Paraneoplastic alopecia areata surrounding a low-grade cutaneous carcinoma with squamous and trichoblastic features

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INTRODUCTION

Low-grade cutaneous carcinoma with squamous and trichoblastic features is an uncommon cutaneous malignancy with follicular differentiation. Alopecia areata (AA) is an autoimmune folliculocentric skin disease. We present an uncommon case of a 50-year-old woman in whom AA developed on the scalp surrounding a low-grade cutaneous carcinoma with squamous and trichoblastic features. Our case study reviews the limited relevant literature and hypothesizes that the $CD8^+$ T lymphocytic infiltrate within our patient's tumor likely instigated the AA.

CASE REPORT

A 50-year-old woman without any personal or familial history of alopecia or autoimmune disease developed an asymptomatic erythematous papule on the posterior aspect of the mid-scalp. Five months later, she developed an area of alopecia surrounding this papule and was referred for excision.

Pathology demonstrated a circumscribed neoplasm with focal irregular infiltration into the deep adipose tissues. The tumor was contiguous with the epidermis, had deep trichoblastic and superficial squamous components merging together, and had a distinct cellular fibrous stroma (Fig 1). Fibromyxoid stroma with separation artifact was absent. Both portions of the tumor showed low-grade cytologic atypia with occasional mitotic figures and apoptotic bodies. The tumor displayed a patchy, mild inflammatory reaction. The deep margin was focally involved.

Abbreviation used:

AA: alopecia areata

The adjacent nonneoplastic skin showed prominent features of AA (Fig 2). A brisk, peribulbar lymphocytic inflammation was present around the majority of follicles. Other AA features included follicular miniaturization, increased proportion of catagen/telogen follicles, trichomalacia, abnormally thin hair shafts, lack of follicular scarring, and retained sebaceous glands.

Histologic differential diagnoses for the tumor included basal cell carcinoma with adnexal differentiation, basosquamous carcinoma, trichoepithelioma, trichoblastoma, and other indeterminate/low-grade pilar neoplasms. The distinct tumor stroma without separation artifact, absence of high-grade atypia, degree of immaturity with lack of horn cysts, and broad epidermal connection with squamous differentiation were features that did not favor a diagnosis of basal cell carcinoma, basosquamous carcinoma, trichoepithelioma, and trichoblastoma, respectively. The case was sent for external consultation, and a final diagnosis of low-grade cutaneous carcinoma with squamous and trichoblastic features was rendered.

Immunohistochemistry performed retrospectively demonstrated a predominance of $CD3^+$ T cells, with a $CD4^+/CD8^+$ ratio of approximately 2:1. Both $CD8^+$ and $CD4^+$ T cells invaded into the hair bulb epithelium. Tumor-associated inflammation had a similar

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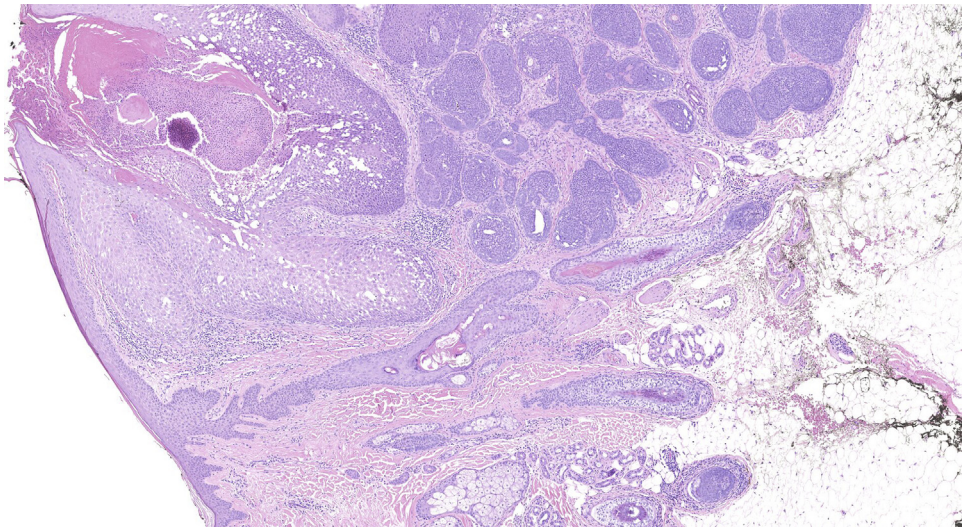

Fig 1. Tumor showing squamous and basaloid/trichoblastic features, with adjacent peribulbar inflammation. (Hematoxylin-eosin stain; original magnification: ×50.)

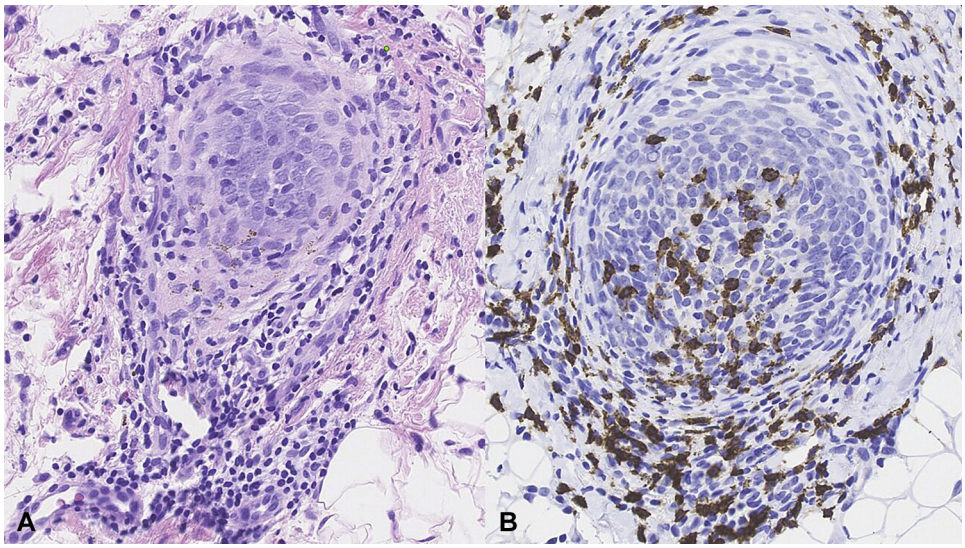

Fig 2. **A** and **B**, Peribulbar inflammation with lymphocytes infiltrating the bulbar epithelium (both photographs are from the same follicle). (**A**, Hematoxylin-eosin stain; **B**, CD8 immunohistochemistry stain; original magnifications: **A**, ×400; **B**, ×400.)

immunohistochemistry profile. SOX-10 and MART-1 immunostaining showed melanocytes within the epidermis, length of the follicles, and hair bulbs but not within the tumor. Normal skin with noninflamed follicles was not available for melanocyte density comparison.

Following tumor excision, the patient was referred to Dermatology. She had no associated body alopecia or nail changes. Initial examination revealed a 4.5 × 3.0−cm patch of nonscarring alopecia with peripheral exclamation mark hairs. Centrally in the alopecia patch was a surgical scar without features concerning for residual malignancy (Fig 3). The hair pull test was positive. Clinical and pathologic diagnoses were consistent with AA.

Prior to AA treatment, wide local excision was necessary because the neoplasm had a positive deep margin. Re-excision pathology demonstrated a scar without residual tumor. The adjacent skin again demonstrated AA features.

Dermatology follow-up revealed a patch of AA unchanged from the initial assessment with a well-healed central scar. Treatment with intralesional triamcinolone acetonide (5 mg/mL, 0.5 mL) was administered. Follow-up 2 and a half months later demonstrated no further alopecia and substantial

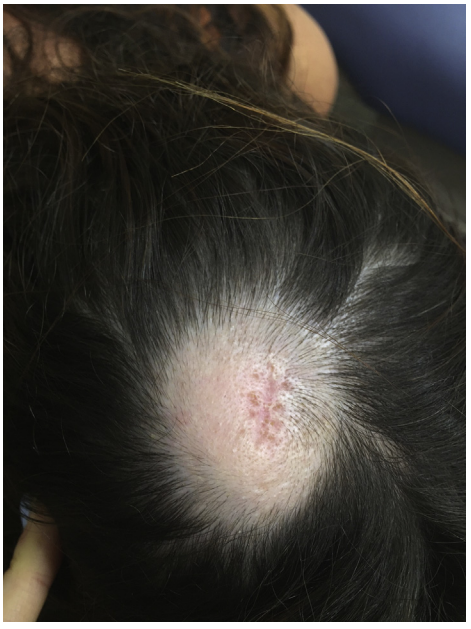

Fig 3. Patch of nonscarring alopecia measuring 3.0 × 4.5 cm with classic exclamation mark hairs at the periphery and a surgical scar in the center.

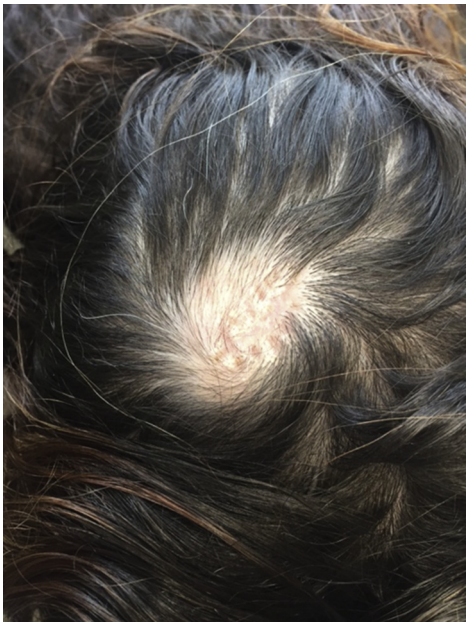

Fig 4. Regrowth of alopecia following intralesional triamcinolone acetonide injections with a persistent surgical scar in the center.

regrowth (Fig 4). There were no concerns regarding tumor recurrence and no further treatment was required.

DISCUSSION

AA develops from immune privilege breakdown at the hair follicle when late anagen hair follicles are infiltrated by T lymphocytes.[1] $CD8^+$ T cells comprise the majority of these lymphocytes and are responsible for the follicular damage, which prematurely forces the hair follicle into catagen phase.[1,2]

Low-grade trichoblastic carcinoma is rare, with fewer than 50 published cases.[3] There are no distinct clinical features. Histopathology shows trichoblastic basaloid cells embedded in a distinct cellular fibrous stroma with papillary mesenchymal bodies, lacking stromal separation artifact. These tumors resemble a trichoblastoma, but show infiltrative extension into deep subcutaneous adipose tissue and skeletal muscle.[3]

Generalized nonscarring alopecia in association with malignancy is reported with chemotherapy, radiotherapy, endocrine therapy, stem cell transplantation, and targeted therapy and after surgery.[4] Reports of AA development due to a cutaneous malignancy are limited.

In our case, AA likely occurred as a result of a paraneoplastic response. Paraneoplastic syndromes are characterized by an aberrant immune response to a malignancy.[5] Paraneoplastic AA has been reported resulting from noncutaneous carcinomas including thymoma, Hodgkin lymphoma, and gastric cancer.[6] Hara et al[7] (1995) reported a patient with squamous cell carcinoma on the lower portion of the left leg, who subsequently developed both AA and vitiligo at distant sites, likely due to a paraneoplastic syndrome. This describes AA development following a cutaneous malignancy; however, the observed AA was distant to the primary tumor site.

This case also has similarities to perinevoid alopecia, a variant of AA adjacent to a halo nevus. However, in this case the tumor is a pilar epithelial malignancy lacking melanocytes rather than a benign melanocytic lesion.

The literature scarcely reports low-grade cutaneous carcinoma with squamous and trichoblastic features; however, trichoblastic tumors are well-documented. Duverger et al[8] (2019) reported dense $CD8^+$ T cells present in the stroma of 60% of trichoblastic carcinoma cases. Additionally, Guo et al[9] (2015) found $CD8^+$ T lymphocytes largely infiltrate the hair follicles associated with AA lesions. Furthermore, $CD8^+$ T cell density and AA disease severity correlate.[10] In our patient, the peribulbar infiltrate contained $CD8^+$ cells. We postulate that the $CD8^+$ T cells present within our patient's tumor initiated the AA observed. We hypothesize that the inflammatory reaction to the neoplasm impacted the immune privilege of the surrounding follicles, allowing $CD8^+$ T cells to attack the hair follicles densely surrounding this scalp tumor, thereby precipitating our patient's AA.

Our case of AA development following the formation of low-grade cutaneous carcinoma with squamous and trichoblastic features illustrates a rare case of paraneoplastic AA colocalizing with a primary cutaneous malignancy. We suggest that $CD8^{+}$T lymphocytes within our patient's neoplasm attacked normal anagen hair follicles, causing AA. Additional research may focus on AA development, colocalizing and distant to cutaneous malignancies, and should alert dermatologists to this uncommon paraneoplastic association.

Conflicts of interest

None disclosed.

REFERENCES

1. Juárez-Rendón KJ, Rivera Sánchez G, Reyes-López MÁ, et al. Alopecia areata. Current situation and perspectives. Article in English and Spanish. *Arch Argent Pediatr*. 2017;115(6): e404-e411. https://doi.org/10.5546/aap.2017.eng.e404
2. Cetin ED, Savk E, Uslu M, Eskin M, Karul A. Investigation of the inflammatory mechanisms in alopecia areata. *Am J Dermatopathol*. 2009;31(1):53-60. https://doi.org/10.1097/DAD.0b013e318185a66e
3. Hua C, Velter C, Osio A, et al. Locally aggressive trichoblastic tumours (low-grade trichoblastic carcinomas): clinicopathological analysis and follow-up. *Acta Derm Venereol*. 2018;98(1): 126-127. https://doi.org/10.2340/00015555-2678
4. Freites-Martinez A, Shapiro J, van den Hurk C, et al. Hair disorders in cancer survivors. *J Am Acad Dermatol*. 2019;80(5): 1199-1213. https://doi.org/10.1016/j.jaad.2018.03.056
5. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc*. 2010;85(9): 838-854. Published correction appears in *Mayo Clin Proc*. 2011;86(4):364. https://doi.org/10.4065/mcp.2010.0099
6. Álvarez Otero J, Fernández Fernández F, de la Fuente Aguado J. Alopecia areata as a paraneoplastic syndrome of gastric cancer. *Rev Esp Enferm Dig*. 2017;109(1):83-84. https://doi.org/10.17235/reed.2016.4455/2016
7. Hara M, Hunayama M, Aiba S, et al. Acrokeratosis paraneoplastica (Bazex syndrome) associated with primary cutaneous squamous cell carcinoma of the lower leg, vitiligo and alopecia areata. *Br J Dermatol*. 1995;133(1): 121-124. https://doi.org/10.1111/j.1365-2133.1995.tb02504.x
8. Duverger L, Osio A, Cribier B, et al. Heterogeneity of PD-L1 expression and CD8 tumor-infiltrating lymphocytes among subtypes of cutaneous adnexal carcinomas. *Cancer Immunol Immunother*. 2019;68(6):951-960. https://doi.org/10.1007/s00262-019-02334-8
9. Guo H, Cheng Y, Shapiro J, McElwee K. The role of lymphocytes in the development and treatment of alopecia areata. *Expert Rev Clin Immunol*. 2015;11(12):1335-1351. https://doi.org/10.1586/1744666X.2015.1085306
10. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: disease characteristics, clinical evaluation, and new perspectives on pathogenesis. *J Am Acad Dermatol*. 2018;78(1):1-12. https://doi.org/10.1016/j.jaad.2017.04.1141