In conclusion, we think that when assessing a patient with characteristics similar to those described here, the differential diagnosis should include drug-induced photosensitive rash, especially after initiation of treatment such as leflunomide, as in the present case. Additional tests, for example, patch (and photopatch) testing, are essential if we are to make an appropriate diagnosis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Mitotic Rate as a Prognostic Factor in Melanoma: Implications for Disease Management☆

El índice mitótico como factor pronóstico y sus implicancias en el manejo del melanoma

To the Editor,

Sentinel lymph node (SLN) involvement is the most important prognostic factor in nonmetastatic melanoma. Predictors of nodal involvement include Breslow thickness, ulceration, and mitotic rate.[1]

The eight edition of the American Joint Committee on Cancer (AJCC-8) melanoma staging system removed mitotic rate as a predictive factor in melanoma because of its poor reproducibility secondary to low intraobserver and interobserver reliability.[2] The National Comprehensive Cancer Network Guidelines (version 1.2018), by contrast, suggest that SLN biopsy should be considered in patients with T1a melanoma (<0.8 mm, nonulcerated) and a mitotic rate of > 2 mitoses/mm^2, particularly if they are young. There is ample evidence that mitotic rate is predictive of SLN positivity (Table 1). According to a multicenter European study, SLN positivity was the most important prognostic factor in thin melanomas (n = 4249, Breslow thickness < 1 mm), and the only predictor of this positivity was a mitotic rate of > 2 mitoses/mm^2. T1a melanoma was associated with an overall risk of SLN positivity of 3.4% (or 1.2% for patients with a mitotic rate of 0 mitoses/mm^2), but this risk was 20% for > 2 mitoses/mm^2, which is even higher than that observed for T1b melanoma (8%).[3] In melanoma patients downstaged to T1a under the AJCC-8 criteria, the 3-year disease-free survival rate was 95%. This rate was significantly lower, however, at 80%, in those with a mitotic rate of > 3 mitoses/mm.[4] A US study of 17 204 patients with melanoma with a Breslow thickness of 0.01-1 mm reported a linear relationship between mitotic rate and SLN involvement. After adjustment for known prognostic factors, patients with a rate of > 1 mitoses/mm^2 were twice as likely to have SLN involvement than those with < 1 mitoses/mm^2. The risk of SLN involvement was 7.9% in patients with 1 mitosis/mm^2, but 21.8% and 44.5% for those with 5 and > 10 mitoses/mm^2, respectively. A recent European study that included a large cohort for the development (n = 3666) and validation (n = 4227) of a nomogram to improve the selection of patients with thin melanoma (Breslow thickness, < 1 mm) for SLN biopsy showed that age, Breslow thickness, a mitotic rate of > 1 mitosis/mm^2, ulceration, lymphovascular invasion, and regression > 75% were all significant predictors of SLN involvement. The resulting nomogram performed better than models based on current international recommendations at identifying which patients with thin melanomas should undergo SLN biopsy and showed that the higher

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Table 1 Mitotic Rate as a Prognostic Factor in Melanoma.

Melanomas with a Breslow thickness <1 mm
A mitotic rate > 2 mitoses/mm^2 appears to be the only risk factor for SLN involvement.[3]
There is a linear association between number of mitoses and risk of SLN involvement (5.4% for 0 mitoses/mm2, 21.8% for 5 mitoses/mm^2, 38.3% for 10 mitoses/mm^2).[5]
T1a melanoma with a mitotic rate > 2 mitoses/mm^2 is associated with a higher risk of SLN involvement than T1b melanoma (20% vs. 8%).[3]
Three-year disease-free survival is worse in patients with a mitotic rate > 3 mitoses/mm.[2,4]
A mitotic rate > 10 mitoses/mm2 is associated with an almost 7-fold increased risk of mortality compared with one of 0-3 mitoses/mm^2.[10]
Mortality risk increases by 23% for each unit increase in mitotic rate.[10]
Melanomas with a Breslow thickness > 1 mm
Mitotic rate is predictive of SLN involvement (34.4% of patients with mitosis had positive SLN status versus 12.8% of those without mitosis).[7]
A mitotic rate > 3 mitoses/mm2 is associated with significantly worse disease-free and overall survival.[7,a]
A high mitotic rate may explain the worse survival observed in stage IIC compared with stage IIIA melanoma.[9]
For each unit increase in mitotic rate, mortality risk increases by 5% in patients with stage II melanoma and by 3% in those with stage III melanoma.[10]

Abbreviation: SLN, sentinel lymph node.

[a] In another study with fewer patients (n = 141), a mitotic rate of $\geq$ 2 mitosis/mm^2 was associated with significantly worse disease-free and overall survival.

the number of mitoses, the greater the likelihood of SLN involvement.[6] Based on these studies, we strongly recommend rigorous assessment of patients with thin melanomas and a high mitotic rate and consider that SLN biopsy should always be contemplated.

The predictive value of mitotic rate is not limited to thin melanomas. One Italian study of 1524 patients with melanoma with a Breslow thickness > 1 mm found a significant association between mitotic rate and SLN involvement. In particular, a rate of > 1 mitosis/mm^2 was associated with worse disease-free survival (hazard ratio, 1.82; 95% CI, 1.02-3.24; P = .043).[7] Similar results were obtained in a Canadian study of thin melanomas (n = 1072), where a mitotic rate of > 1 mitosis/mm^2 was the only associated factor for SLN involvement in patients with a Breslow thickness of 1.01-2.0 mm.[1] A Spanish study of 141 patients with a mean Breslow thickness of 2.6 mm reported that $\geq$ 2 mitoses/mm^2 was associated with worse disease-free and overall survival rates.[8] Another study of 128 patients attempting to explain the paradoxically worse survival rates observed in patients with stage IIC versus IIIA melanoma found that an age of 55 years or older and a mitotic rate of > 5 mitoses/mm^2 were independent predictors of overall survival.[9] The authors suggested that stage IIC and IIIA melanomas might be biologically distinct and that mitotic rate should be considered in this subgroup of patients. A large US study of 71 235 patients with melanoma that used 3 cutoff points for mitotic rate (0-3, 4-10 and > 10 mitoses/mm^2) found a linear association between mitotic rate and disease-specific survival for stages I, II, and III. In patients with stage I melanoma, the 5-year disease-specific survival rate was 98.3% for patients with a mitotic rate of 0-3 mitoses/mm^2 versus 79.7% for those with a rate of > 10 mitoses/mm^2. The corresponding rates were 86.1% versus 72.9% for patients with stage II melanoma and 72.5% (0-3 mitoses/mm^2) versus 49.7% for those with stage III melanoma. Mortality risk increased by 23% for each unit increase in mitotic rate among patients with stage I disease, and the corresponding increases for patients with stage II and III disease were 5% and 3%, respectively. Patients with stage I disease and > 10 mitoses/mm^2 had an almost 7-fold increased risk of mortality compared with those with 0-3 mitoses/mm^2.[10] A recent Australian study of 156 children and adolescents younger than 20 years with a median Breslow thickness of 1 mm showed that mitotic rate had greater prognostic value than Breslow thickness, and was the only independent predictor of recurrence-free survival.[11]

Mitotic rate is an important prognostic factor in melanoma. We recommend individualized management of patients with a high mitotic rate, and believe that those with a Breslow thickness of > 1 mm should be considered for SLN biopsy and undergo staging studies and close follow-up. Diagnostic procedures should also be optimized to increase the reproducibility of mitotic rate assessment.

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Risk Factors for Melanoma in a Latin American Population: A Case-Control Study☆

Factores de riesgo para melanoma en una población latinoamericana: estudio de casos y controles

To the Editor,

Melanoma incidence continues to rise in different populations and ethnic groups worldwide.[1–3] Epidemiological data and known risk factors for melanoma are mostly based on studies of US, Australian, and European populations. Few population-based studies have been conducted in Latin American or Hispanic communities.[4]

Latin America is known for its significant ethnic diversity secondary to interracial relationships that vary from one country to the next depending on population structure and migration history. In Colombia, for example, the population results from interactions between indigenous/native populations, Spanish people, and Africans, with mestizos representing the largest segment. The aim of this study was to identify possible risk factors for cutaneous melanoma in a Colombian population in the city of Medellín, Colombia.

We conducted a retrospective age- and sex-matched case-control study. Cases were patients with a histopathologically confirmed diagnosis of in situ or invasive melanoma, while controls were randomly selected patients without a personal history of melanoma who were seen for any dermatologic condition. The ratio of cases to controls was 1:2. We analyzed the medical records of patients older than 18 years seen at Clínica Aurora, a specialized skin cancer center, in Medellín between May 2014 and October 2017. We included both incident and prevalent cases of melanoma. In other words, we studied patients newly diagnosed with melanoma during the study period and those with an existing diagnosis. The required sample size was estimated at 62 cases and 125 controls using an alpha error of 5%, a beta error of 20% (95% confidence level and 80% statistical power) and an odds ratio (OR) of 3 associated with the presence of multiple melanocytic nevi as the main risk factor for melanoma. The calculations were performed in the statistical software program Epi Info.

We analyzed the medical records of 187 patients (62 cases and 125 controls). Their phenotypic, sociodemographic, and sun exposure characteristics are given in Table 1. Table 2 summarizes the characteristics of the patients with melanoma. Table 3 presents the results of the bivariate and multivariate analyses.

Similarly to previous reports in the literature,[5–7] our multivariate analysis showed that patients with melanoma were more likely to have a history of recreational or intermittent sun exposure (OR = 4.2; 95% CI, 1.8-9.6) and a lifetime history of sunburn (OR = 5.6; 95% CI, 2.2-14.6), suggesting that these patterns of exposure are risk factors for melanoma in our study population. In contrast, the use of 2 or more sun protection measures exerted a protective effect (OR = 0.2; 95% CI, 0.1-0.5). Unlike other studies, we did not observe an association between number of common or atypical nevi and melanoma risk.[5,8] We observed a protective effect for a personal history of basal cell carcinoma, possibly

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