Cytokeratin expression in squamous cell carcinoma arising from hidradenitis suppurativa (acne inversa)

Abstract: We have studied cytokeratin (CK) expression in two cases of well-differentiated and poorly differentiated squamous cell carcinoma (SCC) arising from hidradenitis suppurativa (HS) (acne inversa). In both cases, type A (infundibular-like keratinized) epithelia were observed. In type A epithelia, CK 1 and 10 expressions were decreased, and CK 14 and 17 were detectable in the whole layers. CK 7, 8, 15, 16 and 18 were not detected in type A epithelia. In tumor nests of well-differentiated SCC, CK 1 and 10 expressions were downregulated, and CK 14 expression was upregulated. In tumor nests of poorly differentiated SCC, CK 1 and 10 were not expressed, but simple epithelial keratins (CK 8, 18 and 19) were expressed. These changes of CK expression are related to malignant transformation from the sinus tract (type A epithelium) in HS to SCC.


Hidradenitis suppurativa (HS), known as acne inversa, is a therapy-resistant disease, and is considered to be a follicular occlusion disease. HS occurs commonly in the axilla, perineum, extragenitalia and inguinal regions. The etiology of HS remains unclear. Genetic factors, bacterial infection, abnormal host response, hormonal factors, glucose intolerance, obesity, smoking and disordered function of neutrophils may tend to lead to HS. Clinical features show undermined sinus tracts and fistulae with suppurative exudates. HS is rarely complicated with squamous cell carcinoma (SCC), known as Marjolin ulcer, in which the chronic long-standing inflammatory ulcer may result in malignant transformation.

Cytokeratin (CK) is the most diversified of intermediate-sized filaments, and is classified into 20 subtypes. It is a crucial marker in studying the origin and differentiation of epithelial tumors. CK expression has been reported in sinus tracts in HS. Sinus tracts in HS are classified into three types: type A epithelium (infundibular-like keratinized epithelium with keratohyaline granules), type B epithelium (non-infundibular keratinized epithelium without keratohyaline granules) and type C epithelium (non-keratinized epithelium; so-called leaf-like structure). To our knowledge, no immunohistochmical study of CK has been reported in SCC arising from HS.

The aim of this study is to determine CK expression in SCC and evaluate the origin and state of differentiation of the tumor.

Materials and methods
Two cases with SCC arising from HS were studied.

Case 1
A 72-year-old man presented with an asymptomatic nodule on his buttock in April 1994. The patient had inflamed follicular draining sinus and suppurative nodules for 30 years. These lesions were treated with oral antimicrobial agents with fair response, and incision at the practitioner without operation. He noticed cauliflower-like nodules on the buttock several years ago. No metastasis was found. The
Cauliflower-like nodules were excised. He died of cholangiocarcinoma in November 1994.

Case 2
A 50-year-old man presented with nodules on the buttock in November 2004. He had widespread suppurative nodules and fistulae on the buttock for 30 years. These lesions were treated with oral antimicrobial agents (rifampicine and clindamycin) and isotretinoin. These drugs were effective during the treatment for 10 weeks. Afterward, the patient was treated with infliximab 5 mg/kg once a month five times. The patient had multiple extended ulcers with exudates and necrosis on the right buttock (Fig. 1). Ultrasonic echo showed metastasis in the right inguinal lymph node. Multiple chemotherapies were not effective. The patient died of metastasis in the lung in June 2005.

The excised specimens were fixed in formalin, and embedded in paraffin. We performed an immunohistochemical study using the labeled streptavidin biotin (LSAB) method. We used 10 anti-keratin antibodies as follows: 34βE12 (CK 1),6 LP5K (CK 7),7 LP3K (CK 8),7 LHP1 (CK 10),8 LL002 (CK 14),7 LHK15 (CK 15),9 LL025 (CK 16),7 E3 (CK 17),7 GD3 (CK 18),7 and b170 (CK 19).10 All were purchased from Novocastra Laboratories Ltd (Newcastle upon Tyne, United Kingdom). Our immunohistochemical study used labeled streptavidin-biotin method (Dako, Carpentaria, CA, USA) as reported previously.9 Normal skin from the buttock served as control.

Results
Hematoxylin and eosin staining
Case 1
Continuous with the epidermis, type A epithelium and tumor nests were observed in the dermis (Fig. 2). Tumor cells consisted of well-differentiated keratinocytes with low-grade atypia. Well-differentiated SCC was observed. Infundibular hyperkeratosis and granulomatous lesion were observed.

Case 2
Continuous with the epidermis, type A epithelium and tumor nests were found in the dermis (Fig. 3). Tumor cells are poorly differentiated atypical cells showing pleomorphism with mitotic activity and condensed hyperchromatin. Infundibular hyperkeratosis and granulomatous lesion were observed. Poorly differentiated SCC was observed. The prognosis of SCC was fatal.

Immunohistochemical study
Case 1
CK expression was the same in type A epithelium and tumor nests. CK 1 (Fig. 4) and CK 10 were partly expressed in type A epithelium and tumor nests. CK 14 was detectable throughout tumor nests.
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(Fig. 5). CK 16 was expressed in tumor nests. CK 17 was expressed throughout tumor nests. The remaining CKs (CK 7, 8, 15, 18 and 19) were not detected in tumor nests.

Case 2
Epithelial components were divided into two categories: type A epithelium and tumor nests.

Type A epithelium. CK 1 (Fig. 6) and CK 10 were detected in a small area in the overlying epidermis and type A epithelium. CK 14 and 17 (Fig. 7) were expressed throughout the whole epithelium. CK 7, 8, 15, 16, 17, 18 and 19 were not detected.

Tumor nests. Trace amounts of CK 1 (Fig. 6) and CK 10 were detectable in tumor nests. CK 14 and 17 (Fig. 7) were found in tumor nests. CK 18 (Fig. 8) and CK 19 were expressed in tumor nests. CK 8 was weakly positive. CK 7, 15 and 16 were not present.

Discussion
HS is a long-standing recurrent therapy-resistant disease. One of its most important complications is SCC (Marjolin ulcer), which rarely originates from the sinus tracts in HS.11 CK expression in the sinus tract is very diversified.4,5

In HS, as previously reported,5 type A epithelium contained CK 1 and 10 in the suprabasal layers, and CK 14 in the basal layer. The other CKs (CK 7, 8, 15, 16, 17, 18 and 19) were not detected in type A epithelium.

In SCC arising HS, type A epithelia (infundibular-like keratinized epithelium with keratohyaline granules) were observed in both cases.

In case 1 (well-differentiated SCC), CK 1 and 10 were detected in type A epithelium and tumor nests, but CK 1 and 10 expressions in SCC were relatively decreased rather than those in HS. Although CK 14 was detected in only basal cells in type A epithelia in HS,5 CK 14 was detectable in all layers in type A and in tumor nests in SCC. CK 17, which was not expressed in type A epithelia in HS,3 was clearly expressed in type A epithelia and tumor nests in SCC. Transformation from sinus tract to SCC may be related to downregulation of stratified keratin (CK 1 and 10) and upregulation of undifferentiated keratin (CK 14) and CK 17.

In case 2 (poorly differentiated SCC), type A epithelium was also found in SCC. CK 1 and 10 were scarcely detected in type A epithelium and tumor nests in SCC. CK 14 was detectable throughout the
whole layer in type A and in tumor nests in SCC. Interestingly, simple epithelial embryonic keratins, CK 8, 18 and 19, were detected in tumor nests but not in type A epithelium. In our previous report, simple epithelial keratins such as CK 7, 8, 18 and 19 were not detected in HS. Kurzen et al. reported the presence of CK 7 and 19 in type III epithelium (non-cornifying, strongly inflamed), which was not found in our previous report. The difference in CK expression may be related to the stage of differentiation of the sinus tract. Markey et al. reported simple epithelial keratin in poorly differentiated SCC. They suggested that the presence of these keratins may be related to tumor invasion, metastasis and change in epidermal-mesenchymal interaction. Downregulation of stratified differentiated keratin (CK 1, 10), upregulation of undifferentiated keratin (CK 14) and expression of simple epithelial keratins (CK 7, 8, 18, 19) are involved in malignant transformation in HS with poor prognosis.

HS is a long-standing therapy-resistant disease, and is related to endocrine factors in women. Recently, an anti-tumor necrosis factor-α inhibitor, infliximab, has proved to be an effective therapy. Gottlieb et al. reported that CK 16 expression was down-regulated by infliximab in psoriasis. Administration of infliximab may regulate differentiation of the sinus tract. Keratin expression in sinus tracts after treatment with infliximab for HS deserves to be investigated. We have studied two cases of SCC from HS. Further cases should be studied to investigate CK expression.

References