Follicular involvement is frequent in lentigo maligna: Implications for treatment

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Background: Follicular involvement of lentigo maligna (LM) is considered a histopathologic hallmark, but its prevalence and characteristics have not been well defined. The depth of intrafollicular extension by neoplastic melanocytes may have clinical importance in the treatment of LM.

Objective: To describe the prevalence and features of follicular involvement in LM, including depth of follicular growth by melanocytes.

Methods: A single-center retrospective study of 100 consecutive cases of surgically excised LM that was treated from 2013 to 2015. The slide review for cases with residual LM on the debulk specimen was performed by a dermatologic surgeon and dermatopathologist to characterize follicular involvement.

Results: Of 100 specimens, 72 met the inclusion criteria for histopathologic evaluation. Follicular involvement was seen in 95.8% of specimens (95% confidence interval, 88.3%-99.1%), with a mean of 68% of follicles involved in a single specimen. The mean depth of intrafollicular growth by lesional melanocytes was 0.45 mm (standard deviation, 0.23; range, 0.1-1.1 mm). Tumor cells were confined to the infundibular portion of the hair follicle in 60.9% of specimens.

Conclusion: Superficial follicular involvement is a ubiquitous finding in LM. When treatment options for LM with a depth-dependent modality aiming for tumor clearance are being considered, mean and maximum depths of involvement should be taken into consideration. (J Am Acad Dermatol 2019;80:532-7.)

Key words: adnexa; follicular involvement; lentigo maligna; melanoma.

Lentigo maligna (LM) and LM melanoma (LMM) are subtypes of melanoma in situ (MIS) and melanoma, respectively; they typically occur in elderly individuals on sun-damaged skin, most commonly on head and neck locations.[1] Surgical excision, whether staged local excision or Mohs micrographic surgery, is generally the preferred choice of treatment.[2] However, nonsurgical treatment modalities such as off-label imiquimod or radiation may be used at the provider's discretion depending on patient age, coexisting medical comorbidities, lesion size, location, and patient preference after discussion of the risks and benefits.[2-8]

Abbreviations used:

CI:	confidence interval
LM:	lentigo maligna
LMM:	lentigo maligna melanoma
MIS:	melanoma in situ
PSU:	pilosebaceous unit
SD:	standard deviation

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Standard guidelines for melanoma histopathologic reporting exist; however, the presence, absence, and extent of follicular involvement is not routinely reported, despite being a histopathologic hallmark of the lentigo maligna subtype.[9] Supplemental diagnostic modalities such as dermoscopy and reflectance confocal microscopy have suggested follicular involvement as one means of distinguishing LM from benign facial pigmented lesions.[10-12] Most importantly, however, follicular involvement, particularly the depth of atypical melanocytes extending along the adnexa, may have clinical significance in treatment of LM. The depth of atypical adnexal melanocytes likely affects the efficacy of tissue-sparing surgical procedures in these cosmetically and functionally important areas, as well as that of depth-dependent therapies such as radiation and topical agents in cases in which epidermal penetration is limited. Follicular involvement by MIS may also account for some cases of locally persistent LM after surgery. If neoplastic melanocytes are located deep within a follicular unit and the surgical excision transects such follicles (which may be overlooked during margin assessment), the risk of local recurrence is increased.

CAPSULE SUMMARY

- Follicular involvement is a characteristic of lentigo maligna with unknown frequency.
- Of lentigo maligna specimens, 95.8% demonstrated intrafollicular lesional melanocytes, with a mean depth of 0.45 mm.
- When managing lentigo maligna, one should assume follicular involvement.

The tumor cells of melanomas in the head and neck region have been shown to extend much deeper down adnexa than those in other anatomic locations.[13] A higher recurrence rate after nonsurgical treatment has been reported for LM on the nose than for LM on other facial locations such as the cheek.[3] Greveling et al studied the histologic parameters of recurrences of such LM and determined that the nose had a significantly higher density of pilosebaceous units (PSUs) when compared with the cheek, as well as a significantly greater maximum depth of the PSUs.[3] This included a comparatively greater depth of extension of the atypical melanocytes along the PSUs. This data suggest that anatomic location may influence risk of recurrence, and perhaps the primary reason behind the anatomic differences in recurrence rates is due to the depth and density of the follicular units. This may have a profound implication for treatment, as a higher PSU density may harbor a greater collection of neoplastic melanocytes in deeper portions of the appendages.

The aim of our study was to (1) characterize the incidence of follicular involvement in LM and (2) define the extent of follicular involvement seen, including the depth of lesional melanocytes.

METHODS

This was a single-center retrospective study. Institutional review board exemption was obtained. The first 100 consecutive patients who underwent staged excision for biopsy-proven LM at our institution from 2013 to 2015 were reviewed.[14,15]

Pathology reports for each patient were reviewed. For all patients with residual LM on the tumor debulking specimen noted in the pathology report, slides were pulled and examined by a board-certified dermatopathologist and fellowship-trained Mohs micrographic surgeon. Cases with more than 75% of the specimen with scarring from biopsy-obliterating adnexal structures and those with invasive or microinvasive disease were excluded from evaluation to limit cases to MIS, as invasive melanoma may have different tendencies for follicular involvement. One case was excluded on account of reactive changes complicating the histologic interpretation, and 1 outside case was excluded because of inability to obtain the biopsy slides for review and confirmation. A total of 72 cases remained for analysis. The most representative section with complete epidermis from each glass slide was used for analysis. Lesion location, follicular involvement, percentage of residual in situ disease, and the degree of scar noted (none, minimal, moderate, or severe) were recorded.

Follicular involvement was defined as atypical melanocytes that were microscopically judged to be part of the LM; MIS present in the follicular epithelium is typically at the infundibular stromal junction. It was further characterized in terms of percentage of follicles involved, deepest involvement along the follicle in millimeters (distance from the surface of the follicular ostium to the most deeply located intrafollicular neoplastic melanocyte), and deepest anatomic portion of the follicle involved.

Descriptive statistics and graphic methods were used to describe the surgical and histologic characteristics of these LM. Ninety-five percent exact binomial confidence intervals (CIs) were used to

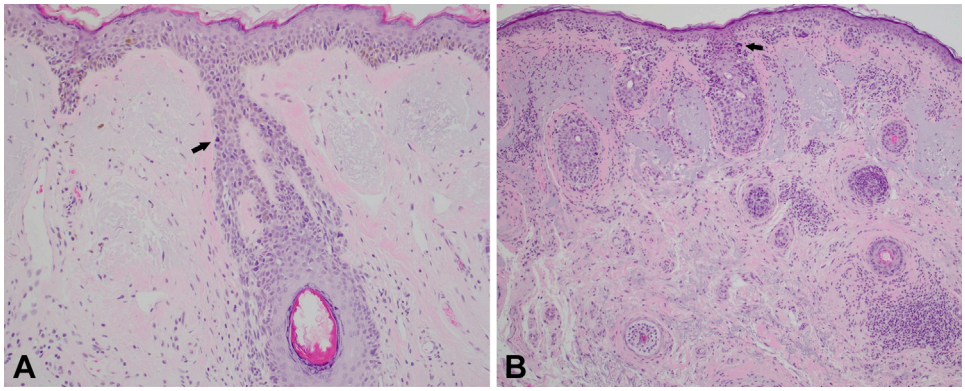

Fig 1. **A**, Lentigo maligna melanoma in situ with follicular involvement. An increased density of solitary units of melanocytes with nuclear atypia is seen at the dermoepidermal and follicular dermal junction (*arrow*). **B**, Lentigo maligna melanoma in situ with follicular involvement. Nests and solitary units of melanocytes are present at the dermoepidermal and follicular infundibular stromal junction (*arrow*). (**A** and **B**, Hematoxylin-eosin stain; original magnification: ×10.)

provide a range of prevalence estimates for follicular involvement based on our sample size. Of the 72 samples in the data set, 69 exhibited follicular involvement. These 69 lesions were evaluated for depth of involvement and deepest involvement along the follicle. Linear regression was used to assess any differences in depth of involvement and deepest involvement by anatomic site of the surgical procedure. All analyses were performed with Stata software (version 14.2, Stata Corp, College Station, TX).

RESULTS

Of the total of 100 pathology specimens, 72 met the inclusion criteria of MIS with residual tumor present on the debulking tissue. Tumor location was the cheek in the majority of cases (n = 29), followed by the forehead (n = 9), scalp (n = 9), and nose (n = 8). There were 4 cases on the ear and 3 cases on the eyelid. There were 2 cases each involving the chin, lip, and neck, followed by 1 case each involving the eyebrow, glabella, temple, and leg.

Slide review revealed follicular involvement in 69 of 72 specimens (95.8% [95% CI, 88.3%-99.1%]). Fig 1, *A* and *B* show typical cases of follicular involvement. The mean percentage of follicles involved in a single histologic section was 68.4% (standard deviation [SD], 24.3%). The mean depth of atypical melanocyte extension within the adnexa was 0.45 mm (SD, 0.23; range, 0.1-1.1 mm), corresponding to infundibular involvement in 42 of 69 specimens (60.9% [95% CI, 48.4%-72.4%]). Seven of 69 specimens (10.1% [95% CI, 4.1%-19.8%]) demonstrated atypical melanocytes reaching the sebaceous duct, and 19 of 69 cases (28% [95% CI, 17.4%-39.6%]) showed involvement of the sebaceous lobule. One case extended to the level of the eccrine glands (1%), with a maximum depth of 1.1 mm.

Anatomic site–specific differences were observed for deepest involvement along the follicle. Fig 2 presents boxplots of depth by anatomic location. Compared with lesions on the cheek, which had an average depth of 0.41 mm (SD, 0.20), lesions on the forehead (depth, 0.57 mm [SD, 0.21]) and scalp (depth, 0.68 mm [SD, 0.26]) were significantly deeper (P = .05 and .002, respectively). No significant differences in depth were observed between cheek lesions and lesions on the ear or other combined anatomic locations (chin, eyebrow, eyelid, or neck).

The average percentage of follicles involved for each specimen was 68.3% (SD, 24.3%). Fig 3 presents the distribution of the percentage of follicles involved by anatomic site of the surgical procedure. Compared with lesions on the cheek, which had an average percentage of involvement of 65.4%, only lesions on the ear (percentage of involvement, 83.2%) showed a significant difference (P = .03). No other site (forehead [percentage of involvement, 77.0%], scalp [percentage of involvement, 67.3%], or other combined anatomic locations [chin, eyebrow, eyelid, and neck]) showed a statistical difference.

DISCUSSION

Follicular involvement by LM is a common phenomenon, and its extent is relevant for treatment. In this study, we systematically examined cases from staged excision specimens with 2 independent readers to better quantify the presence of atypical melanocytes within distinct anatomic regions of the hair follicle. We demonstrated that 95.8% of all LM debulking specimens contained atypical melanocytes involving follicular units. Furthermore,

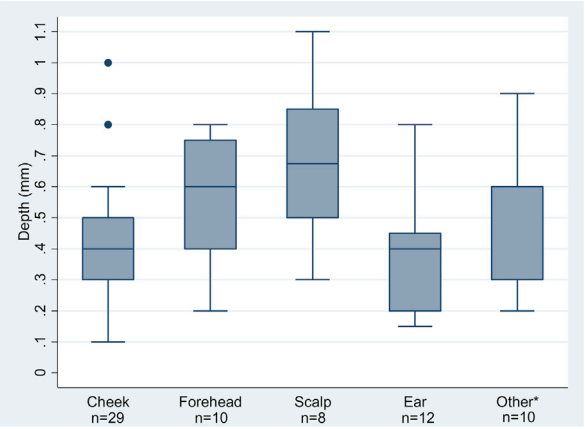

Fig 2. Boxplot of follicular depth by anatomic site (n = 69). *Other includes the chin (n = 2), eyebrow (n = 1), eyelid (n = 3), lip (n = 2), and neck (n = 2).

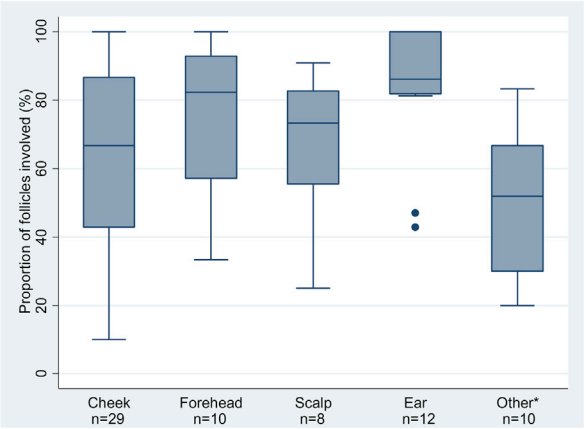

Fig 3. Boxplot of the proportion of follicles involved per lesion by anatomic site (n = 69). *Other includes the chin (n = 2), eyebrow (n = 1), eyelid (n = 3), lip (n = 2), and neck (n = 2).

a majority of follicles in each section had some degree of involvement, indicating a high frequency of occurrence even within each specimen. This is consistent with prior reports highlighting follicular involvement as a hallmark for the LM subtype. However, despite its ubiquity, follicular involvement is under-recognized, and deep follicular extension is not routinely documented in pathology reports of LM. Clinical providers must be aware that the lack of reporting does not exclude the existence of follicular involvement; rather, on the basis of our findings and prior studies, follicular extension should be assumed in cases of LM.

With comparable results, another study analyzed 100 cases of primary cutaneous melanomas of various histologic subtypes and revealed that 82% of cases of MIS possessed tumor cells within 1 or more hair follicles, with 69.5% of cases limited to the follicular infundibulum. Extension of tumor cells to the isthmus occurred in 29.3% of cases, with only 1 case (1%) demonstrating tumor cells beneath the hair follicle bulge. Pozdnyakova et al included LM and superficial spreading subtypes, each of which had cases of follicular involvement as well as follicular sparing.[13] Of note, 97% of their LM cases showed some degree of follicular involvement, as did 97.2% of cases on the head and neck; in contrast, only 73.4% of their cases on non–head and neck regions showed follicular involvement. Tumors of the head and neck demonstrated a greater tendency to extend deeper than non–head and neck tumors did. The face is known to have a higher density of PSUs,[16] with certain facial regions also demonstrating more deeply located PSUs,[3] which may offer an explanation for the deeper extension of tumors into the head and neck. Pozdnyakova et al did not observe any differences in involvement between types of follicles (large terminal and small vellus) or stage of development of the hair follicle.[13]

The diagnosis of LM and LMM relies on a multitude of histologic features, and it is important to recognize that follicular involvement alone does not confirm the diagnosis. The presence of superficial follicular involvement has been noted in normal-appearing, yet sun-damaged skin,[17] as well as in other types of melanoma such as the rare variant follicular melanoma[1,18,19] and folliculotropic metastases of melanoma.[18] However, we advocate that the overall importance of follicular involvement within a confirmed diagnosis of LM not be underestimated, as it may ultimately affect treatment success.

The density and depth of follicular involvement in LM are pertinent when considering various treatment options. In our study, the infundibulum was the most common region of involvement, with the average depth of atypical melanocyte extension along the adnexa of 0.45 mm. However, there were cases of deeper extension, with a maximum reported depth up to 1.1 mm, corresponding to the level of the eccrine glands. Tissue-sparing surgical modalities, although the criterion standard of care, are likely to have higher rates of recurrence if the depth of surgery is not sufficient to remove the entire follicular unit. For instance, on more cosmetically sensitive regions such as the ear and nose, follicles are commonly transected in the interest of tissue sparing. Radiation therapy, which is highly depth dependent, has been less effective at minimizing in-field recurrences with more superficially directed treatment.[20] One large review recommends a treatment depth of at least 5 mm to achieve adequate clearance, as the review's authors identified follicles

extending as deep as 4.5 mm in some regions.[20] The presence of extensive follicular involvement may explain why laser and light therapies are not effective, as the depth of penetration is limited. For example, an erbium-doped yttrium-aluminum-garnet laser (wavelength, 2940 nm) removes approximately 15 to 25 μm per pass and a carbon dioxide laser (wavelength, 10,600 nm) laser approximately 100 to 150 μm per pass; therefore, numerous passes would be required to reach an adequate depth, and the risk of scarring or dyspigmentation may increase.[21,22] The depth of penetration of topical agents rarely exceeds the epidermis. Whether immune response modifiers such as imiquimod can herald an adequate inflammatory response substantially beyond the depth of penetration is unclear. However, it is well known that the hair follicle is an immune-privileged site, which may hold potential implications in the efficacy of imiquimod or other immune-modifying therapies in regions with concentrated PSUs.[23] Combination therapies have been proposed to increase the depth of topical penetration, though treatment success remains inferior to that of surgical modalities.[3,24]

A few conflicting studies on follicular involvement in LM do exist within the literature. One study did not find statistical significance of follicular depth or involvement as prognostic indicators for LM recurrence after imiquimod monotherapy despite a 78.2% rate of occurrence of follicular involvement.[25] However, the study's authors did note significant risk of recurrence with an increased total number of melanocytes per millimeter, confirming a role for melanocyte density. Increased melanocyte density has been correlated in other studies with increased numbers of PSUs.[3] Powell et al observed a correlation between the presence of adnexal spread and a positive response to imiquimod therapy, which is difficult to explain, as one would expect the opposite to be true.[26] This ambiguity heralds the need for further investigation into the presence, extent, and implications of follicular involvement in LM.

CONCLUSION

Follicular involvement in LM is very prevalent. The presence and depth of follicular involvement may have clinical implications for depth-dependent treatment modalities such as tissue-sparing surgery, radiation, and topical therapy. Extension of MIS into deeper portions of the follicles should be documented in pathology reports.

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