CONCISE COMMUNICATION

High-grade trichoblastic carcinoma arising through malignant transformation of trichoblastoma: Immunohistochemical analysis and the expression of p53 and phosphorylated AKT

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ABSTRACT

Trichoblastoma (TB) is a benign cutaneous adnexal neoplasm. The lesion typically presents as a slow-growing, solitary, well-circumscribed nodule measuring up to 3 cm in diameter. On rare occasions, TB causes malignant transformation into an aggressive form described as high-grade trichoblastic carcinoma. Four such cases have been reported to date; all were described as high-grade trichoblastic carcinomas. Here, we describe the case of a 72-year-old Japanese male patient with a rapidly enlarging subcutaneous tumor on his lower back, which was diagnosed as high-grade trichoblastic carcinoma. Histopathologically, the tumor featured both benign and malignant components, and a transition zone between these states was clearly evident. In the immunohistochemical analysis, a malignant component was positive for p53 and showed stronger staining of phospho-AKT Ser473 in comparison with a benign component. These results suggest that loss of p53 function and activation of phosphatidylinositol 3-kinase–AKT signaling pathways played important pathogenic roles in malignant transformation of the present case.

Key words: AKT, high-grade trichoblastic carcinoma, malignant transformation, p53, trichoblastoma.

INTRODUCTION

Trichoblastoma (TB) is a benign cutaneous adnexal neoplasm composed of tumor cells resembling follicular germinative cells. The lesion typically presents as a slow-growing, solitary, well-circumscribed nodule measuring up to 3 cm in diameter.1 Histopathologically, well-circumscribed basaloid tumor nests with a peripheral palisading pattern, similar to that of basal cell carcinoma (BCC), are evident in the dermis. However, TB differs from BCC by the features of symmetrical silhouette, lack of any epidermal connection, (usual) absence of retraction artifacts, scarcity of the mucin deposition in or around the tumor nest, and lack of cytological atypia.2 On very rare occasions, TB transform into a malignant form. While conventional BCC were reported to arise in association with TB,3 TB can also transform into an aggressive form of carcinoma. Four such cases have been reported to date, and all were described as high-grade trichoblastic carcinomas.4–6 Here, we report another such case, in which a detailed immunohistochemical analysis was performed.

CASE REPORT

A 72-year-old Japanese man presented with a rapidly enlarging subcutaneous tumor on his lower back. He had noticed a subcutaneous nodule in this region approximately 35 years prior and had consulted a doctor. The lesion was diagnosed through incisional biopsy as an unspecified benign tumor and had been under observation for more than 30 years. Although the nodule had enlarged gradually over this time, growth became rapid in the few months prior to his initial visit to us. Physical examination revealed a dark red, exophytic, firm subcutaneous mass over 10 cm in diameter (Fig. 1a). Computed tomography revealed a 92 mm × 48 mm low-density region with calcification (Fig. 1b). On magnetic resonance imaging, the lesion was of low signal intensity on T1-weighted imaging (Fig. 1c) and exhibited a mixture of high and low signal intensities on T2-weighted imaging, suggestive of a malignant tumor (Fig. 1d). Based on a histopathological diagnosis of a malignant adnexal tumor made after incisional biopsy, the tumor was totally excised with surgical margins of 10 mm, including the fascia.

The cut appearance of the tumor exhibited two different components: a white-to-yellow multilobulated solid region and...
a yellow-to-brown region with cystic or necrotic change (Fig. 1e). Histopathologically, a well-circumscribed tumor was present in the subcutaneous tissue without any epidermal connection (Fig. 1f). The tumor featured both benign and malignant components. Although there was no portion where benign and malignant cells coexisted within a single nest, a transition zone between these states was clearly evident (Fig. 2a,b). The benign component exhibited proliferation of basophilic tumor nests, surrounded by a fibroblast-rich stroma. These nests were composed of basaloid, follicular germinative cells exhibiting a peripheral palisading pattern. However, mucin deposition was not evident (Fig. 2c,d). The malignant component exhibited anastomosing tumor nests of various sizes composed of epithelial cells with atypical nuclei (Fig. 2e,f). Immunohistochemically, the malignant component was positive for p53 (Fig. 2g,h) and the Ki-67 index was 30% (Fig. 2i,j). In an effort to understand the pathobiology of the malignant transformation more closely, we performed further immunohistochemical analyses using the following antibodies: a rabbit polyclonal anti-CD117 antibody (c-KIT; DAKO, Carpentaria, CA, USA); a mouse monoclonal anti-estrogen receptor (ER) antibody (1D5; DAKO); an anti-progesterone receptor (PgR) antibody (PgR638; DAKO); a rabbit monoclonal anti-human epidermal growth factor receptor-2 antibody (EP1045Y; Biocare Medical, Concord, CA, USA); a rabbit monoclonal anti-c-MET antibody (D1C2; Cell Signaling Technology, Beverly, MA, USA); a rabbit monoclonal anti-phospho-p44/42 mitogen-activated protein kinase Thr202/Tyr204 antibody (D13.14.4E; Cell Signaling Technology) a rabbit monoclonal anti-phospho-RAC-alpha serine/threonine-protein kinase (AKT) Ser473 antibody (D9E; Cell Signaling Technology); and a rabbit monoclonal anti-phospho-STAT3 antibody (D3A7; Cell Signaling Technology). Phospho-AKT Ser473 staining was stronger in tumor cells of the malignant region of the tumor (Fig. 2k,l), suggesting activation of phosphatidylinositol 3-kinase PI3-AKT signaling pathways. The other staining tests were negative.

By reference to the clinical course and histological findings, the tumor was diagnosed as a high-grade trichoblastic carcinoma that developed through malignant transformation of TB. Further radiological examination revealed no malignant metastases. At the 1.5-year postoperative follow up, there was no evidence of recurrence or metastasis.

DISCUSSION

The term of “trichoblastic carcinoma” has been interpreted in two pathobiological concepts. In one sense, it has been recognized as a synonym of BCC. As BCC histologically resembles follicular germs of embryonic skin and occasionally shows follicular differentiation, it has been interpreted as a malignant neoplasm with limited follicular differentiation in contrast with its benign counterpart, TB. In another sense, it has been...
interpreted more restrictively, recognizing only neoplasms in which the epithelial–stromal relationship resembled that of TB. In contrast to BCC, which are recognized as “low-grade trichoblastic carcinomas” based on their indolent clinical course, most trichoblastic carcinomas of the latter interpretation comprise a distinct disease entity with the features of high-grade histology, metastatic potential and association with pre-existing TB, hence nominated as “high-grade trichoblastic carcinoma”. (Differences between BCC and high-grade trichoblastic carcinoma are summarized in Table 1.)

The high-grade trichoblastic carcinomas reported earlier shared several characteristics. Clinically, sudden enlargement of long-standing TB accompanied by inflammation in the elderly were reported. Histologically, both the typical TB portion and the carcinoma portion composed of epithelial cells exhibiting high-level mitotic activity were evident, demarcated by a clear transition zone. In our present case, the tumor showed a well-circumscribed structure. The benign portion exhibited proliferation of basophilic tumor nests, surrounded by a fibroblast-rich stroma. While these tumor nests showed a peripheral palisading pattern, mucin deposition was not evident, suggesting the features of TB. Together with the similar of other clinicopathological features with past reported cases, it is plausible to make a diagnosis of high-grade trichoblastic carcinoma in our present case (Table 1).

Because the mechanisms of malignant transformation in high-grade trichoblastic carcinoma remain unclear due to its rarity, we explored pathobiological differences between pre- and post-malignant tissue through immunohistochemical staining. As a result, p53 and phospho-AKT Ser473 showed a stronger staining pattern in the malignant component. Expression of p53 in tumor cells is reported to reflect abnormal protein stabilization, mediated through a p53 mutation that plays an important role in cancer development by causing the loss of tumor-suppressor function. Positive staining of phospho-AKT Ser473 reflects the activation of a PI3-AKT signaling pathway. Activation of it is associated with the development and progression of various cancers by regulating metabolism, survival, apoptosis, growth and proliferation of tumor cells through the
phosphorylation of several effectors.\(^9\) Several studies have found a significant high expression rate of p53 and phospho-AKT Ser473 in non-melanoma skin cancer including squamous cell carcinoma and BCC.\(^10–12\) These results imply that accumulation of multiple pro-oncogenic events in long-standing TB will cause malignant transformation.

In conclusion, this case afforded another instance of clear evidence of malignant transformation of a TB. The tumor featured a completely different benign TB region and malignant regions. Immunohistochemically, the positivity of phospho-AKT Ser473 and p53 suggested that loss of p53 function and activation of PI3-AKT signaling pathways played important pathogenic roles in malignant transformation.

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Table 1. Clinicopathological features of basal cell carcinoma, high-grade trichoblastic carcinoma and present case

| Clinical features                                  | BCC | High-grade trichoblastic carcinoma | Present case |
|----------------------------------------------------|-----|-----------------------------------|-------------|
| Susceptible age                                    | Elderly | Elderly                           | Elderly     |
| Predilection site                                  | Face    | Trunk or limbs                    | Trunk       |
| Pre-existing longstanding nodule                  | Absent  | Present                           | Present     |
| Circumscribed structure                            | Occasionally | Frequent                      | Present     |
| Rapid growth                                       | Absent  | Present                           | Present     |
| Inflammation                                       | Absent  | Present                           | Present     |
| Metastasis                                         | Extremely rare | Frequent                    | Absent      |
| Pathological features                              | Mostly present | Present in TB portion            | Present in TB portion |
| Proliferation of basaloid cell with                | Absent  | Present                           | Present     |
| nuclear palisading pattern                        | Present | Usually absent                    | Absent      |
| Co-localization of anastomosing                     | Present | Absent                            | Absent in TB portion |
| tumor nests composed of epithelial cells exhibiting high-level mitotic activity | Present | Absent                            | Absent in TB portion |
| Epidermal connection of basaloid tumor nest        | Frequent | Scarce                           | Absent in TB portion |
| Retraction artifacts around basaloid tumor nest    | Frequent | Scarce                           | Absent in TB portion |
| Mucin deposition in basaloid tumor nest            | Frequent | Scarce                           | Absent in TB portion |
| Cytological atypia in basaloid cells               | Frequent | Occasional                        | Mostly absent |