DERMATOPATHOLOGY

Nuclear and cytoplasmic features in the diagnosis of banal nevi, Spitz nevi, and melanoma

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Background: Many authors have described cytologic features in a variety of melanocytic lesions but, to our knowledge, a statistical analysis of sensitivity, specificity, and overall accuracy of these features alone or in combination has not been performed.

Objective: We sought to determine the diagnostic value of nuclear and cytoplasmic characteristics in the diagnosis of melanocytic lesions via multivariate statistical analysis.

Methods: This is a retrospective observational study conducted on 300 melanocytic lesions. We evaluated a series of distinctive features; subsequently a multivariate model was used to determine sensitivity and specificity.

Results: Major features that favor a diagnosis of melanoma include: pleomorphism with enlarged nuclei, mitotic figures, notching/corrugation of the nuclear envelope, and peppered moth nucleus. Features with intermediate value include: solid hyperchromasia, vesicular nucleus with single round nucleolus, and nuclear/cytoplasmic ratio greater than 4:1.

Limitations: Limitations of this study include its retrospective nature, and the reliance on the original diagnostic classification of each neoplasm.

Conclusion: Our data suggest that some nuclear alterations have greater value in the diagnosis of benign and malignant melanocytic lesions. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.06.051.)

Key words: banal nevi; chromatin; cytology; cytoplasm; melanoma; nucleus; Spitz nevus.

The analytical process that results in a diagnosis of melanocytic neoplasms is complex. Historically, certain cytologic features presented in specific melanocytic neoplasms more frequently than others. As a result, we decided to study the diagnostic value of nuclear and cytoplasmic characteristics in the diagnosis of melanocytic lesions via multivariate statistical analysis. Specifically, we established the frequency of the nuclear and cytoplasmic features found in previously diagnosed melanomas and compared them with banal nevi and Spitz nevi.

METHODS

This is a retrospective observational study conducted on 300 cases, including 100 cases each of banal nevus, Spitz nevus, and melanoma. The cases were consecutively retrieved from the archives of the Ackerman Academy of Dermatopathology, New York, NY, representing a period between 2012

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and 2014. The original diagnoses were rendered by a number of dermatopathologists in our group and were confirmed by intradepartmental consultation and ancillary studies when required. Cases with "atypical" in the diagnostic field or microscopic description were excluded in our analysis to avoid ambiguity. We also excluded cases in which inadequate material was present to assess for all of the cytologic features listed. For each case, hematoxylin and eosin–stained slides were evaluated for 14 features: the presence of mitotic figures, abnormal mitotic figures, nuclear cytoplasmic ratio greater or less than 4:1, pleomorphism with enlarged nuclei (variation in nuclear size >40 μm), nuclear molding, hyperchromasia, notching or corrugation of the nuclear envelope, flattening of adjacent nuclei, nuclear pseudoinclusions, vesicular nuclei with single round nucleoli, multiple nucleoli, inconspicuous nucleoli, dusty cytoplasm, and peppered moth chromatin pattern (Fig 1). A precise definition for each of the features is summarized in Table I. Concordance for each of the histologic features was achieved among the investigators using a modified Delphi methodology. The fields with the most prominent abnormalities seen at low power (×100) were chosen for further evaluation by high-power magnification (×400 and/or ×600). Representative microphotographs of 5 high-power fields were taken for each case. These were stored in tagged image file format and subsequently retrieved and evaluated in a blinded fashion for the absence or presence of every feature in 0% to 20% or in greater than 20% of nuclei.

We assessed the highest degree of cellular atypia in the most atypical area of the photomicrograph, and the frequency of atypical melanocytes was assessed according to the stated definitions above. A digital atlas of photomicrographs was built to create a visual analog scale of the percentage of cells containing each feature.

Statistical methods

Data management and analysis were performed using software (SPSS, Version 22, IBM Corp, Armonk, NY). Univariate analyses were performed to select a set of features to be tested for inclusion in a multivariate model. All features with a P value less than 0.1 were included in the stepwise logistic regression model. Estimated odds ratios with confidence intervals were calculated. Sensitivity, specificity, and overall accuracy of the models were computed at each step of the logistic regression. All P values are 2-sided. P values less than .05 were considered significant. Overall accuracy was calculated by the sum of true positives plus true negatives divided by all cases. All cases in which greater than 20% of cells showed a given feature were also quantified in a separate table and P values were obtained. In this second step, multivariate model analyses could not be performed because we would have had to exclude some of the features because of the small number of cases showing a given feature.

CAPSULE SUMMARY

- A variety of nuclear and cytoplasmic features have been described as characteristic for melanoma, but each criterion has not been studied statistically for validity.
- We used a stepwise logistic regression multivariate analysis to determine the independent diagnostic value of a series of cytologic features.
- Features found to be independently useful in establishing a diagnosis of melanoma include pleomorphism with enlarged nuclei, notching of the nuclear envelope, mitotic figures, and a peppered moth chromatin pattern.

RESULTS

The frequency of cytologic features found in banal nevi, Spitz nevi, and melanomas are summarized in Table II (available at http://www.jaad.org). Comparison of cases in which greater than 20% of cells showed a given feature according to their diagnosis are summarized in Table III (available at http://www.jaad.org).

Banal nevi

The cytologic features that proved helpful for the diagnosis of banal nevus versus Spitz nevus or melanoma were nuclear cytoplasmic ratio less than 4:1, vesicular nucleus with prominent nucleoli, inconspicuous nucleoli, pleomorphism with enlarged nuclei, flattening of adjacent nuclei, pseudoinclusions, and peppered moth nuclear pattern (P value $< .05$) (Fig 2 and Table IV [available at http://www.jaad.org]). Sensitivity, specificity, and overall accuracy of these features independently and when combined are summarized in Table V (available at http://www.jaad.org). Nuclear cytoplasmic ratio less than 4:1 had the highest specificity, but overall accuracy of 66.7%. A 91.5% specificity, 79% sensitivity, and 87.3% overall accuracy was found if all of these features were detected collectively. Only the following features were found to be significant (P value $< .001$) when greater than 20% cells expressing the feature was required: single prominent nucleoli, dusty cytoplasm, vesicular nuclei