

Keratin profiles may differ between intraepidermal and intradermal invasive eccrine porocarcinoma

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Abstract. We report two cases of eccrine porocarcinoma (EPC), one of intraepidermal EPC (IEEPC) and one of intradermal invasive EPC (IDEPC) in an immunohistochemical study of cytokeratins (CK) using nine different anti-keratin antibodies against CK1, 7, 8, 10, 14, 16, 17, 18 and 19. IEEPC expressed terminal differentiated CK1 and CK10. In contrast, IDEPC expressed simple-epithelial keratins such as CK7, 8, 18 and 19. Keratin expression of IEEPC preserves the immunophenotypes of normal epidermis. IDEPC, however, expresses poorly differentiated keratin. These results suggest that the keratin profiles of EPC are correlated with the invasive degree and reflect the clinical prognosis of EPC.

Introduction

Eccrine porocarcinoma (EPC) is a rare malignant tumor of the eccrine sweat glands. The histogenesis of EPC is unclear, but it is believed that EPC arises from the acrosyringium (1). EPC may develop *de novo* or arise from a longstanding eccrine poroma or hidrakanthoma simplex (2). Histopathologically, EPC is classified into two entities: Intraepidermal (*in situ*) porocarcinoma and intradermal porocarcinoma (3). Cytokeratin (CK) is the most diversified intermediate-sized filament. Monospecific antikeratin antibodies enable the clarification of the origin and differentiation of epithelial tumors (4). However, no systemic immunohistochemical studies using mono-specific antikeratin antibodies have yet been reported for EPC.

Patients and methods

Case reports. We report on two cases of EPC. Case 1: A 75-year-old male presented with an asymptomatic keratotic

nodule on the right thigh persisting for three years. Case 2: A 76-year-old male presented with a red elevated nodule on the left shoulder.

The lesions were surgically excised. Each specimen was fixed in neutral formalin, embedded in paraffin, and stained with H&E. Serially-cut sections were used in the present immunohistochemical study.

The anti-keratin antibodies used in this study were 34ßB4 (CK1) (5), LP2K (CK 7) (5), LP3K (CK8) (6), LHP1 (CK10) (5), LL002 (CK14) (5), LHK15 (CK15) (7), LL025 (CK16) (5), E3 (CK17) (5), 5D3 (CK18) (5) and b170 (CK19) (8) (all from Novocastra Laboratories Ltd., Newcastle upon Tyne, UK). We used the labeled streptavidin-biotin method (LSAB, Dako, Carpinteria, CA, USA) as reported previously (9). Normal skin from the thigh was used as a control. CK expression in normal eccrine sweat glands has been summarized in previous reports (10-12).

Results

H&E staining. In case 1, histopathologically tumor cells were composed of small basaloid cells, and formed with broad anastomosing cords. Tumor cells were confined to the epidermis, and had large atypical hyperchromatinic nuclei (Fig. 1). The epidermis showed acanthosis with a proliferation of tumor cells. In the epidermis, residue of the intraepithelial sweat duct was observed. Basaloid cells are atypical with mitosis and hyperchromatic irregularly shaped nuclei. In this case, no underlying tumor was found. This case was diagnosed as intraepidermal EPC *in situ*.

In case 2, invasive tumor nests proliferated from the epidermis to the dermis (Fig. 2). Tumor nests were markedly delineated from normal spinous cells (Borst-Jadasson appearance) and developed downward from the epidermis extensively. Tumor cells were hyperchromatic and basophilic with atypical nuclei and mitosis. The tumor formed anastomosing epithelial islands.

Immunohistochemical study. CK expression in the normal epidermis, the acrosyringium, IEEPC, IDEPC and the hidrakanthoma simplex (HS) is summarized in Table I.

In case 1, CK1 and CK10 (Fig. 3) were expressed homogeneously throughout the tumor nests. CK14 was not detected in the tumor cells, and was expressed in the basal

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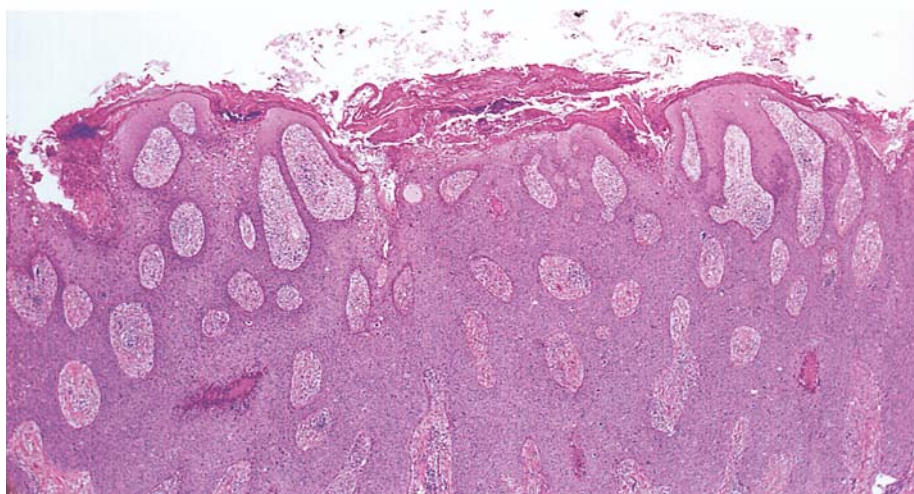


Figure 1. H&E (original magnification x20): Case 1 (IEEPC), tumor nests of small basaloid cells with broad anastomosing cords are confined to the epidermis, and composed of large atypical nuclei with condensed chromatin.

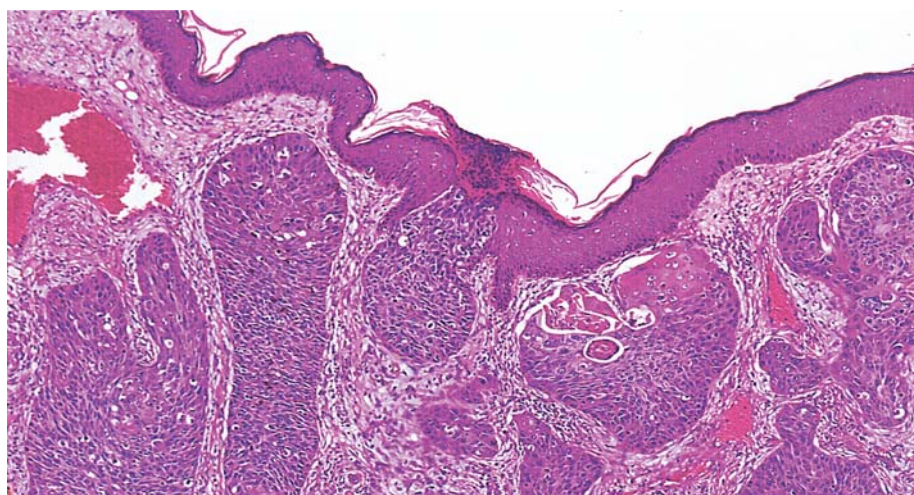


Figure 2. H&E (original magnification x50): Case 2 (IDEPC), invasive tumor nests continuous with the epidermis are situated in the dermis. Tumor nests with high grade atypia and mitotic activity delineate from normal spinous cells.

Table I. CK expression in normal epidermis, the acrosyringium, IEEPC, IDEPC and HS.

Type of CK	Epidermis		Acrosyringium		IEEPC	IDEPC	HS
	Suprabasal cells	Basal cell	Luminal cells	Periluminal cells			
CK1	+	-	+	+	+	-	-
CK7	-	-	-	-	-	+	-
CK8	-	-	-	-	-	+	-
CK10	+	-	+	+	+	-	-
CK14	-	+	-	-	-	+	+
CK15	-	-	-	-	-	-	-
CK16	-	-	-	-	-	-	-
CK17	-	-	-	-	-	+	+
CK18	-	-	-	-	-	+	-
CK19	-	-	+	-	-	+	-

CK, cytokeratin; IEEPC, intraepithelial eccrine porocarcinoma; IDEPC, intradermal eccrine porocarcinoma; HS, hidradenoma simplex.

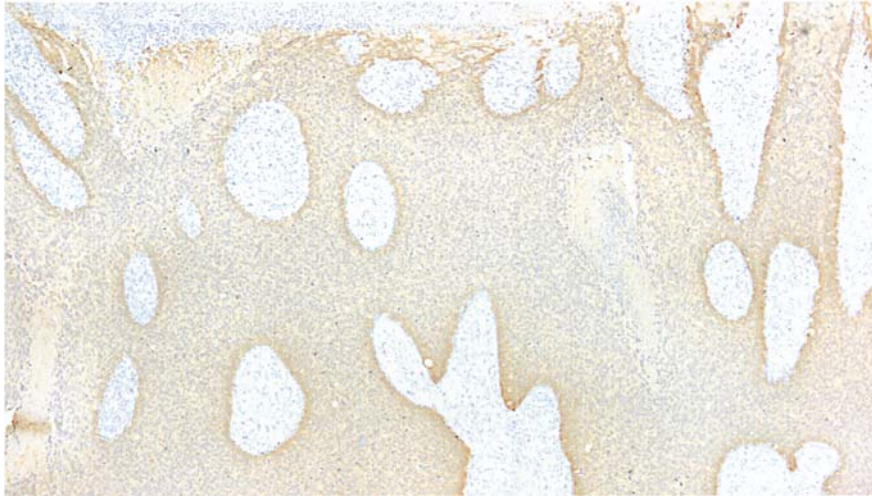


Figure 3. Immunohistochemical staining of CK10 in case 1 (IEEPC) (original magnification x40): Tumor cells are positive for CK10.

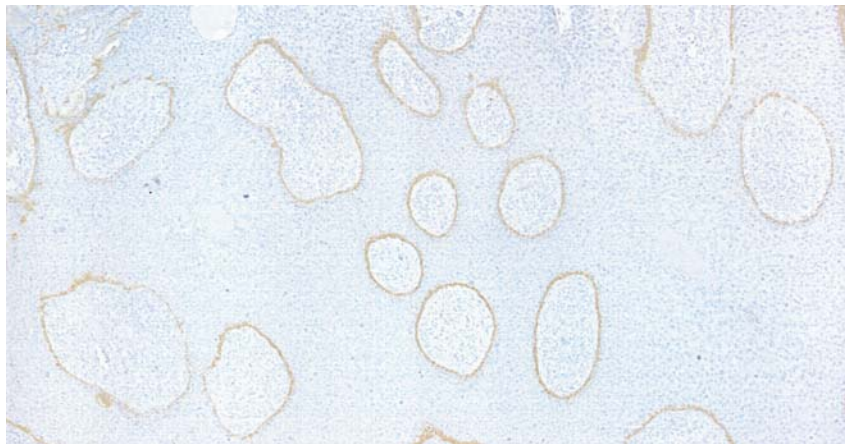


Figure 4. Immunohistochemical staining of CK14 in case 1 (IEEPC) (original magnification x40): CK14 is not expressed in tumor cells, but in basal cells.

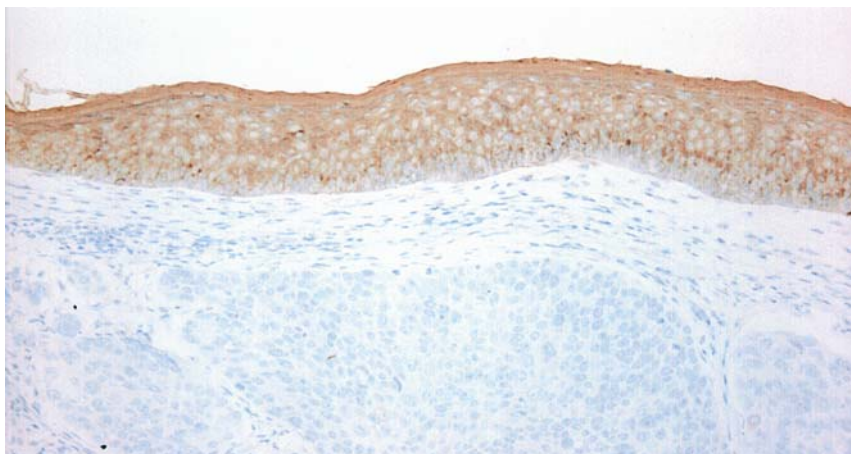


Figure 5. Immunohistochemical staining of CK1 in case 2 (IDEPC) (original magnification x100): CK1 is expressed in the suprabasal layer of the epidermis, but tumor nests were negative for CK1.

layer (Fig. 4). CK7, 8, 15, 16, 17, 18 and 19 were undetectable.

In case 2, opposed to case 1, CK1 (Fig. 5) and CK10 were not detectable in tumor nests. CK14 was positive in the

tumor cells, with an especially high intensity in the outermost (basal) layer (Fig. 6). CK15 was present randomly in some tumor cells. CK17 was expressed throughout the tumor nests (Fig. 7). CK18 was strongly positive in the tumor nests (Fig. 8),

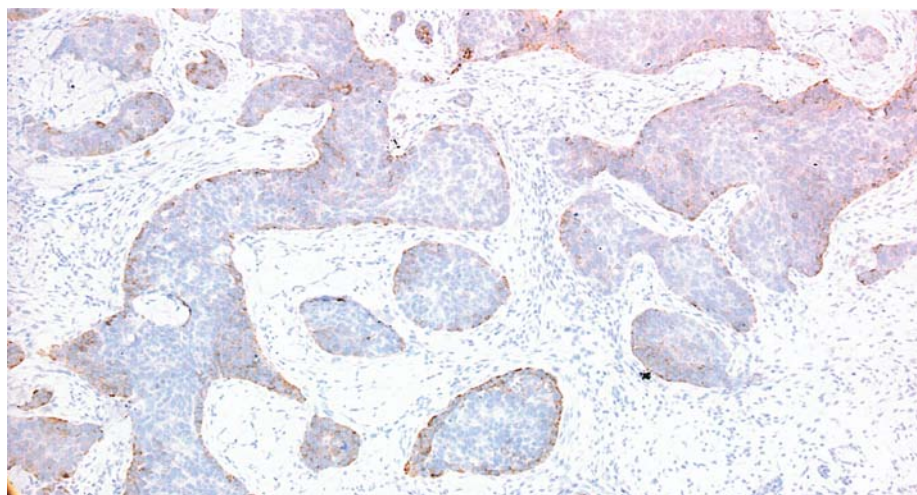


Figure 6. Immunohistochemical staining of CK14 in case 2 (IDEPC) (original magnification x50): CK14 is expressed in the tumor cells with the highest intensity in the outermost (basal) layer.

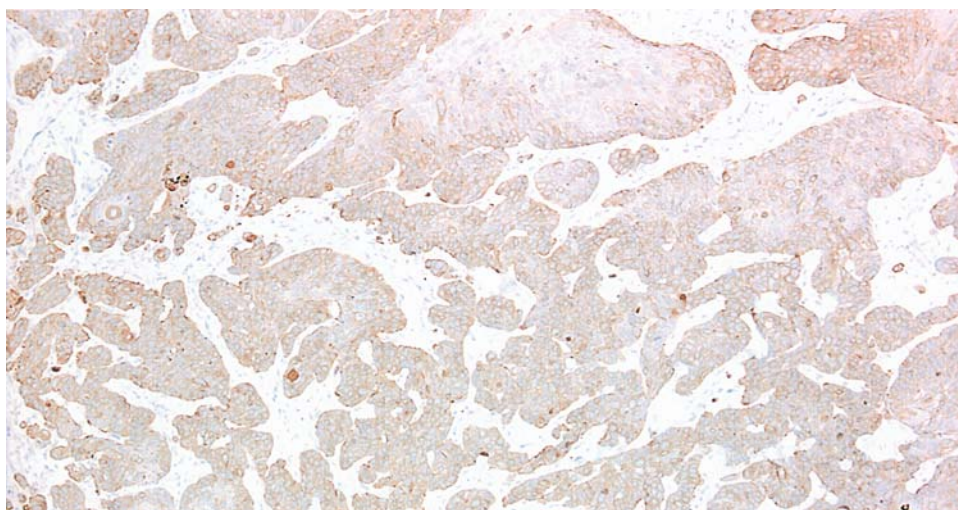


Figure 7. Immunohistochemical staining of CK17 in case 2 (IDEPC) (original magnification x50): CK17 is present in all the layers of tumor nests.

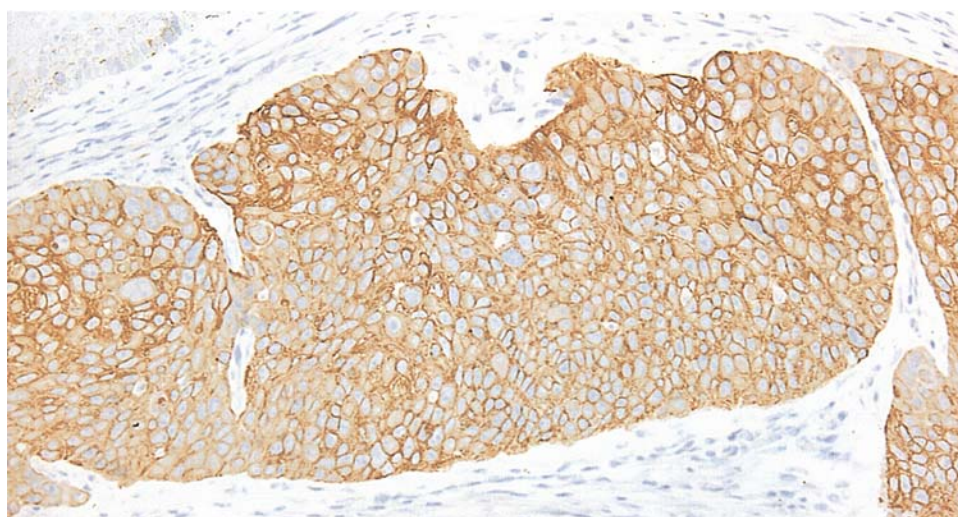


Figure 8. Immunohistochemical staining of CK18 in case 2 (IDEPC) (original magnification x100): CK18 is strongly positive in the tumor nests.

and CK19 was positively detected. CK7 and 8 were weakly positive. However, CK16 was undetectable.

Discussion

EPC is believed to be a tumor originating from the acrosyringium, based on its morphological characteristics (1). Histopathologically, EPC is classified into two entities: Intraepidermal EPC (IEEPC) and intradermal EPC (IDEPC). Case 1 was diagnosed as IEEPC, and case 2 as IDEPC. CK expression in normal sweat glands has been reported previously (10,11,13).

In case 1 (IEEPC), the tumor cells displayed the differentiated epidermal keratins CK1 and 10, and lacked the undifferentiated keratin of CK14. Simple epithelial or embryonic keratins such as CK7, 8 and 18 were undetectable in the tumor cells. Hyperproliferative keratins such as CK16 and 17 were also negative. In general, CK1 and 10 expressions are reduced in carcinoma because of impaired differentiation. The CK expression pattern of case 1 (IEEPC) supports more differentiated characteristics with indolent prognosis. Tazawa *et al* (13) reported the presence of differentiated keratin (CK10) and the absence of CK7, 8, 18 and 19 in IEEPC (intraepithelial nests). Our results are consistent with this report (10).

Case 2 lacked the differentiated keratins (CK1 and 10) and expressed the simple epithelial keratins (CK7, 8, 18 and 19), undifferentiated basal keratin (CK14) and hyperproliferative keratin (CK17). The presence of CK7, 8, and 18 indicate non-differentiation and hyperproliferation in EPC. Subsequently, this supports a poor prognosis of IDEPC. The present study clearly revealed the difference in keratin profiles of IEEPC and IDEPC. The difference in the origin of IEEPC and IDEPC is not conclusive in the present study.

Concerning CK expression in the acrosyringium, periluminal cells are positive for CK1 and 10, and negative for CK19. In the tumor cells in IEEPC, CK1 and 10 were expressed, and CK19 was not detected. Therefore, IEEPC may arise from either the periluminal cells in the acrosyringium or the spinous cells in suprabasal layers in the epidermis.

In our case of IDEPC, the Borst-Jadasson appearance was found in H&E staining. In hidroacanthoma simplex (HS), the Borst-Jadasson appearance is generally observed (14). Therefore, case 2 resembled HS because of the Borst-Jadasson appearance. In case 2, CK1 and 10 were not expressed. Instead, CK14 and 17 were expressed in IDEPC. We have previously reported CK expression (12) in HS which possessed CK14 and 17 without CK1, 8, 10, 18 and 19. In our case, we speculated that IDEPC arose from HS, and the keratin expression of CK8, 18 and 19 may be related to the malignant transformation from HS to IDEPC. EPC may arise from HS (15,16). In IDEPC, simple epithelial or embryonic keratins are expressed. Markey *et al* (17) reported that differentiation-specific keratins were delayed or lost in dysplastic lesions, and that embryonic or simple epithelial keratins (CK8 and 18) were observed in the intra-dermal areas in poorly differentiated squamous cell carcinoma.

Watanabe *et al* (18) also reported that the simple epithelial CK expression in cutaneous squamous cell carcinoma may be a marker for its capability of invasion and metastatic potential. We suggest that the difference in CK expression between IEEPC and IDEPC correlates with the malignancy of keratinocytes, tumor invasion and the change of epithelial-mesenchymal interaction as reported previously (17). Our present study showed expansion of tumor cells in different differentiation levels.

Further investigation is necessary to evaluate the clinical prognosis and CK expression of EPC.

References

1. Hashimoto K, Mehregan AH and Kumakiri M: Tumors of the skin appendages. Butterworth, Boston, pp15-18, 1987.
2. Klein W, Chan E and Seykora JT: Tumors of the epidermal appendages. In: Lever's Histopathology of the Skin. Elder DE, Elenitsas R, Johnson BL Jr and Murphy GF (eds). 9th edition. Lippincott-Raven, Philadelphia, pp902-903, 2004.
3. Brenn T and McKee PH: Eccrine porocarcinoma. In: Pathology of the skin. McKee PH, Calonje E and Granter SR (eds). 3rd edition. Elsevier Mosby, pp1622-1627, 2005.
4. Moll R, Franke WW, Schiller DL, *et al*: The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 31: 11-24, 1982.
5. Markey AC, Lane EB, MacDonald DM and Leigh IM: Keratin expression in basal cell carcinomas. Br J Dermatol 126: 154-160, 1992.
6. Lane EB, Bartek J, Purkis PE and Leigh I: Keratin antigens in differentiating skin. Ann NY Acad Sci 455: 241-258, 1995.
7. Jih DM, Lyle S, Elenitsas R, *et al*: Cytokeratin 15 expression in trichoepitheliomas and a subset of basal cell carcinomas suggests they originate from hair follicle stem cells. J Cutan Pathol 26: 113-118, 1999.
8. Lindberg K and Rheinwald JG: Suprabasal 40kd keratin (K19) expression as an immunohistologic marker of premalignancy in oral epithelium. Am J Pathol 134: 89-98, 1989.
9. Kurokawa I, Nishijima S, Kusumoto K, *et al*: Cytokeratin expression in steatocystoma multiplex. Br J Dermatol 146: 534-536, 2002.
10. Kurokawa I, Mayer-da-Silva A and Gollnick H: Presence of cytokeratins in human sweat gland epithelia - an immunohistochemical study of monoclonal antibodies KL1, CK8.60, PKK2, CK8.12, CK8.13, CK4.62, and RPN 1160 using APAAP technique. J Dermatol 15: 308-315, 1988.
11. Langbein L, Rogers MA, Praetzel S, Cribier B, Peltre B and Gössler N: Characterization of novel human type II epithelial keratin K1b specifically expressed in eccrine sweat glands. J Invest Dermatol 125: 428-444, 2005.
12. Kurokawa I, Nishijima S, Kusumoto K, Senzaki H, Shikata N and Tsubura A: A case report of hidroacanthoma simplex with an immunohistochemical study of cytokeratins. Int J Dermatol 44: 775-776, 2005.
13. Tazawa T, Ito M, Fujiwara H, Imai S, Akai S and Niizuma K: Monoclonal antibody analysis of keratin expression in carcinoma of sweat glands. J Cutan Pathol 19: 407-415, 1992.
14. Brenn T and McKee PH: Hidroacanthoma simplex. In: Pathology of the skin. McKee PH, Calonje E and Granter SR (eds). 3rd edition. Elsevier Mosby, pp1617-1619, 2005.
15. Ishikawa K: Malignant hidroacanthoma simplex. Arch Dermatol 104: 529-532, 1971.
16. Bardach H: Hidroacanthoma simplex *in situ* porocarcinoma: A case suggesting malignant transformation. J Cutan Pathol 5: 236-248, 1978.
17. Markey AC, Lane EB, Churchill LJ, MacDonald DM and Leigh IM: Expression of simple epithelial keratins 8 and 18 in epidermal neoplasia. J Invest Dermatol 97: 763-770, 1991.
18. Watanabe S, Ichikawa E, Takahashi H and Otsuka F: Changes of cytokeratin and involucrin expression in squamous cell carcinomas of the skin during progression to malignancy. Br J Dermatol 132: 730-739, 1995.