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Clinical characteristics associated with Spitz nevi and Spitzoid malignant melanomas: The Yale University Spitzoid Neoplasm Repository experience, 1991 to 2008

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Abstract

Background—Spitz nevi and Spitzoid malignant melanomas are uncommon and may be difficult to distinguish histopathologically. Identification of clinical features associated with these lesions may aid in diagnosis.

Objective—We sought to identify clinical characteristics associated with Spitz nevi and Spitzoid malignant melanomas.

Methods—We conducted a retrospective cohort study of Spitz nevi and Spitzoid malignant melanomas from the Yale University Spitzoid Neoplasm Repository diagnosed from years 1991 through 2008. Descriptive statistics and multivariate logistic regression were used to compare select patient- and tumor-level factors associated with each lesion.

Results—Our cohort included 484 Spitz nevi and 54 Spitzoid malignant melanomas. Spitz nevi were more common ($P = .03$) in females (65%; $n = 316$) compared with Spitzoid malignant melanomas (50%; $n = 27$), occurred more frequently in younger patients (mean age at diagnosis 22 vs 55 years; $P < .001$), and more likely presented as smaller lesions (diameter 7.6 vs 10.5 mm; $P < .001$). Increasing age (odds ratio 1.16, 95% CI [1.09, 1.14]; $P < .001$) and male gender (odds ratio 2.77, 95% CI [1.17, 6.55]; $P < .02$) predicted Spitzoid malignant melanoma diagnosis.

Limitations—Small sample size, unmeasured confounding, and restriction to a single institution may limit the accuracy and generalizability of our findings.

Conclusions—Age and gender help predict diagnosis of Spitz nevi and Spitzoid malignant melanomas.

Capsule Summary

- Spitz nevi and Spitzoid malignant melanomas are uncommon and may be difficult to distinguish histopathologically.
- Age and gender help predict diagnosis of Spitz nevus and Spitzoid malignant melanoma.
- Consideration of patient-level clinical information in rendering histopathologic diagnosis may improve risk assessment and aid in the differentiation of these neoplasms.

Although Spitz nevi usually arise during childhood or early adulthood, they may appear at any age.^{1, 2, 3, 4, 5} Spitzoid malignant melanomas are melanomas bearing histologic resemblance to Spitz nevi. Unified interpretation of histopathologic criteria and clinical characteristics for distinguishing these lesions are lacking. This may result in substantial uncertainty regarding their diagnosis and management, particularly given that these lesions are infrequently encountered by dermatologists and dermatopathologists compared with common melanocytic nevi and conventional melanomas.

Given that histopathologic examination remains an imperfect gold standard for diagnosing Spitz nevi and Spitz malignant melanomas, incorporation of additional clinical criteria may aid in evaluation of these neoplasms.^{2, 6, 7, 8, 9, 10} To date, however, most clinicopathologic studies of Spitz nevi and Spitzoid malignant melanomas have been restricted to case reports and small case series of limited generalizability with very few large studies,^{2, 6, 7, 8, 9, 10} constraining our ability to confidently identify clinical features significantly associated with Spitz nevus versus Spitzoid malignant melanoma diagnoses. Given this knowledge gap, there is a need to leverage larger cohorts of patients with Spitz nevi and Spitzoid malignant melanomas to characterize both potential patient- and tumor-level factors that may assist in classification of these lesions.

Accordingly, we conducted a retrospective cohort study to assess clinical features associated with Spitz nevi and Spitzoid malignant melanomas, as diagnosed by an expert panel of dermatopathologists. Based on prior research,^{6, 7, 8} we hypothesized that age, gender, and anatomic location of tumor would be significant predictors of Spitz nevus and Spitzoid malignant melanoma diagnoses.

Methods

We conducted a retrospective cohort study of all cases of classic Spitz nevi and Spitzoid malignant melanomas from the Yale University Spitzoid Neoplasm Repository between January 1, 1991, and December 31, 2008. This repository is a biospecimen databank of Spitzoid neoplasms diagnosed at the Yale University Dermatopathology Laboratory and cases contributed from other national and international institutions.

Only cases of typical or classic Spitz nevi—composed of epithelioid and/or spindled melanocytes—were included in the study. Spitz nevi that exhibited any atypical features (eg, asymmetry, lack of circumscription, lack of uniform maturation, confluence of nests and focal sheetlike growth pattern, and/or numerous mitotic figures) were excluded. Each Spitz

nevus was further subclassified as junctional, intradermal, or compound based on the distribution of melanocytes. The histopathologic review of all cases of Spitz nevi, performed by one of the authors (R. L.), was done in a blind fashion, without knowledge of patient age, gender, anatomic site, and recorded diagnosis. All cases of Spitzoid malignant melanoma similarly underwent blinded review by a consensus group of dermatopathologists from the Yale University Dermatopathology Laboratory.

For each case we obtained the following associated patient characteristics: age at diagnosis, gender, anatomic location of tumor (categorized as head and neck, trunk, upper extremities, and lower extremities), diameter of tumor in millimeters, and laterality of tumor (categorized as left vs right). We also obtained the clinical impression at the time of biopsy for each specimen as described by the submitting physician. We compared unadjusted differences in the baseline distribution of these variables between cases of Spitz nevi and Spitzoid malignant melanomas using Student t test, binomial test of proportions, χ^2 test, or Fischer exact test, as appropriate. In addition, we calculated yearly distributions in the relative proportions of histopathologic subtypes of Spitz nevi over the study period.

To further evaluate potential predictors resulting in diagnosis of Spitz nevus versus Spitzoid malignant melanoma, we performed multivariate logistic regression to derive odds ratios and 95% confidence intervals associated with the following covariates chosen a priori as independent explanatory variables: age at diagnosis, gender (referent category female), and anatomic location (referent category head and neck). We limited risk-adjusted evaluation to these covariates to avoid potential model “overfitting” given the relatively small number of Spitzoid malignant melanomas in our cohort.¹¹ We assessed goodness of fit following acquisition of logistic regression estimates using the c-statistic, and assumed by convention that any c-statistic value greater than 0.8 would demonstrate excellent discrimination.¹²

Given that Spitzoid melanomas are typically invasive and therefore unlikely to be mistaken for junctional Spitz nevi, we conducted a sensitivity analysis excluding the latter cases to test the robustness of our results. Finally, we calculated postestimation marginal risk-adjusted probabilities of Spitzoid malignant melanoma diagnosis associated with our model covariates. This allowed us to examine the likelihood of this diagnosis as a continuous probabilistic outcome as a function of age, stratified by gender and anatomic location.

Statistical analyses were performed using software (Stata SE 12.1, StataCorp, College Station, TX). All statistical tests were 2-tailed with alpha equal to 0.05. This study was approved by the Yale University Human Research Protection Program.

Results

Our cohort included 484 cases of Spitz nevi and 54 cases of Spitzoid malignant melanomas. Of the Spitz nevi, 58 were classified as junctional, 333 were classified as compound, and 93 were classified as intradermal (Fig 1). Significantly more ($P = .03$) patients given the diagnosis of Spitz nevus were female (65%; $n = 316$) compared with those patients given the diagnosis of Spitzoid malignant melanoma who were female (50%; $n = 27$) (Table I). Patients given the diagnosis of Spitz nevus were significantly ($P < .001$) younger (mean age

at diagnosis 22 years; range 1–61 years) than those given the diagnosis of Spitzoid malignant melanoma (mean age at diagnosis 55 years; range 8–90 years) (Fig 2 and Table I).

Lower extremities were the most common anatomic location for both Spitz nevus (n = 202; 41.7%) and Spitzoid malignant melanoma (n = 27; 50%), whereas head and neck were the least common. No significant differences were observed for the overall distribution of lesional anatomic locations or laterality between the 2 groups (Fig 3, Fig 4, and Table I) although Spitzoid malignant melanomas were significantly ($P < .001$) larger in diameter than Spitz nevi (10.5 vs 7.6 mm) (Table I).

The overall distribution of prebiopsy clinical impressions differed significantly ($P < .001$) between the 2 groups. The 5 most common clinical impressions for Spitz nevi were: nevus (30.0%; n = 144), atypical nevus (20.9%; n = 101), Spitz nevus (14.1%; n = 68), other (6.6%; n = 32), and dermatofibroma (4.8%; n = 23) (Table I). The 5 most common clinical impressions for Spitzoid malignant melanoma were: melanoma (25.9%; n = 14), atypical nevus (16.7%; n = 9), basal cell carcinoma (13.0%; n = 7), nevus (11.1%; n = 6), and other (11.1 %; n = 6) (Table I).

Results from multivariate logistic regression showed that diagnosis of Spitzoid malignant melanoma was significantly associated with increasing age (odds ratio 1.16 [1.09, 1.14]; $P < .001$) and male gender (odds ratio 2.77 [1.17, 6.55]; $P < .02$), although no significant associations were observed by anatomic location of tumor (Table II). Postestimation marginal risk adjusted probabilities also showed increasing likelihood of Spitzoid malignant melanoma with increasing age, with the greatest probability associated with those tumors located on the lower extremities for both genders, compared with other anatomic locations (Fig 5). The postregression c-statistic associated with our model was 0.91, indicating a strong ability of our model to accurately classify lesions as Spitz nevus or Spitzoid malignant melanoma based on the specified predictor variables. Sensitivity analyses excluding the 58 cases of junctional Spitz nevi in our cohort yielded similar results as above.

Discussion

Given the potential difficulty in accurately distinguishing Spitz nevus from Spitzoid malignant melanoma based solely on microscopic evaluation, incorporation of additional clinical information may aid in diagnosis of these lesions, thereby raising or lowering the pretest probability of malignancy or benignancy before histopathologic examination. To our knowledge, our study is the largest to date examining clinical characteristics associated with diagnosis of these lesions. This information may prove useful in reducing—but not entirely eliminating—diagnostic uncertainty and appropriately contextualizing potential therapeutic options for those dermatologists and dermatopathologists confronted with Spitzoid neoplasms.

Our results show that Spitz nevi and Spitzoid malignant melanomas may be associated with select clinical characteristics—specifically age at diagnosis, gender, and tumor size—whereas other clinical features may be less informative, such as anatomic laterality or prebiopsy clinical impression. In particular, our results are consistent with prior studies describing

younger age at diagnosis for patients with Spitz nevi (mean age range: 18.8-22 years in published literature^{2, 6, 7, 8}), compared with older age at diagnosis for patients with Spitzoid malignant melanoma,² confirming that Spitz nevi may arise in adults and children.^{2, 6, 7, 8, 9, 10, 13} Like prior case series of Spitz nevi, we also found predominance of these lesions in female patients,^{6, 7, 8, 9, 10} which were also more likely to be smaller in size compared with Spitzoid malignant melanomas. In our study the most common histopathologic type of Spitz nevi was compound, followed by intradermal and junctional. These findings differ somewhat from those of Requena et al,⁶ who reported compound Spitz nevi to be the most common histopathologic type, followed by junctional and intradermal histopathologic subtypes.

Also similar to prior studies,^{1, 6, 7, 8, 10} we found that the lower extremities were the most common location for Spitz nevi, followed by the upper extremities and trunk,^{7, 10} although Weedon and Little⁹ studied 211 patients with Spitz nevi and found the trunk as the most common anatomic location and upper extremities as the least common location. Although the head and neck region—particularly the face—is often considered the most common anatomic location for Spitz nevus in many textbooks of dermatology,^{14, 15, 16} our results diverge from this assessment. The head and neck region was the least common location in our cohort of Spitz nevi, congruent with other studies,^{6, 7, 8, 10} suggesting that re-examination of this conventional wisdom may be in order.

Although we identified the lower extremity as the most common site for Spitzoid malignant melanoma in our cohort, also consistent with prior research,¹⁷ we found that anatomic location did not predict diagnosis of Spitzoid malignant melanoma versus Spitz nevus in multivariate modeling. However, the marginal risk-adjusted probabilities observed suggest that Spitzoid malignant melanoma may be more common on the lower extremities in older individuals when stratified by gender, indicating potential effect modification of these variables on the likelihood of disease. We believe larger studies are needed to better assess the relationship between anatomic location and risk of these lesions.

Finally, our results highlight the difficulty in accurate identification of both Spitz nevi and Spitzoid malignant melanomas based on prebiopsy clinical impression alone. Fewer than 1 in 7 cases in our cohort were suspected to be Spitz nevi, whereas approximately 3 in 4 cases of Spitzoid malignant melanomas were suspected as nonmelanomas. These findings parallel those of prior research^{6, 7} and underscore the clinical heterogeneity that may be exhibited by these lesions and the need for biopsy and histopathologic confirmation.

Our study has several limitations. We recognize there is no fully objective gold standard for diagnosing Spitz nevus and Spitzoid malignant melanoma, which currently relies on the interpretation of histopathologic criteria that may vary across individual dermatopathologists. Therefore, our results may be subject to errors of misclassification in diagnosis of these lesions. We attempted to minimize this concern through use of consensus histopathologic diagnosis involving multiple dermatopathologists. Similarly, this is a single institutional study, and results from our analyses may be not generalizable to other care settings where histopathologic evaluation and diagnosis of Spitz nevi and Spitzoid malignant melanomas may differ. In addition, our study included a relatively small number of the latter

lesions, which constrained our ability to evaluate and risk-adjust for other potentially important patient- and tumor-level covariates of interest. Despite these concerns, our c-statistic calculation demonstrates excellent goodness of fit and discriminatory ability of our reduced multivariate model to accurately classify Spitz nevi and Spitzoid malignant melanomas. Finally, our study design excluded cases of Spitz nevi with any atypical features, and our results should not be extrapolated to this category of neoplasms without appropriate caution.

Future, population-based studies are needed to definitively identify and characterize the spectrum of characteristics associated with Spitz nevus and Spitzoid malignant melanoma diagnoses. Nevertheless, we believe our results narrow an important knowledge gap concerning clinical predictors of Spitz nevi and Spitzoid malignant melanomas and may inform ongoing efforts to optimize risk assessment, diagnosis, and consequent dermatologic care for these lesions.

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Fig 1. Yearly trends in Spitz nevi by histologic subtype.

Absolute nevi counts and proportions by year denoted by bars and numbers above bars, respectively. Compound Spitz nevi were most common, followed by intradermal and junctional histopathologic subtypes. ‡Derived from Student t test. §Derived from binomial test of proportions. //Derived from χ^2 test. ¶Derived from Fisher exact test.

Fig 2. Age distribution of Spitz nevi and Spitzoid malignant melanomas.

Spitz nevi were predominantly seen in children and young adults. A smaller number also occurred in adults up to the seventh decade. The number of Spitzoid malignant melanomas increased with increasing age.

Fig 3. Anatomic distribution of Spitz nevi.

Localization of 484 Spitz nevi and frequency of anatomic distribution. The most common sites of involvement were front and back of thighs.

Fig 4. Anatomic distribution of Spitzoid malignant melanomas.

Localization of 54 Spitzoid malignant melanomas and frequency of anatomic distribution. The anterior thighs, posterior lower legs, back, and arms were the most common sites of involvement.

Fig 5. Probability of Spitzoid malignant melanoma by age, gender, and location.

The probability of Spitzoid malignant melanoma diagnosis was greatest among lesions presenting on the lower extremities in men, whereas lesions occurring in the head and neck region among women had the lowest risk.

Table I.

Characteristics of Spitz nevi and Spitzoid malignant melanomas

Characteristic	Spitz nevus n = 484 (90)	Spitzoid malignant melanoma n = 54 (10)	P value
Age at diagnosis, y [†]	22 [14]	55 [21]	<.001 [‡]
Gender [*]			
Female	316 (65)	27 (50)	.03 [§]
Male	168 (35)	27 (50)	
Ratio	1.9	1	
Anatomic location [*]			
Head and neck	77 (15.9)	4 (7.4)	.37 ^{//}
Trunk	84 (17.3)	12 (22.2)	
Upper extremities	120 (24.8)	11 (20.4)	
Lower extremities	202 (41.7)	27 (50)	
Missing	1 (0.2)	0	
Laterality [*]			
Left	232 (51.1)	22 (40.7)	.6 ^{//}
Right	222 (48.9)	28 (51.9)	
Missing	30 (6.2)	4 (7.4)	
Diameter, mm [†]	7.6 [4.2]	10.5 [5.7]	<.001 [‡]
Clinical impression [*]			
Nevus	144 (30.0)	6 (11.1)	<.001 [¶]
Atypical nevus	101 (20.9)	9 (16.7)	
Spitz nevus	68 (14.1)	1 (1.9)	
Melanoma	13 (2.7)	14 (25.9)	
Dermatofibroma	23 (4.8)	1 (1.9)	
Wart	17 (3.5)	0	
Hemangioma	16 (3.3)	2 (3.7)	
Basal cell carcinoma	8 (1.7)	7 (13.0)	
Other	32 (6.6)	6 (11.1)	
Missing/not specified	62 (12.8)	8 (14.8)	

* Values expressed as frequency (percent).

[†] Values expressed as mean [SD].

[‡] Derived from Student *t* test.

[§] Derived from binomial test of proportions.

^{//} Derived from χ^2 test.

[¶] Derived from Fisher exact test.

Table II.

Adjusted risk of Spitzoid melanoma versus Spitz nevus

Characteristic	Odds ratio [95% CI]	P value
Age	1.16 [1.09-1.14]	<.001
Gender		
Female	1	na
Male	2.77 [1.17-6.55]	<.02
Anatomic location		
Head and neck	1	na
Trunk	1.89 [0.28-12.8]	<.51
Upper extremities	1.76 [0.26-11.9]	<.56
Lower extremities	4.1 [0.64-26.3]	<.14

CI, Confidence interval; *na*, not applicable.