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Case Report

A case of trichogerminoma: a rare cutaneous follicular neoplasm

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Summary

Trichogerminoma, first described by Sau et al. in 1992, is a rare cutaneous adnexal neoplasm of the hair germ cell and usually associated with benign clinical course and favorable outcome. About 30 cases have been reported, all with similar histological features. However, due to a small but potential risk of malignancy, complete excision of the tumor is the treatment of choice. There is still controversy over its inclusion into the spectrum of trichoblastoma.

Herein, we report an additional case occurring in the left buttock of a 47-year-old female, presenting with a subcutaneous solitary nodule composed of lobules of basaloid cells, with peripheral palisading and round cell nests or "cell balls" arranged in the central part. The lobules are separated by a fibrous or myxoid stroma. There are no clefts separating the tumor cells and surrounding stroma, but clefts separating stroma by the surrounding adipose tissue can be seen. Typical mitotic figures are frequently present (4-5 per 10 high-power fields). Immunohistochemistry shows the tumor cells are positive for pan-CK (AE1/AE3), CK5/6, p40, GATA 3, whereas they are negative for CK7, CK20, chromogranin A, synaptofisin, androgen receptor, estrogen receptor, and calretinin. Staining for CK20, synaptofisin, and chromogranin A detect Merkel cells scattered within the lobules. Ki67 highlights a nuclear proliferative rate of about 20%.

Trichogerminoma should be distinguished from other trichogenic tumors made up of basaloid cells or hair follicular differentiation. The mainly differential diagnosis includes trichoblastoma, trichoepitelioma, tricholemmoma, and basal cell carcinoma.

Herein, we report a case of trichogerminoma which, unlike the cases previously reported, showed numerous mitotic figures and a higher Ki67 nuclear proliferative rate.

Key words: trichogerminoma, trichoblastoma, basal cell carcinoma, hair germ tumor

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Conflict of interest
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Introduction

Tumors with hair follicular differentiation are difficult to diagnose due to the variety and similarity of the lesions. They recapitulate to different degrees of hair follicle development and characteristically exhibit an intimate relationship between epithelial and stromal elements. Hair follicle differentiation can be rudimentary, corresponding to presumptive primary epithelial germ formation, or more advanced with representation of various components of the mature folliculo-sebaceous apparatus. Trichogerminoma is a rare cutaneous follicular tumor with differentiation towards the hair germ epithelium. In 1992, Sau et al. [1], from the Armed Forces Institute of Pathology, reported 14 cases of a benign hair germ neoplasm and firstly proposed a new term of trichogerminoma. In 2002, Kazakov et al. [2] showed the immunohistochemical uniqueness of trichogerminoma and the tumor was confirmed as being a unique entity, and pointed subtle immunohistochemical differences between trichogerminoma and trichoblastoma, yet there is still controversy about this. A

review of the literature published revealed a total of 30 trichogerminoma cases published in 12 reports [1-12]. Trichogerminoma is a follicular germinative cell tumor, histopathologically characterized by the formation of multiple lobules composed of basaloid cells with concentrically arranged rounded nests or cell balls in the central parts and peripheral condensation. Clinically, trichogerminoma can be confused with epidermal cyst, trichoepithelioma, and basal cell carcinoma.
Herein, we report a case of trichogerminoma developed on the left buttock of a middle-aged woman.

Materials and methods

Fixation tissue is carried out in 10% neutral buffered formalin for 24 hours. Once tissue is embedded in paraffin, a 3-4 micron tissue section is cut onto charged glass slides.
The detection system for immunostaining is BOND Polymer Refine Detection on staining platform LEICA BOND III for these antibodies: 30 min at 100°C in Bond Epitope Retrieval Solution 1 used to antigen retrieval for CD10 (clone 56C6; Leica; 1:50); 10 min at 37°C with Bond Epitope Retrieval Enzyme for antibodies Cytokeratin 7 (clone OV-TL 12/30; Menarini; 1:500) and pan-cytokeratin AE1/AE3 (clone AE1/AE3; Cell Marque; 1:1000); synaptophysin (clone 27G12; Leila; 1:200); chromogranin A (clone DAK-A3; Dako; 1:100); Cytokeratin 20 (clone KS20.8; Menarini; 1:500); Calretinin (polyclonal; Menarini; 1:100); GATA 3 (clone L50-823; Menarini; 1:1000); Estrogen receptor (clone SP1; Biocare; 1:50); Androgen receptor (clone AR441; Dako; 1:30).
Roche's antibodies, ready to use, are detected on platform BenchMark ULTRA using UltraView Universal DAB Detection Kit, 64 minutes of antigen retrieval with Cell Conditioning 1 and incubation 16 minutes for MIB1 (clone 30-9); p40 (clone BC28; Roche).

Case presentation

A 47-year-old female patient presented with a subcutaneous solitary nodule on the left buttock without any clinical symptoms. The skin above the nodule had no difference with other areas. The lesion was a protuberant, palpable, well-demarcated, movable nodule, which was non-ulcerated, firm, movable and 15 mm in diameter. The pre-operative diagnosis was epidermal cyst/granuloma. Excisional biopsy was performed and the lesion was partially removed. The surgical specimen consisted of a 25×15 mm skin ellipse with soft tissue attached to a maximum depth of 20 mm. The gross examination of the surgical specimen demonstrated a deep dermal and subcutaneous solid mass of 15×10 mm in size, extendeding to the deep margin (Fig. 1). There was no internal necrosis or hemorrhage.
Histological examination (Fig. 2) revealed a sharply circumscribed nodule composed of multiple lobules separated from the surrounding soft tissue by a fibrous pseudo-capsule. The neoplasm was located in the deep dermis and mostly in the subcutis, with no connection to the superficial epidermis. The lobules were made up of basophilic epithelial cells separated by a fibrous or myxoid stroma. There were no clefts separating the tumor cells and the surrounding

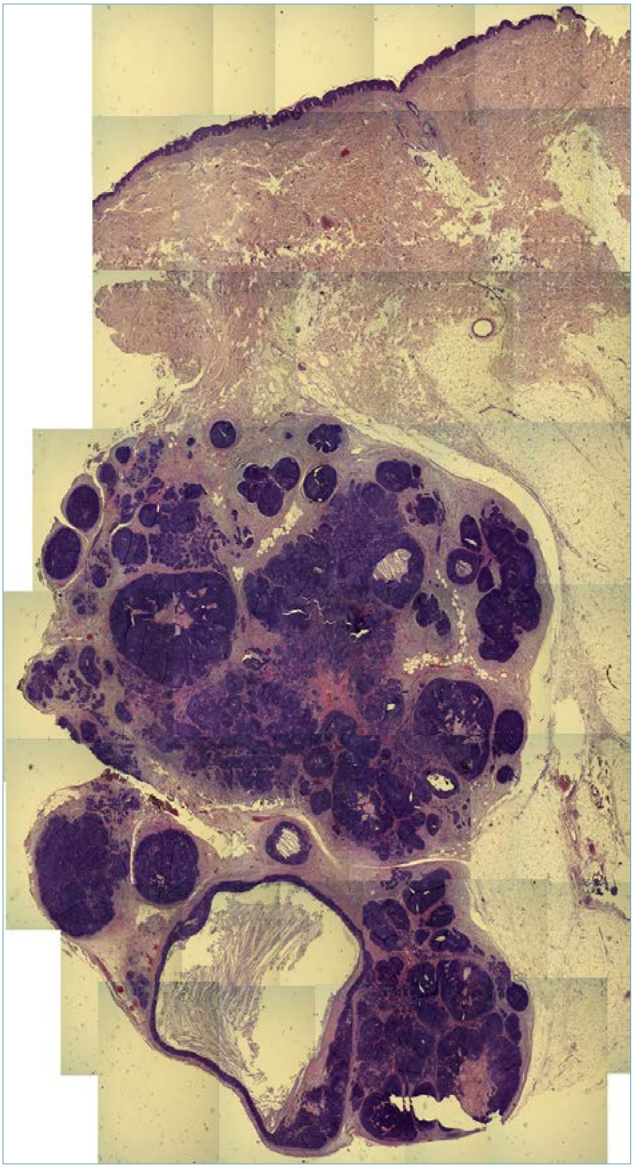

Figure 1. (*Hematoxylin and eosin*). Whole mount image of tumor.

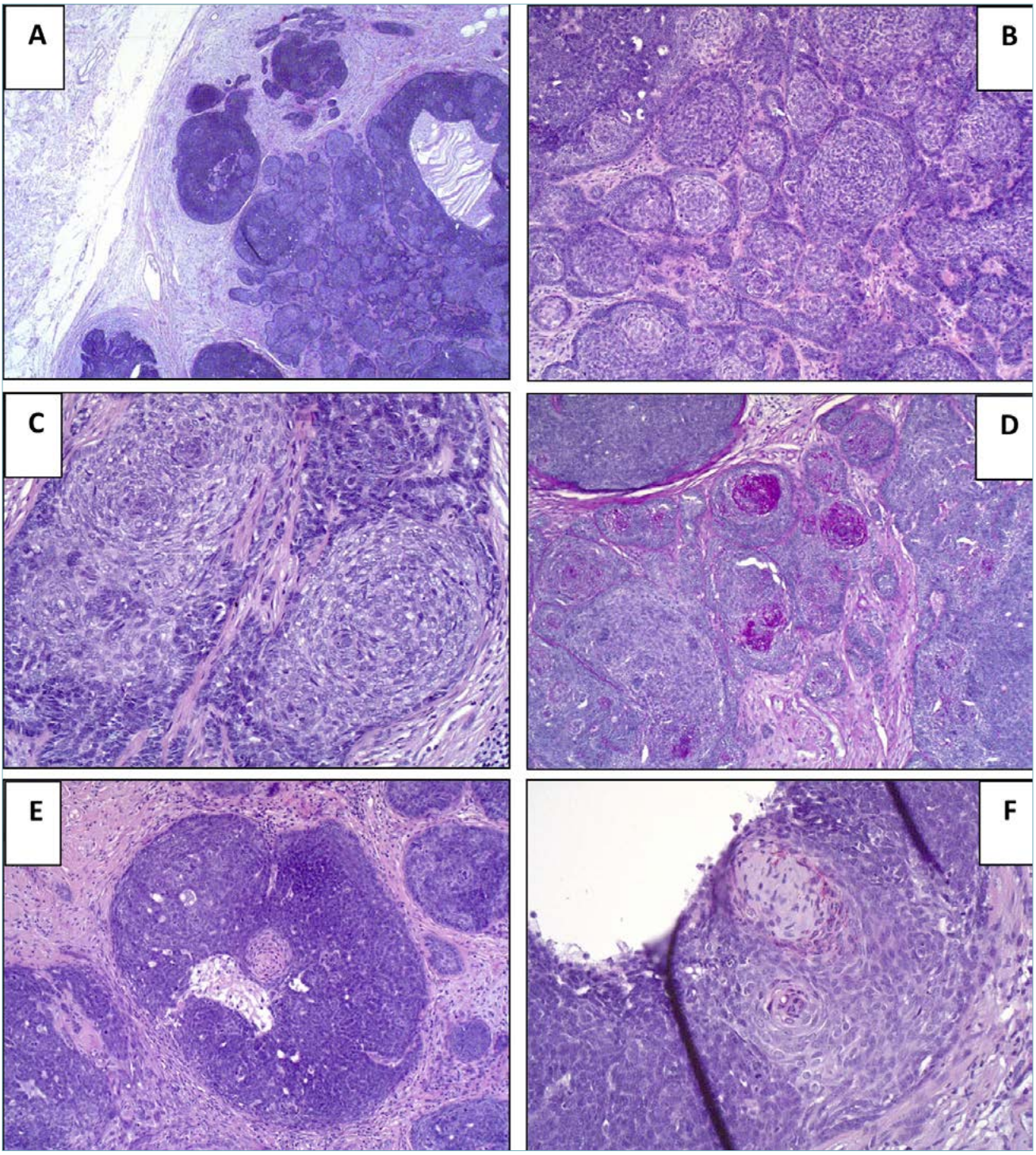

Figure 2. (*Hematoxylin and eosin*). (A) (2.5x) A sharply circumscribed, symmetrical tumor made up of interconnected regular basaloid lobules within a clear-cut fibrocytic stroma. (B) (10x) & (C) (20x) Cords and nodules of basophilic, germinative, cells with peripheral palisading of nuclei and central slightly eosinophilic nests or "cell balls". (D) (20x) Cell balls with clear cytoplasm with glycogen accumulation (PAS). (E-F) (10x & 20x) Occasional representation of hair germ-like structures.

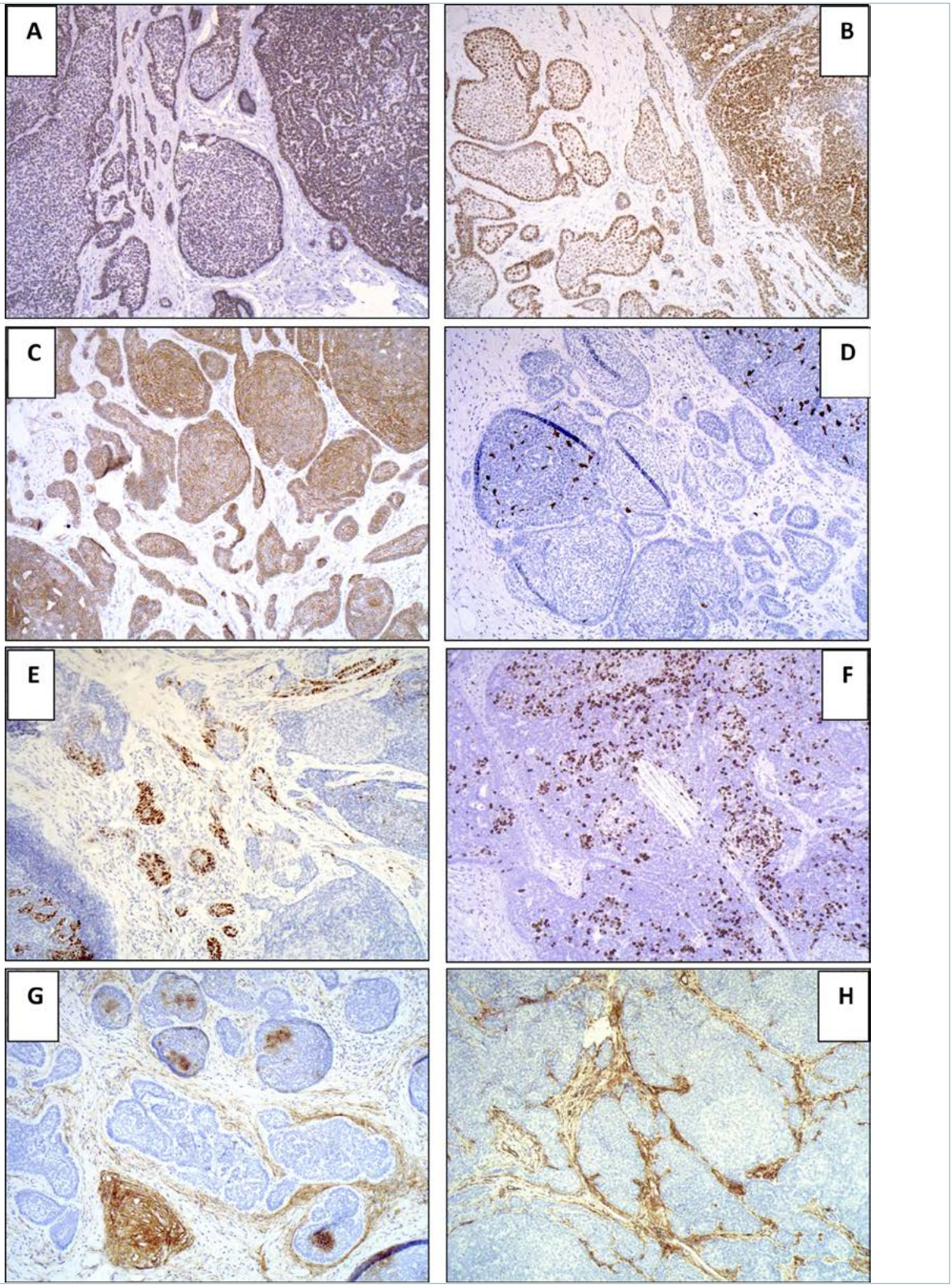

Figure 3. (*Immunohistochemistry*). (A) p40. (B) GATA 3. (C) β-catenin. (D) Cytokeratin 20. (E) Estrogen Receptor. (F) Ki-67/MIB 1. (G) CD10. (H). CD34.

stroma, although clefts separating stroma by the surrounding adipose tissue could be seen. The lobules were composed of basophilic epithelial cells. Characteristically, some of the lobules had concentrically, densely packed round nests or "cell balls" of pale cells with large nuclei, dispersed chromatin, and nucleoli, clear cytoplasm with glycogen accumulation. The outer layer of the lobules was composed of undifferentiated columnar basaloid cells displaying peripheral palisading appearance. In some areas, strands and cords of germ cells extended from the periphery of the lobules. Typical mitotic figures were frequently present (4-5 per 10 high-power fields), while apoptotic cells were observed occasionally. The myxoid stroma showed a moderate number of fibroblasts and mast cells, and inflammatory infiltration of some lymphocytes and mononuclear cells was observed surrounding the epithelial lobules. No perineural invasion, vascular or lymphatic invasion was demonstrated at the periphery of the tumor.

Immunohistochemical staining (Fig. 3) showed the tumor cells were positive for pan-CK (AE1/AE3), CK5/6, P40, GATA 3, and just in a few areas positive for CD10, whereas they were negative for CK7, CK20, chromogranin A, synaptophysin, androgen receptor, estrogen receptor, and calretinin. GATA 3 had a relatively weaker staining in the central part than in the periphery. There were Merkel cells scattered within the lobules and the epidermis around the tumor, which disclosed separately by staining for CK20, synaptophysin, and chromogranin A. Ki67 highlighted a middle nuclear proliferative rate (about 20%). The myxoid stroma around the nests displayed focally expression of CD34 and CD10.

Based on histopathological and immunohistochemical findings, the case was consistent with the diagnostic criteria of trichogerminoma according to Sau's description [1].

Discussion

Trichogerminoma is a rare cutaneous adnexal neoplasm that demonstrates differentiation towards the hair germ epithelium. In 1992, Sau et al. reported 14 cases of a benign hair germ neoplasm under the new term of trichogerminoma [1]. Before 1992, tumors similar to trichogerminoma may have been reported as trichoblastic fibroma by some authors. Grouls and Hey reported 6 cases of trichoblastic fibromas which microscopic features are identical to those seen in trichogerminoma [13].

By reviewing the English literature about 30 cases of trichogerminoma have been reported. Trichogerminoma mainly affects older people (mean age: 53 years), with male:female ratio of approximately 2:1. The main clinical presentation is a single solitary, slowly growing, dermal or subcutaneous nodule without any clinical symptoms. The tumors are mostly located on the head and neck, trunk, extremities and hip. Most of reported cases exhibited a benign biological behavior and had no recurrence or metastasis after complete surgical excision, although transformation into high-grade carcinoma with metastatic disease and death has also been reported [1]. Accordingly, complete excision is recommended because of the malignant potential.

Histologically, trichogerminoma is characterized by sharply circumscribed, well-demarcated, pseudo-encapsulated dermal and subcutaneous nodules, subdivided into lobules separated by variable amounts of a concentric fibroblast-rich stroma with variable condensation, cellularity and mucin content. The lobules are composed of uniform basaloid cells, with vesicular nuclei, dispersed chromatin and prominent nucleoli, showing prominent peripheral palisading, with scattered densely packed, round nests or "cell balls" resembling hair bulbs.

"Cell balls" are characteristically present throughout the neoplasm as micronodular aggregates of neoplastic cells with internal concentricity and peripheral condensation, or nuclear palisading, or both. Small keratin microcysts may be present within the cellular balls, along with apoptotic foci, and structures showing clear cell change resembling abortive hair bulbs. Retraction spaces, well developed hair follicles and hair shafts are not observed. The stroma shows a moderate number of fibroblasts and mast cells. Occasionally, trichogerminoma showes a connection to the overlying epidermis [11], containes melanin pigments [5,11], showes focal sebaceous differentiation [11] or pilomatrical differentiation [12].

Immunohistochemically, the tumor cells express AE1/AE3, CK5/6, CAM5.2, GATA3 [14] and p40 [15], and stain negatively for CK20, CK7, and calretinin. There is no increase in the numbers of CK20-positive Merkel cells in the epidermis overlying the tumor; however, a few Merkel cells are scattered in tumor lobules. Immunoreactivity for CD117 (c-KIT), which is usually negative for follicular tumors [16], is observed in the tumor nests of "extra-ball areas". The tumor cells are diffusely positive for β-catenin showing a membranous pattern [11]. Kazakov et al. [2] noted in their study that tumor nodules expressed AE1/AE3, CK5/8, CK5/6, Cam5.2, while they were negative for CK20, CK7, and calretinin. Of note, calretinin staining was negative in trichogerminoma, but positive in selected cases of trichoblastomas. They also observed the absence of CK20 positive Merkel cells within trichogerminoma and in the

overlying epidermis. Some studies have reported that Merkel cells are abundant in 42% to 60% trichoblastomas [4,17], either within the tumor itself or in the epidermis overlying the tumor. However, several CK20-positive Merkel cells scattered in the tumor nests have been described also in trichogerminoma [11].

In our case, histological features were identical to those described in trichogerminoma, which showed the lobules composed of the basaloid epithelial cells, characteristic cell balls, and hair follicular differentiation of varying degrees. The immunophenotype showed diffuse expression of β-catenin, showing a membranous pattern, P40, and GATA 3, as described in literature. However, the present case showed mitotic figures frequently present (4-5 per 10 high-power fields), and a Ki67 nuclear proliferative rate (about 20%) higher than described in literature (about 5%).

Trichogerminoma should be distinguished from other trichogenic tumors made up of basoloid cells or hair follicular differentiation. The mainly differential diagnosis includes trichoblastoma, trichoepitelioma, tricholemmoma, and basal cell carcinoma. Trichoblastoma is made up of basaloid cells, but with less advanced hair differentiation than trichogerminoma. Trichogerminoma should be an independent concept, as a histological variant of trichoblastoma, since they have basic common features and distinct differences.

Trichogerminoma partially contains components of conventional trichoblastoma. Therefore, Kazakoz suggests that it represents just a variant of trichoblastoma [18]. However, individual histological features of round, densely packed pale centrolobular cells distinguish trichogerminoma from trichoblastoma and deserve to its recognition. Indeed, the centrolobular areas of clear cells have also been observed in trichoblastoma, but this pattern is not a dominant microscopic appearance [19]. Trichoepithelioma is histologically characterized by islands of basaloid cells and with peripheral palisading and it has characteristic keratin cysts. Trichoepithelioma differs from trichogerminoma by its lack of concentric rounded nests in the lobules. Despite the similarity to trichoblastoma/trichoepitelioma, trichogerminoma has never been reported in association with Brooke-Spiegler or multiple familiar trichoepitheliomas syndrome. Trichilemmoma is a benign clear cell adnexal neoplasm, composed of glycogen-rich clear cells, characterized by periodic acid-Schiff positive glycogen, with columnar cells at the periphery, indicative of outer root sheath differentiation, that rest upon a thickened basement membrane. Basal cell carcinoma is made up of proliferative basaloid cells with peripheral palisading, which usually shows tumor-stroma retraction spaces and attachments to the overlying epidermis. Basal cell carcinoma with follicular differentiation is a tumor with basaloid cells budding from the epidermis or follicles with a horn cyst resembling a follicular structure. However, it shows a lack of papillar formation and there are no centrolobular balls of concentric pale cells.

Herein, we report a rare case of trichogerminoma which, in contrast to previously reported cases, showed numerous mitotic figures and a higher Ki67 nuclear proliferative rate. Trichogerminoma appears to have a benign course. Notwithstanding, because of the small but potential risk of malignancy, complete excision of the tumor is the treatment of choice.

References

1 Sau P, Lupton GP, Graham JH. Trichogerminoma. Report of 14 cases. J Cutan Pathol 1992;19:357-365. https://doi.org/10.1111/j.1600-0560.1992.tb00606.x

2 Kazakov DV, Kutzner H, Rutten A, et al. Trichogerminoma: a rare cutaneous adnexal tumor with differentiation toward the hair germ epithelium. Dermatology 2002;205:405-408. https://doi.org/10.1159/000066427

3 Paeng SS, Sohn JH, Kim DH, et al. Trichogerminoma. A case report. Korean J Pathol 1996;30:340-343.

4 Pozo L, Diaz-Cano SJ. Trichogerminoma: further evidence to support a specific follicular neoplasm. Histopathology 2005;46:108-110. https://doi.org/10.1111/j.1365-2559.2005.01955.x

5 Shin JH, Jung JH, Yoo J, et al. Pigmented trichogerminoma. A case report. Korean J Pathol 2007;41:187-189.

6 Tellechea O, Reis JP. Trichogerminoma. Am J Dermatopathol 2009;31:480-483. https://doi.org/10.1097/DAD.0b013e31818ffcc3

7 Kim M, Choi M, Hong JS, et al. A case of trichogerminoma. Ann Dermatol 2010;22:431-434. https://doi.org/10.5021/ad.2010.22.4.431

8 Huang ECH, Chen HH, Lin TY, et al. Trichogerminoma. A case report, historical review and reconceptualization. J Taiwan Soc Plast Surg 2012;21:230-235.

9 Chen LI, Hu JT, Li Y. Trichogerminoma, a rare cutaneous follicular neoplasm with indolent clinical course: report of two cases and review of literature. Diagn Pathol 2013;8:210. https://doi.org/10.1186/1746-1596-8-210

10 Lozano-Masdemont B, Rodríguez-Soria VJ, Gómez-Recuero-Muñoz L, et al. Trichogerminoma: a neoplasm with follicular differentiation and a characteristic morphology. Actas Dermosifiliogr 2016;107:789-791. https://doi.org/10.1016/j.ad.2016.04.013

11 Goto K, Takai T, Anan T, et al. Reappraisal of the Confusing Concept "Trichogerminoma" and the Il-Defined Finding "Cell Balls": Clinicopathologic Analysis of 6 Cases of Trichogerminoma and Comparison With 2 Cases of Basal Cell Carcinoma With Cell Ball-Like Features. Am J Dermatopathol. 2018; 40:543-545. https://doi.org/10.1097/DAD.0000000000000921.

12 Epperson J, Libow L. A Case of trichogerminoma with pilomatrical differentiation and a unique immunohistochemical profile. Am J Dermatopathol 2017; 39:e13-e16.

13 Grouls V, Hey A. Trichoblastic fibroma (fibromatoid trichoepithelioma). Pathol Res Pract 1988;183:462-468. https://doi.org/10.1016/S0344-0338(88)80094-3

14 Mertens RB, de Peralta-Venturina MN, Balzer BL, et al. GATA3 expression in normal skin and in benign and malignant epidermal

and cutaneous adnexal neoplasms. Am J Dermatopathol 2015; 37:885-891. https://doi.org/10.1097/DAD.0000000000000306

[15] Lee JJ, Mochel MC, Piris A, et al. p40 exhibits better specificity than p63 in distinguishing primary skin adnexal carcinomas from cutaneous metastases. Hum Pathol 2014;45:1078-1083. https://doi.org/10.1016/j.humpath.2014.01.006

[16] Goto K. Immunohistochemistry for CD117 (KIT) is effective in distinguishing cutaneous adnexal tumors with apocrine/eccrine or sebaceous differentiation from other epithelial tumors of the skin. J Cutan Pathol 2015;42:480-488. https://doi.org/10.1111/cup.12492

[17] Schulz T, Hartschuh W. Merkel cells are absent in basal cell carcinomas but frequently found in trichoblastomas. An immunohistochemical study. J Cutan Pathol 1997;24:14-24. https://doi.org/10.1111/j.1600-0560.1997.tb00780.x

[18] Kazakov DV. Cutaneous adnexal tumors. Philadelphia: Lippincott Williams & Wilkins 2012, p. 219.

[19] Ackerman AB, de Viragh PA, Chongchitnant N. Trichoblastoma. In: Ackerman AB, de Viragh PA, Chongchitnant N, eds. Neoplasms with follicular differentiation. Philadelphia: Lea & Febiger, 1993, pp. 359-422.