Trichoblastic Carcinoma ("Malignant Trichoblastoma") with Lymphatic and Hematogenous Metastases

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We report an aggressively behaving malignant trichogenic tumor arising in a trichoblastoma (TB) with widespread lymphatic and hematogenous metastases in a 55-year-old man with a concomitant B-cell chronic lymphocytic leukemia. The primary tumor had been present and unchanged for as long as 40 years before excision. Typical trichogenic TB with dystrophic calcification and even ossification was still present peripheral to the malignant transformation. The malignant neoplasm consisted of basaloid cells, spindle cells arranged in fascicles and densely packed rounded nests or "cell balls." The metastases consisted of immature basaloid cells and cell balls, and the recurrences became successively more undifferentiated. The residual TB reacted with antibodies to cytokeratin (CK) 6, 8, 14, and 17 and focally to S-100; the malignant primary tumor reacted uniformly with antibodies to vimentin and only focally with antibodies to CK and S-100. The metastatic tumor had lost epidermal CK expression but maintained expression of S-100 in paraffin-embedded tissues. Trichoblastic differentiation was confirmed in frozen tissues with antibodies to hair keratins. No expression of *p53* or *bcl-2* was identified, but p-glycoprotein (*MDR-1* gene related) was expressed by primary and metastatic tumor cells. We believe that this neoplasm is best classified as a trichoblastic carcinoma arising in a TB in association with a B-cell chronic lymphocytic leukemia. This case illustrates that TBs have the potential for malignant transformation and aggressive behavior.

KEY WORDS: Cytokeratin, Hair appendage tumor, Hair keratin, Malignant transformation, Trichoblastic carcinoma, Trichoblastoma.

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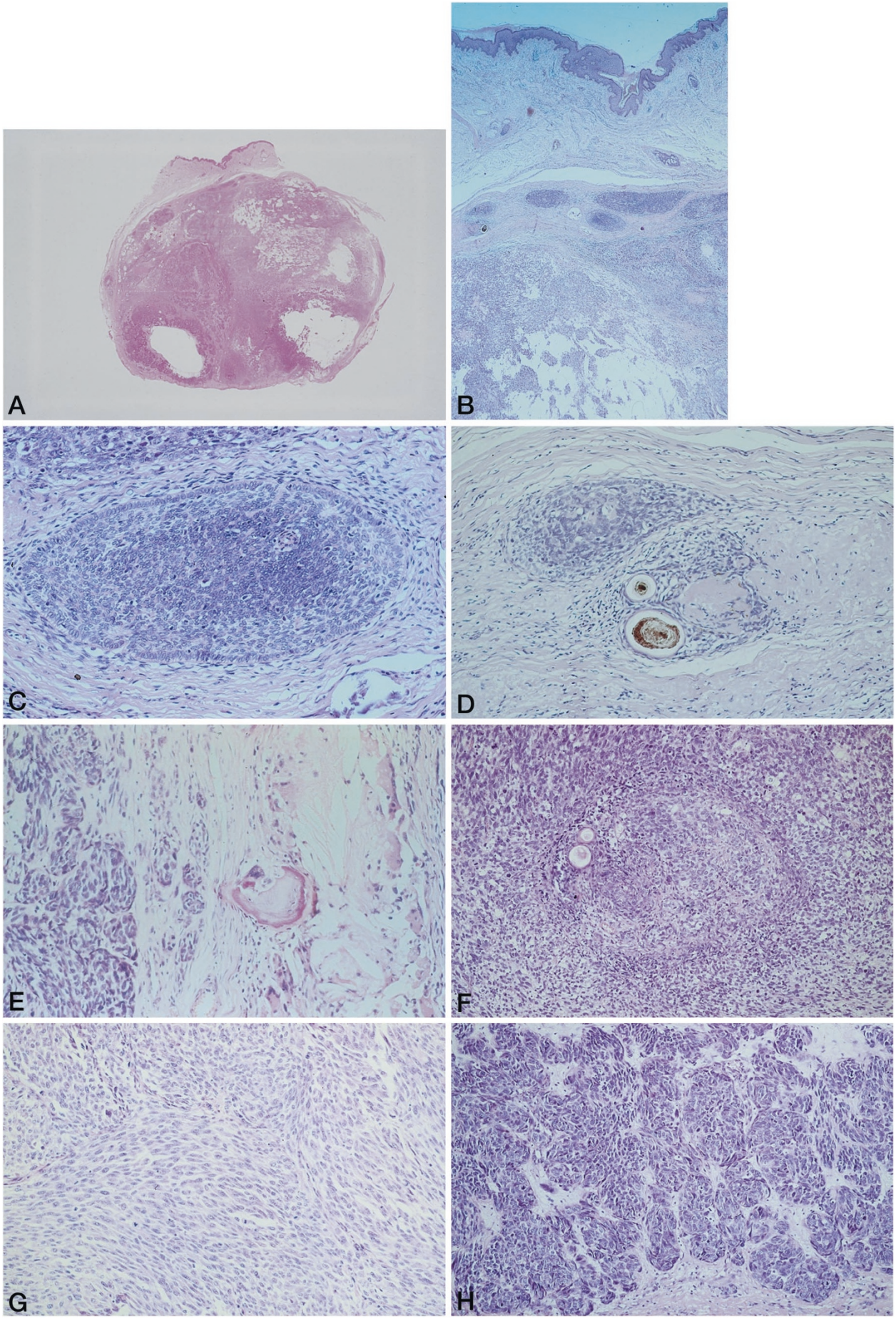
Trichogenic adnexal tumors are rare neoplasms, the vast majority of which are benign. They have been separated in the past into trichoblastic fibromas, trichogenic trichoblastomas (TBs), and trichogenic myxomas according to their relative contents of epithelial and mesenchymal components (1). Other authors use the term TB for all benign cutaneous neoplasms that are constituted mostly of germinative follicular cells, and distinguish five patterns: large nodular, small nodular, cribriform, racemiform, and retiform (2). Histologic differentiation of TB ranges from rudimentary to mature forms of bulbs and papillae, outer and inner root sheaths, and hair (2). Variants of TB, such as a giant TB (3), adamantinoid TB (cutaneous lymphadenoma) (4), pigmented TB (5), a rippled-pattern TB (6), and nodular desmoplastic TB (7), have been reported. To our knowledge, no "malignant trichoblastomas" or malignant transformations have been described. We report an exceptional case of malignant hair appendage tumor, which we refer to as trichoblastic carcinoma (TC), in a patient with concomitant B-cell chronic lymphocytic leukemia (B-CLL) with bone marrow involvement. The primary tumor still showed portions of benign TB with multiple transitions to malignant proliferations with rudimentary trichogenic differentiation. The metastases consisted predominantly of undifferentiated cells whose trichogenic derivation could be confirmed only by demonstration of hair keratin expression in frozen material. We present a detailed analysis of this exceptional case along with a discussion of the cause and differential diagnosis of malignant hair appendage tumors.

CASE REPORT

A 55-year-old, apparently healthy man had excised a movable, 3.5-cm deep dermal nodule of the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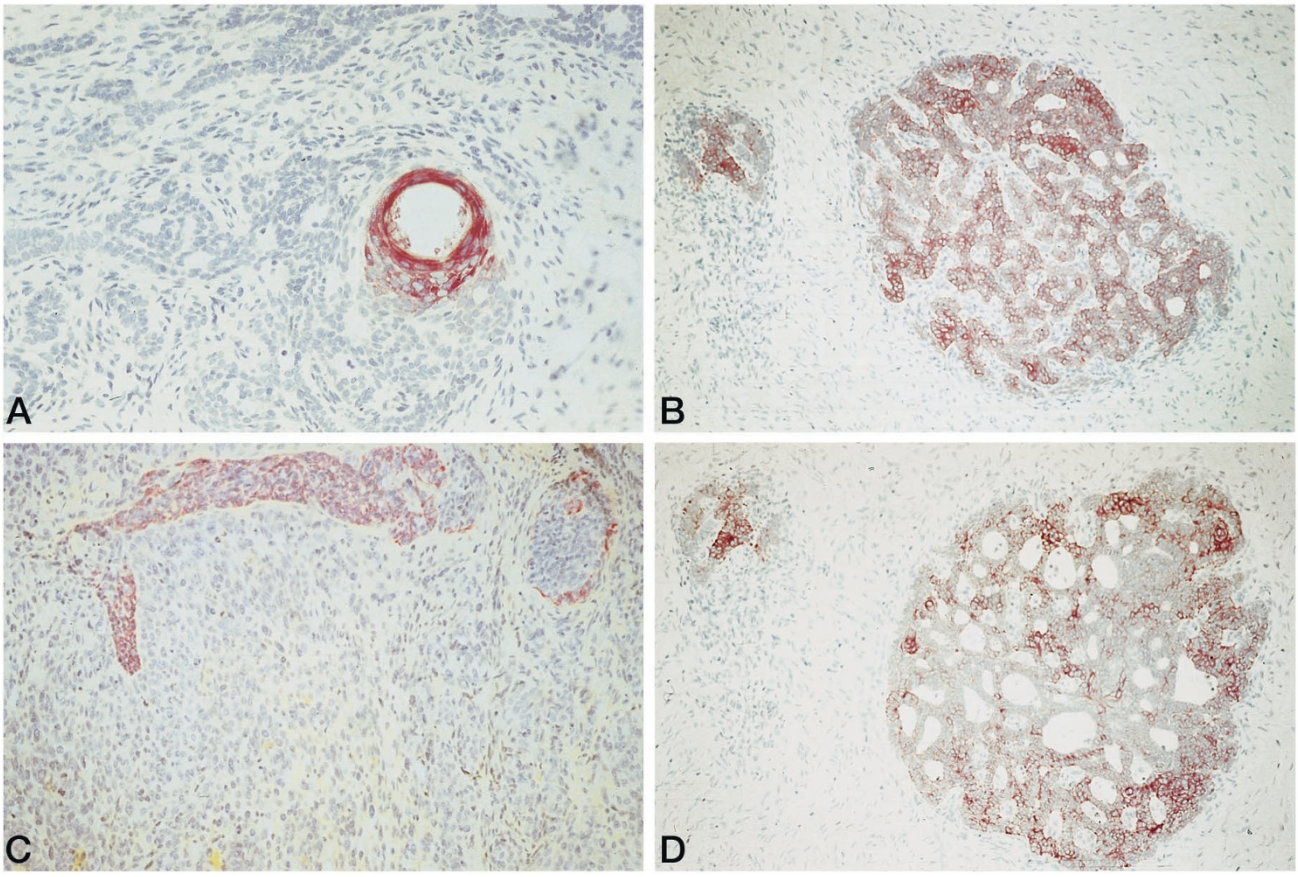

FIGURE 2. **A**, CK 6 staining of infundibular cysts in the trichoblastoma (TB) portion (×128). **B**, CK 8 staining of TB (×200). **C**, CK 14 staining in a transition zone of benign to malignant areas of the neoplasm (×128). **D**, CK 17 stains only individual cells in TB (×200).

deltoid region of the right arm. The nodule had been present and unchanged for more than 40 years but suddenly became symptomatic with rapid enlargement, painful burning sensation, and redness. Within 6 months, the patient was diagnosed with metastatic TC in one axillary lymph node (LN) with extracapsular spread and a B-CLL in all axillary LNs with concomitant bone marrow infiltration by B-CLL. The CLL was left untreated. Four months later, an axillary 15-cm recurrence of the TC was treated surgically. Detection of a solitary 8-cm liver metastasis resulted in three cycles of chemotherapy (Pharmorubicin-cisplatin), followed by 3 months of radiation therapy (total 50 Gy) for another axillary recurrence with initial disappearance of the axillary tumor. The chemotherapy resulted in massive tumor necrosis with liver rupture, which was treated with partial hepatectomy. Despite continuing chemotherapy for multiple pulmonary metastases and residual axillary disease, the patient died 21 months after initial diagnosis of the TC. Permission for autopsy was declined.

MATERIALS AND METHODS

Immunohistochemistry was performed with antibodies (Ab) to S-100, HMB45, vimentin, individual cytokeratin (CK) polypeptides 5, 6, 7, 8, 18, and 19; pankeratin; *p53*; *bcl-2* oncogene (all from DAKO Corp., Carpinteria, CA); CK 14 (Novacastra, Newcastle, UK); CK 17 (Progen, Heidelberg, Germany); and p-glycoprotein (*MDR-1* gene product; Immunotech, Marseille, France), using the alkaline phosphatase antialkaline phosphatase (APAAP) method according to standard protocols with the appropriate positive and negative controls. Indirect immunofluorescence was performed on frozen tissue of the axillary mass and liver metastasis with antiserum to type I (gp 19) and type II (gp 16) human

FIGURE 1. **A**, scanning view of the deep dermal cutaneous neoplasm, consisting of a solid tumor with focal cystic degeneration (×1.25). **B**, residual lobules of trichoblastoma consisting of basaloid cells and calcifications adjacent to the malignant proliferation (×20). **C**, follicular germinative cells with peripheral nuclear palisading. **D**, infundibulocystic structures with pale cells, matrical material, and dystrophic melanin-containing hair shafts (×128). **E**, foreign body giant cells, bone formation adjacent to malignant proliferation (×128). **F**, solid malignant proliferation around preexisting infundibulocystic structure (×50). **G,** spindle cells in fascicular arrangement (×200). **H**, tightly packed nests reminiscent of embryonic follicular germ cells (×128).

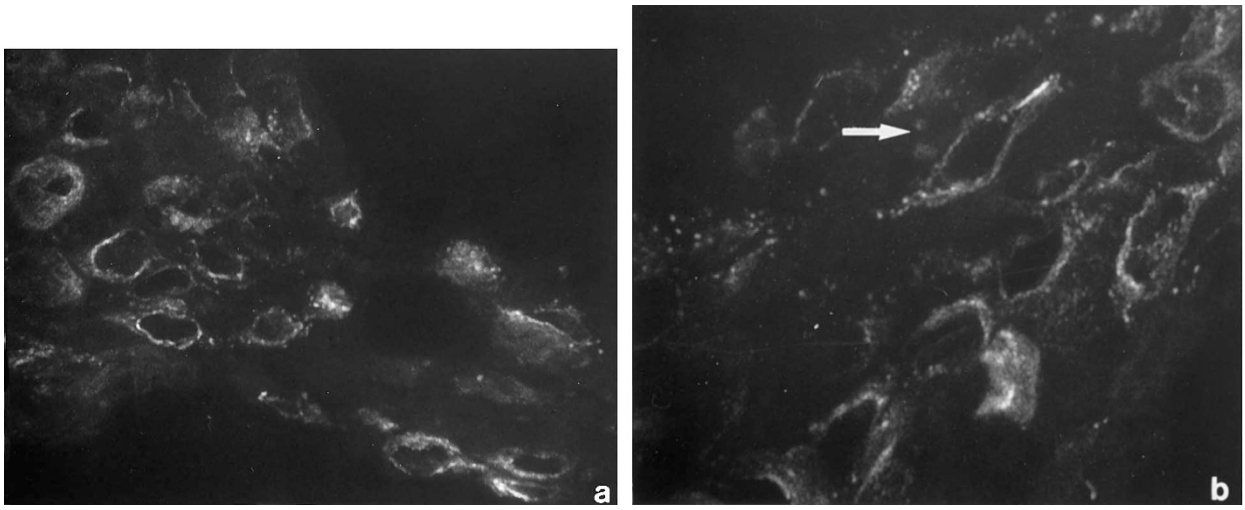

FIGURE 3. Indirect immunofluorescence performed on frozen material of the liver metastasis with (guinea-pig) antiserum to human hair keratin type I demonstrating cytoplasmic staining of the tumor cells. **A**, most cells show a collapsed but readily discernible tonofilament network around the nucleus (×504). **B**, the spindle shaped tumor cells possess rare but distinct tonofilaments stretching throughout the cytoplasm (×800).

hair keratins (8) (generous gift of Prof. W.W. Franke, German Cancer Research Center, Heidelberg, Germany). Paraffin-embedded, formalin-fixed tissue was processed for electron microscopy and flow cytometric analysis according to standard protocols.

Histologic Findings

Primary cutaneous neoplasm

The well-circumscribed and pseudoencapsulated tumor was located in the deep dermis and subcutis without continuity with the epidermis (Fig. 1A). In the superficial and peripheral portions of the neoplasm, typical trichogenic TB was identified (Fig. 1B). The histologic spectrum consisted of small nodules of follicular germinative cells with the peripheral nuclei arranged in palisades and loose fibroblastic stroma recapitulating perifollicular sheaths (Fig. 1C); infundibulocystic structures with melanin-containing dystrophic hair and corneocytes; and immature follicular hair bulbs (Fig. 1D), focally extensive dystrophic calcifications, granulomatous inflammation with foreign body giant cells, and osteoid deposition and even bone formation (Fig. 1E).

Malignant transformation was observed multifocally in several histologic patterns: solid and lobular proliferations of small basaloid cells with large, round nuclei, arising around preexisting trichogenic structures, and spindle cell proliferations in sweeping fascicles (Fig. 1F) or tightly packed nests (Fig. 1G). Very focally, nuclear pleomorphism was noted. The neoplasm was highly vascularized with extensive hemorrhagic cystic necrosis. Rare pigment containing S-100–positive melanocytes and clear cells were identified. Abundant regular and pathologic mitoses as well as apoptotic cells resembling apoptoses in the outer root sheath during early catagen were observed. The fibrous capsule was infiltrated by small lobules of malignant cells and individual malignant cells. Ghost cells, extensive keratinization, and frank necrosis were not identified. The formalin-fixed, paraffin-embedded tumor reacted with Ab against CK 6, 8, 14, and 17 in the residual TB. Individual keratinized cysts reacted with Ab to CK 6; all other cells were negative (Fig. 2A). CK 8 was expressed uniformly with slight emphasis in keratinized areas (Fig. 2B). CK 14 stained all cells of the TB diffusely, whereas only a minority stained with Ab to CK 17. In transition zones from benign to malignant proliferations, benign cells showed immunoreactivity with Ab to CK 14 and 17 (Fig. 2C, D), but the malignant tumor cells did not stain. A majority of benign and malignant cells were S-100 positive, whereas HMB45 was negative. Ab to *p53* and *bcl-2* did not reveal specific staining in the archival tissue, whereas Ab to p-glycoprotein demonstrated diffuse cytoplasmic positivity. Clusters of lymphocytes were found focally around the tumor and perivascularly in the dermis.

Metastases

The axillary LN architecture was completely effaced by a dense infiltration of small (CD 5, CD 20, CD 23, and κ positive) lymphocytes. The metastatic TC consisted of immature large cells with hemorrhagic cystic degeneration and showed extracapsular spread with diffuse infiltration of the adipose tissue, blood, and lymph vessels. The recurrent axillary tumors were composed of sheets and lobules of undifferentiated large cells, "cell balls," and individual basaloid and spindle cells infiltrating between fibrovascular and adipose tissues. The liver

metastasis was highly necrotic with immature undifferentiated spindle and polygonal cells with round to oval nuclei with small nucleoli. Electron microscopic examination of the liver metastasis showed lipid droplets, smooth and rough endoplasmic reticulum, Golgi apparatus, and mitochondria but no tonofilaments, desmosomes, basement membrane, or melanosomes. Flow cytometric examination of the tumor before treatment demonstrated aneuploidy with a DNA index of 1.7 and a high proliferation activity with an S-phase fraction of 31.5%. Formalin-fixed, paraffin-embedded tumor specimens were nonreactive with all Ab to epidermal and trichogenic keratins. The frozen tissues (axilla and liver) demonstrated weak but specific staining for EMA and CK 14 and 17 in fewer than 10% of tumor cells and S-100 in approximately 30% of cells. Demonstration of type I (Fig. 3A, B) and type II hair keratins in frozen tissue confirmed the trichogenic derivation of the tumor cells. *p53* and *bcl-2* were not expressed, but p-glycoprotein was focally positive in the metastatic tumor.

DISCUSSION

We present a carcinoma arising in a TB with subsequent lymphatic and hematogenous metastases in a patient with B-CLL. The residual benign tumor was most consistent with a trichogenic TB with the characteristic CK 6, 8, 14, and 17 pattern (9). Expression of epidermal CK 8 and 19 has been described for the outer root sheath, the medulla, and the bulbar region of hair follicles, whereas CK 14 and 17 are expressed in the inner root sheath. Matrical cells and peripapillary cone and hair shaft cells, however, express only trichogenic hair keratins (8). The malignant proliferation showed only rudimentary trichogenic differentiation (cell balls) and no reaction with epidermal markers in paraffin-embedded material. Loss of epidermal CK expression correlated with decreasing histologic differentiation in the metastases. Although we were not able to document hair keratin expression in our archival formalin-fixed and paraffin-embedded material, the frozen tissue of the metastases was strongly positive for hair keratins confirming the trichogenic derivation of the tumor cells.

The skin nodule had been present and unchanged for more than 40 years, which was evidenced histologically by extensive calcification and even osteoid deposition. Benign hair appendage tumors of more than 20 and 40 years' duration have been described (10, 11). The benign portion of the presented cutaneous neoplasm had histologic similarities to both the giant TB (3) and the so-called trichogerminomas (11), which some authors consider to be a large nodular type of TB (3). In a review of the literature (Embase CD, 1989–present; Knowledge Finder, 1986–present; MEDLINE, 1966–present), we identified only two reports of malignant transformation in benign adnexal neoplasms: (1) a "malignant hair matrix tumor" arising in a trichoepithelioma (10) without reference to metastatic behavior and (2) an undifferentiated carcinoma arising in a "trichogerminoma," which had been present for more than 40 years, with local recurrences and lymphatic metastases (11). Both patients experienced locally aggressive disease. The latter case is very similar to our case in that the carcinoma arose in a nodule that had been present for 40 years and that benign trichogerminoma was present superficially, whereas the deeper portions of the neoplasm consisted of undifferentiated carcinoma. The malignant trichoepithelioma may also be categorized as TB in the opinion of Ackerman (2), who considers trichoepitheliomas to represent superficial TB. Invasive and metastasizing malignant hair appendage tumors are exceedingly rare, and our findings along with the previously reported two cases suggest that malignant transformation in an initially benign lesion can occur, especially in tumors of long duration and in immunocompromised patients. A more frequently encountered malignant hair matrix tumor is the pilomatrixomal carcinoma. Ghost cells, extensive keratinization, necrosis, and the location "head" as described for malignant pilomatricomas (12) were not features in the reported case.

The pathogenesis of the TC is unknown. Malignant transformation may have been provoked by dysregulation of B-cell function and impairment of immune cell function secondary to the CLL (13). Various publications confirm an excess of Merkel cell carcinomas, basal cell and squamous cell carcinomas, and more aggressive variants of squamous cell carcinoma after non-Hodgkin's lymphoma (14–16). Other secondary cancers, however, particularly noncutaneous cancers such as renal cell carcinoma and hepatocellular carcinoma, are related to therapy for the non-Hodgkin's lymphoma (17–19). Therapy-induced skin cancer can be ruled out in our patient as his B-CLL was not treated. Lack of *p53* expression in the TC implies mechanisms other than *p53* mutations are responsible for malignant transformation.

Initially, we hesitated to call this tumor "trichoblastic carcinoma" because low-grade, indolent, nonmetastasizing carcinomas arising *de novo* with differentiation along follicular epithelium, and even basal cell carcinomas arising in hamartomas such as nevus sebaceous, have been called TC (2). A "malignant trichoblastoma," however, has not been described and does not represent an accepted entity and would not do justice to the vast majority of benign appendage tumors with germinative follic-

ular differentiation. The described neoplasm was a highly aggressive tumor that necessitated systemic treatment. Therapy planning was expectantly complicated by the lack of experience with such a tumor. Response to radiation and chemotherapy was short-lived, and the TC proved ultimately to be therapy resistant. P-glycoprotein (*MDR-1* gene product) positivity in the primary TC may be related to the tumor cell resistance to cytotoxic drugs, and it is intriguing to speculate about its usefulness to predict treatment failure in solid tumors similar to leukemias (20).

In summary, this case illustrates a fulminant, treatment-resistant, ultimately fatal course of a carcinoma arising in a TB with widespread metastases in a patient with a low-grade non-Hodgkin's lymphoma. Only analysis of frozen tissue allowed the identification of the poorly differentiated metastases as trichogenic, because the formalin-fixed, paraffin-embedded tissue was nonreactive with the conventional diagnostic antibodies. We believe that this neoplasm is best classified as trichoblastic carcinoma arising in a trichoblastoma. This case very well illustrates the potential for malignant transformation of trichoblastomas.

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