SHORT COMMUNICATION

c-FOS Expression in Metastatic Basal Cell Carcinoma with Spontaneous Basosquamous Transition

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Basal cell carcinoma (BCC) is the most common form of keratinocyte carcinoma (KC). Basosquamous carcinomas (BSCs) or metatypical BCCs are defined as BCCs with discernible squamous differentiation (1). Most BCCs harbour somatic PTCH1 mutations that activate smoothened (SMO), located downstream of the Hedgehog (HH) signalling pathway (1). However, the phenotypic continuum raises the occasional question whether BSC is a clinical entity distinct from BCC or squamous cell carcinoma (SCC) (1). Preclinical studies may address this issue because they revealed that distinct transcriptional programmes govern biological behaviours that differ from one another among KCs (2–4). In a chemically induced tumourigenesis setting, the activator protein 1 transcription factor (TF) c-FOS was shown to be responsible for inflammatory responses that promote SCC development (2, 5). This finding was translated to humans; SCCs express c-FOS with concomitant inflammatory responses, whereas BCCs do not (5). These studies indicate that c-FOS determines SCC lineage (2, 5, 6). As a result, it is reasonable to believe that epigenetic changes underlie the basal to squamous cell carcinoma transition (BST) caused by SMO inhibition. Kuonen et al. (6) recently elaborated on epigenetic plasticity among KCs by analysing SMO inhibitor-induced BSTs. SMO inhibition promoted c-FOS-dependent activation of the epidermal growth factor receptor (EGFR)/RAS/MAPK pathway, the blockade of which using an EGFR inhibitor restored BCC features (6). Here, we describe a case of giant BCC with regional lymph node (LN) metastasis and determine intralesional c-FOS expression levels, hypothesizing that increased c-FOS TF expression levels in tumour cells corroborate BSC's aggressive behaviour caused by spontaneous BST (1).

CASE REPORT

An 85-year-old Japanese man was referred to our clinic with a 10-cm-sized elevated tumour with an ulcer in the centre of the left groin for 1 year (**Fig. 1**a). A skin biopsy diagnosed BCC and computed tomography (CT) revealed a swollen left inguinal lymph node (LN). Groin LN dissection was performed following complete primary lesion resection based on intraoperative rapid diagnosis indicating LN metastases. The patient has been free from local recurrence or metastases 1 year postoperatively.

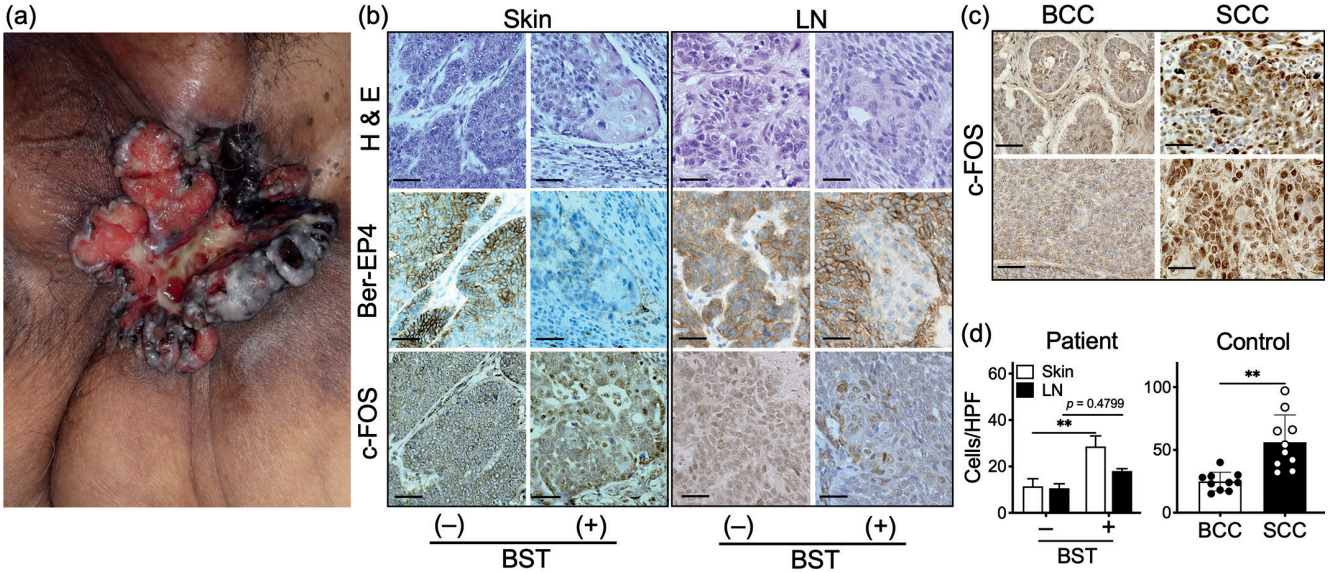

Fig. 1. (a) A 10-cm-sized elevated tumour with an ulcer in the centre of the left groin. (b) Representative histopathological findings of the primary lesion with (+) or without (–) basal to squamous cell carcinoma transition (BST). The BST (+) area exhibited keratinization (haematoxylin and eosin staining) features, along with reduced Ber-EP4 (EpCAM) expression levels and increased nuclear c-Fos expression levels compared with the BST (–) area. *Bars* = 50 μm. (c) Representative immunohistochemical images of c-Fos immunostaining in 10 typical BCC and SCC cases. *Bars* = 50 μm. (d) The image J analysis program was used to quantify the nuclear c-Fos expression levels in the present case and the control BCCs/SCCs. The BST (+) area in the primary lesion (skin) harboured a significantly higher number of nuclear c-Fos-positive cells than the BST (–) area in the current case. The c-Fos expression levels were significantly higher in control SCCs than BCCs. The results were from 5 independent high-power fields (HPF) (the current case) or the means of at least 3 HPFs from each lesion (control BCC/SCC). The $^{**}p < 0.01$, 2-way analysis of variance.

Histologically, both the primary lesion and the metastatic LN comprised typical BCC features with squamous differentiation foci indicative of spontaneous BST (Fig. 1b). The primary lesion's BST area exhibited reduced Ber-EP4 expression levels (Fig. 1b), whereas the metastatic LN did not (data not shown). Expression levels were examined in the BST areas (Fig. 1a) since previous research suggested that nuclear c-Fos staining differentiates SCC from BCC (4, 5), along with typical BCCs and SCCs (Fig. 1c) (5). The BST foci (BST (+)) in the primary lesion and control SCCs exhibited significantly higher nuclear c-Fos expression levels than the non-BST area (BST (–)) or control BCCs, respectively (Fig. 1d). Although the BST foci (BST (+)) in the metastatic LN also exhibited higher c-Fos expression levels, the difference was not statistically significant ($p = 0.4799$) (Fig. 1c).

DISCUSSION

Although a retrospective analysis indicated that SMO inhibition does not increase de novo SCC development in metastasized/locally advanced BCC patients (7), multiple studies have suggested that alternatively activated EGFR/RAS/MAPK pathway diverts tumour cells' addiction away from HH signalling (6, 8) and potentially contributes to aggressive behaviours depending on the patient's immune status or the disease stage (9). These observations indicate the presence of c-FOS-mediated spontaneous BST and partially explain the tendency of BSC to develop LN metastases as opposed to conventional BCC (10). It is unknown whether the c-FOS-positive BST lineage emerged from the nascent stage or during the acquisition of the metastatic phenotype, since the durable stem cell marker has hitherto been unidentified. Moreover, this single case study did not evaluate the degree to which spontaneous BST contributed to LN metastasis. As previously indicated (1, 10), a large primary lesion would be more likely to metastasise. Intriguingly, LN metastatic lesions in the present case retained Ber-EP4 staining and less pronounced c-FOS expression levels than the primary lesion (Fig. 1b, d). This discrepancy suggests that epithelial-mesenchymal interactions, which are a prerequisite for efficient BCC development (11), might have expedited c-FOS-mediated squamous differentiation (2, 5, 6). Our findings, along with the inherent epigenetic plasticity of KCs (5, 6) proven by a series of murine studies (3–5, 11–13), may legitimise epigenetic strategies, such as the local application of histone deacetylase inhibitors (14, 15), instead of or in addition to disease-specific pathway inhibitors, for better KC management.

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The authors have no conflicts of interest to declare.

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