (48)	25 (40)	24 (41)	16 (41)	
Midline	1 (1)	4 (6)	1 (2)	5 (9)	1 (3)	
Body site,* N = 400, n (%)						**<.001**
n†	136	81	70	68	45	
Head and neck	16 (12)	2 (2)	15 (21)	18 (26)	29 (64)	
Trunk‡	60 (44)	47 (58)	14 (20)	25 (37)	6 (13)	
Upper limb	28 (21)	12 (15)	27 (39)	16 (24)	8 (18)	
Lower limb	32 (24)	20 (25)	14 (20)	9 (13)	2 (4)	
Symptoms, N = 311, n (%)						
n†	109	67	47	53	35	
Bleeding	9 (8)	2 (3)	5 (11)	6 (11)	0 (0)	.14
Itching	6 (6)	1 (1)	2 (4)	3 (6)	2 (6)	.74
Pain and irritated*	6 (6)	1 (1)	8 (17)	1 (2)	0 (0)	**.001**
Growing*	38 (35)	7 (10)	12 (26)	15 (28)	11 (31)	**.01**
Changing	25 (23)	10 (15)	4 (9)	9 (17)	10 (29)	.11
New lesion	7 (6)	1 (1)	5 (11)	5 (9)	0 (0)	.10
Presence of colors, n (%)						
Brown,* N = 305	81 (83)	58 (89)	16 (29)	44 (83)	28 (85)	**<.001**
Black,* N = 305	28 (29)	7 (11)	2 (4)	5 (9)	2 (6)	**<.001**
Blue,* N = 305	6 (6)	1 (2)	0 (0)	0 (0)	0 (0)	**.042**
Pink and erythema,* N = 308	32 (32)	18 (28)	49 (88)	20 (38)	7 (21)	**<.001**
Tan skin color, N = 306	6 (6)	4 (6)	8 (14)	6 (11)	3 (9)	.41
Pigmented, N = 353	20 (17)	10 (13)	3 (5)	10 (16)	7 (18)	.24
Irregular color,* N = 285						
n†	107	61	33	51	33	
Yes, n (%)	99 (93)	51 (84)	24 (73)	47 (92)	28 (85)	**.03**
Irregular borders, N = 79						
n†	23	22	7	12	15	
Yes, n (%)	22 (96)	18 (82)	7 (100)	11 (92)	15 (100)	.22
Lesion topography,*§ N = 345, n (%)						**<.001**
n†	111	71	67	58	38	
Flat	36 (32)	40 (56)	13 (19)	25 (43)	29 (76)	
Raised	75 (68)	31 (44)	54 (81)	33 (57)	9 (24)	

Bolded values are statistically significant.

*Calculated by Kruskal-Wallis 1-way analysis of variance for continuous variables and by χ^2 testing for categorical variables.

†Number of patients for whom information on group of variables was available.

‡Trunk includes the upper back and scapula.

§Flat includes macule, patch, and ulcer; raised includes papule, plaque, nodule, and mass.

frequently presents as amelanotic and raised, within this cluster (Fig 4, *A*).[44,45] We found the clinicopathologic features of SK-like lesions similar to those of typical melanomas. SKs are known to be difficult to distinguish from melanoma,[46,47] which is reflected in the assignment overlap between pigmented melanoma (30%) and SK (47%) in CL1 and CL4 (Supplemental Fig 3, *A*). Carrera and colleagues reported 24 of 132 melanoma cases (18%) had clinical and dermoscopic features consistent with SK lesions. Features associated with these 24 SK-like melanomas included hyperkeratosis (34%), yellowish keratin (31%), comedo-like openings (31%), and milia-like cysts (22.4%). Retrospective analysis indicated that the presence of blue-white veil, pseudopods or streaks, and pigment network were helpful in achieving the correct dermoscopic analysis.[48] Thus, nearly 1 in 5 melanoma lesions might be diagnosed as an SK.

Although melanomas with a typical appearance had a high likelihood of being identified by the patient first, nevus-like and lentigo-like lesions were

Table III. Pathologic factors by cluster

Pathologic factor	Cluster 1	2	3	4	5	*P* value*
Pathologic diagnosis,*† N = 400, n (%)						**<.001**
n‡	136	81	70	68	45	
Superficial spreading	87 (64)	66 (81)	40 (57)	39 (57)	16 (36)	
Malignant melanoma in situ	16 (12)	12 (15)	3 (4)	15 (22)	8 (18)	
Nodular	10 (7)	2 (2)	8 (11)	1 (1)	0 (0)	
Lentigo maligna	6 (4)	0 (0)	7 (10)	6 (9)	18 (40)	
Unclassified	15 (11)	0 (0)	6 (9)	5 (7)	2 (4)	
Other	2 (1)	1 (1)	6 (9)	2 (3)	1 (2)	
Thickness, mm, N = 335						
n‡	121	69	65	49	31	
Thickness,* mean ± SD	1.1 ± 1.2	0.48 ± 0.24	1.3 ± 1.5	0.80 ± 0.82	0.49 ± 0.53	**<.001**
Thickness, median	0.63	0.42	0.8	0.54	0.37	
Anatomic level,*§ N = 329, n (%)						**<.001**
n‡	117	68	65	49	30	
II+	36 (31)	38 (56)	12 (18)	20 (41)	17 (57)	
III+	36 (31)	21 (31)	19 (29)	17 (35)	10 (33)	
IV+	45 (38)	9 (13)	34 (52)	12 (24)	3 (10)	
Mitoses,* N = 331						
n‡	118	69	65	49	30	
Mitoses/mm^2, mean ± SD	1.5 ± 2.8	0.38 ± 1.0	3.2 ± 6.3	1.6 ± 3.9	0.20 ± 0.55	**<.001**
Ulceration,* N = 328						
n‡	115	69	65	49	30	
Present, n (%)	11 (10)	0 (0)	7 (11)	2 (4)	0 (0)	**.02**
Regression, N = 201						
n‡	80	37	44	29	11	
Present, n (%)	29 (36)	12 (32)	8 (18)	6 (21)	4 (36)	.20
Lymphovascular invasion, N = 278						
n‡	105	56	58	39	20	
Present, n (%)	9 (9)	5 (9)	9 (16)	5 (13)	2 (10)	.69
Radial growth phase,* N = 302						
n‡	104	68	55	47	28	
Present, n (%)	96 (92)	66 (97)	41 (75)	45 (96)	28 (100)	**<.001**
Vertical growth phase,* N = 327						
n‡	115	68	65	49	30	
Present, n (%)	84 (73)	39 (57)	56 (86)	32 (65)	12 (40)	**<.001**

Bolded values are statistically significant.
SD, Standard deviation.
*Calculated by Kruskal-Wallis 1-way analysis of variance for continuous variables and χ^2 testing for categorical variables.
†Lentigo maligna includes lentigo maligna in situ. Other includes acral lentiginous; amelanotic superficial spreading; and desmoplastic, nevoid, and spindle cell melanomas.
‡Number of patients for whom information on group of variables was available.
§II+ includes II and II-III, III+ includes III and III-IV, IV+ includes IV, IV-V, and V.

more commonly identified by a dermatologist during routine exam. This is consistent with prior findings showing that melanomas identified by dermatologists were associated with thinner tumors.[4,6,15-19]

It is interesting to note that patients with NMSC-like and lentigo/LM-like melanomas had the highest burden of severe dermatoheliosis (33% and 34%, respectively). Furthermore, >90% of patients with NMSC-like, SK-like, and lentigo/LM-like melanomas reported a personal history of sunburns compared with only 70%-80% among typical and nevus-like clusters. As ultraviolet exposure correlates with histologic[49] and genomic[50] melanoma subtyping, it is not surprising that sun damage patterns, even among nonacral cutaneous lesions, might contribute to morphologic diversity.

The results of our study might have potential implications for computer-aided diagnosis (eg, deep learning with convolutional neural networks) and the reliability of digital images. Convolutional neural networks are critically reliant on classic images for their training. Although such models show

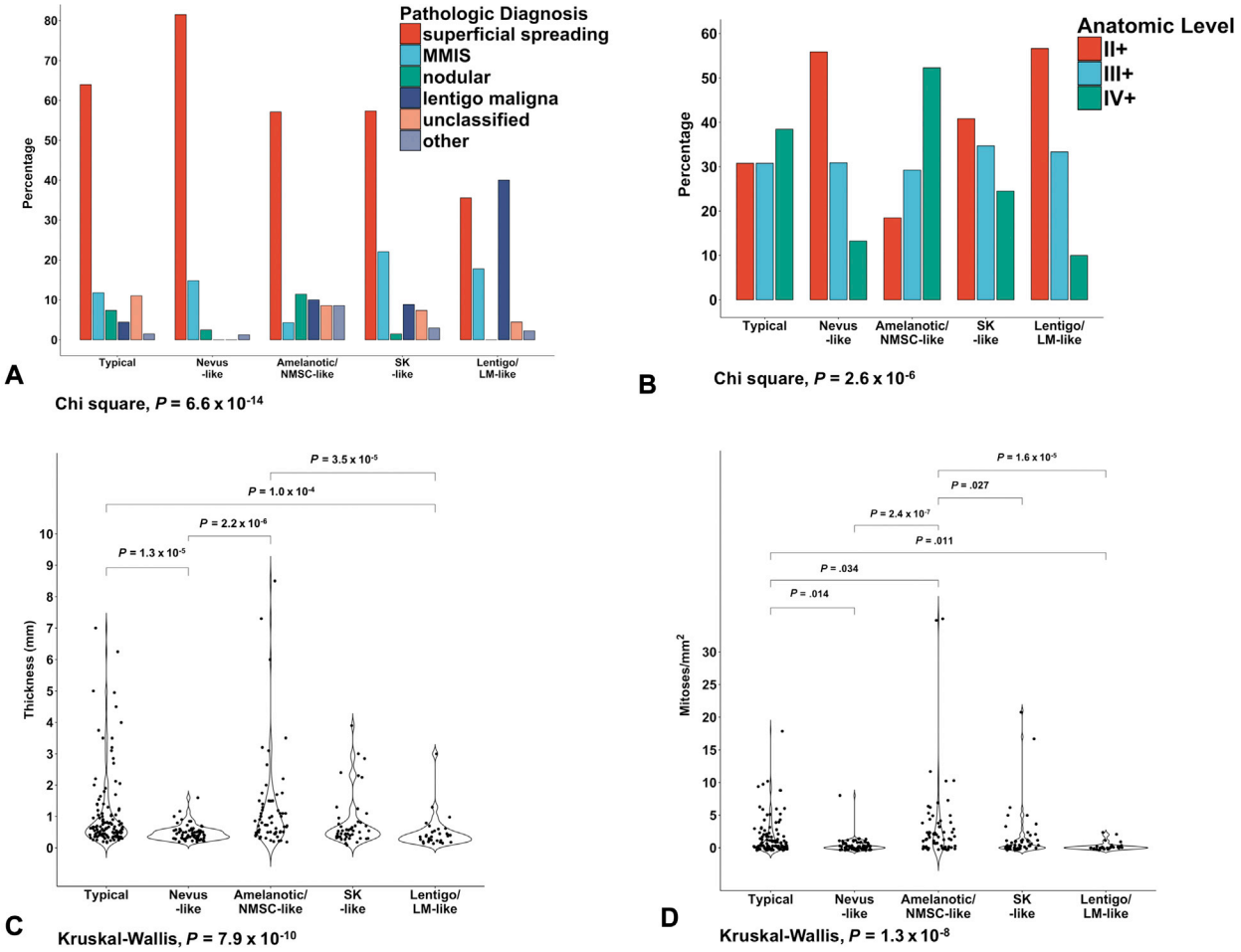

Fig 4. Pathologic comparisons of melanoma morphologic clusters. **A**, Superficial-spreading melanoma was the most common pathologic diagnosis for all clusters except lentigo/LM-like (cluster [CL] 5), which commonly revealed LM melanoma. Nodular and other (desmoplastic, spindle, nevoid) melanomas were most common among the amelanotic/NMSC cluster (CL3). **B**, Nevus-like and lentigo/LM-like melanomas were predominately anatomic level II or II-III, while amelanotic/NMSC-like melanomas (CL3) were anatomic level IV and higher. (II+ includes II and II-III, III+ includes III and III-IV, IV+ includes IV, IV-V, and V.) **C**, Nevus-like (CL2) and lentigo/LM-like (CL5) melanoma clusters were significantly thinner than typical (CL1) and amelanotic/NMSC-like (CL3) clusters. **D**, Typical and amelanotic/NMSC-like melanomas displayed significantly higher mitotic activity compared with nevus-like and lentigo/LM-like melanomas. *LM*, Lentigo maligna; *MMIS*, malignant melanoma in situ; *NMSC*, nonmelanoma skin cancer; *SK*, seborrheic keratosis.

promising diagnostic performance in dermatology,[51,52] a much larger collection of morphologically diverse melanomas are required to fine-tune accuracy. Although some assignment errors have minimal clinical impact because a biopsy is likely to be performed regardless of diagnosis (eg, BCC and SCC vs melanoma), other misclassifications (eg, SK or benign nevi vs melanoma) might have more substantial implications. As alluded to previously, computer-aided diagnoses could be made more reliable by assembling training sets that include images representative of a variety of melanoma appearance classes and by improving performance in niche binary classifications such as SK versus SK-like melanoma, or benign lentigo versus lentigo-like melanoma.

There are several limitations to the study. First, images were intended for site identification only and were quick-captured in the clinic by consumer cameras and cell phones, thereby compromising image resolution and color balance. Although taking images this way is appropriate for clinical practice, picture quality might have been low, reducing the interpretability of the images. Second, the reviewers

were provided images without the opportunity to perform a standard-of-care physical exam. Palpation, redirected lighting, and dermoscopy are all likely to enhance diagnostic accuracy. Studies have shown that, in the hand of expert users, dermoscopy can improve diagnosis of thin melanomas,[53] amelanotic and hypomelanotic melanomas,[54] LM melamonas,[55] and melanoma in situ.[56] Third, study clinicians might have been variably affected by gambler fallacy; in cases of successive melanoma images, physicians might have subjected a bias toward the remaining images being benign by presuming that, in subsequent images, benign lesions were disproportionately evident to offset the number of malignant ones. Fourth, clusters had unequal membership with CL1 containing the most members. Given the resulting small sample sizes, statistical power might have been insufficient to detect certain differences in factors. Fifth, given the random distribution of unknown data, covariance between related factors could not be reliably assessed. Sixth, this study did not include acral or mucosal lesions, which are important melanoma variants with an array of unique and challenging morphologic presentations. Last, this study does not address an important challenge, which is the identification of a biologic, rather than histologic (as in this study), false negative. Melanomas so banal as to elude even initial sampling were not captured in this analysis.

Conclusion

Consensus clustering analysis of 400 melanoma images revealed 5 morphologic classes: typical, nevus-like, amelanotic/NMSC-like, SK-like, and lentigo/LM-like. Nevus-like melanomas were found among young patients and, similar to lentigo-like lesions, were thinner and invaded more superficial anatomic levels. Nevus-like and lentigo-like lesions were more likely identified on routine dermatologic examination than by the patient or patient's family. Amelanotic/NMSC-like melanomas were thick, mitotically active, tender, and associated with prior NMSC. SK-like and typical melanomas were clinicopathologically similar. The melanoma morphology spectrum has been widely reported but poorly codified. Prebiopsy impressions might have inadvertently limited the availability of images of benign simulants within the canon of textbook melanoma photographs. In the absence of an easily accessible and computationally robust neural network for morphologic stratification, we have introduced consensus clustering to empirically define morphologic groupings with hopes of improving diagnostic accuracy.

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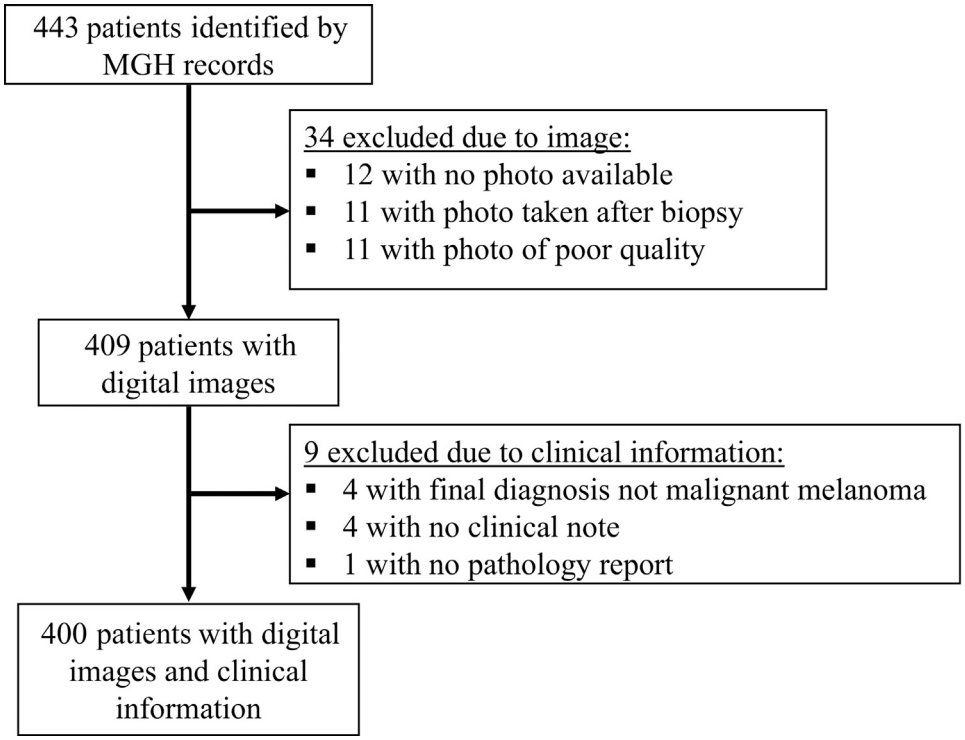
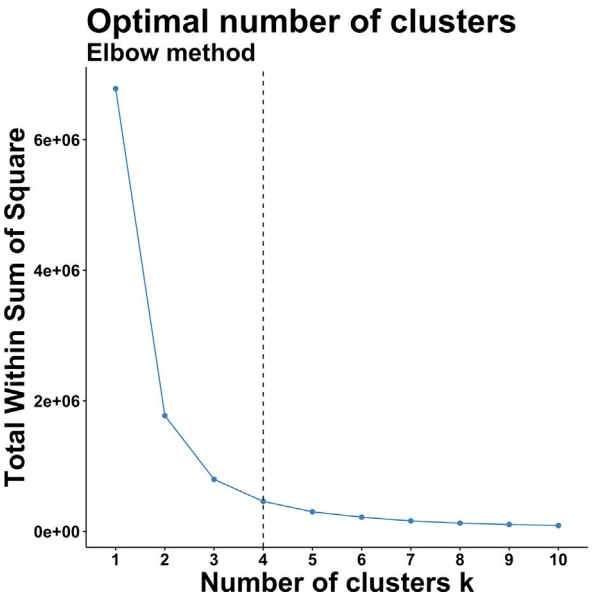
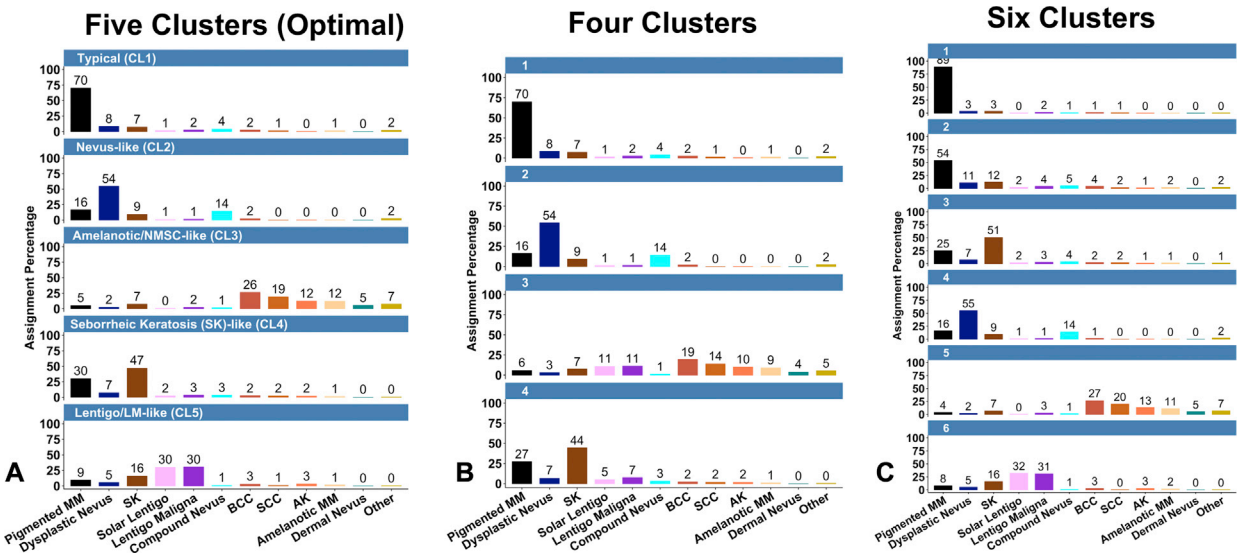


Supplemental Fig 1. Selection of images from patients included in the study. *MGH*, Massachusetts General Hospital.



Supplemental Fig 2. Total within-cluster sum of squares for simulations for k = 1 through k = 10 clusters. Within-cluster sum of squares decreases rapidly until k = 4, suggesting that the statistically optimum cluster number is at least 4 clusters.



Supplemental Fig 3. **A**, Profiles of 4, 5, and 6 morphologic melanoma clusters. Bar height corresponds to assignment percentage. **B**, K-means clustering with 4 centroids. Cluster 3 demonstrates insufficient separation between the amelanotic assignments (BCC, SCC, AK, and amelanotic MM) and the solar lentigo and lentigo maligna assignments. Cluster profiling demonstrates insufficient cluster segregation with 4 centroids. **C**, K-means clustering with 6 centroids. Clusters 1, 2, and 3 are closely related and display a predominance of pigmented melanoma and seborrheic keratosis assignments. Cluster profiling demonstrates cluster redundancy with 6 centroids. *AK*, Actinic keratosis; *BCC*, basal cell carcinoma; *CL*, cluster; *MM*, malignant melanoma; *SCC*, squamous cell carcinoma; *SK*, seborrheic keratosis.