

CASE REPORT

Sebaceous carcinoma of skin expressing KIT and PDGFRA

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ABSTRACT

Only a little is known about expressions of KIT (CD117) and platelet-derived growth factor-alpha (PDGFRA) in sebaceous carcinoma of skin; recently one report showed expression of KIT in 12/13 (92.3%) in sebaceous tumors. No reports of PDGFRA in sebaceous tumors are present. An 82-year-old woman presented a face tumor. Physical examination revealed a polypoid tumor measuring 0.8 cm × 0.7 cm × 0.7 cm with reddish ulcerations in cheek skin. A biopsy was diagnosed as basal cell carcinoma (BCC) with sebaceous differentiation by the pathologist. Further excision of the tumor with wide margins was performed. Histologically, the tumor was polypoid and located in dermis. The epidermis showed ulceration. The tumor was composed of solid nests of atypical cells showing invasive features into dermis. The margins were negative for tumor cells, and no lymphovascular invasion were seen. Numerous islands of bubbly sebaceous atypical cells were seen within solid carcinoma cells with hyperchromasia and nucleoli. Numerous mitotic figures including atypical ones were seen. Focal areas show trichilemmal keratinization. Histochemically, no mucins, argyrophil cells, or argentaffin cells were seen. Immunohistochemically, tumor cells were positive for cytokeratin (CK) AE1/3, CK 34BE12, CK5, CK6, CK14, p63, KIT, PDGFRA, MET, ErbB2, p53 and Ki-67 (labeling index = 82%). The tumor cells were negative for CK CAM5.2, CK7, CK8, CK18, CK19, synaptophysin, chromogranin, NSE, NCAM, S100 protein, vimentin, α -smooth muscle actin, CD34, D31, HMB45, MUC1, MUC2, MUC5AC, and MUC6. The author diagnosed the tumor as sebaceous carcinoma. The patient is now well and has no tumor 18 months after the operation.

Key Words: Sebaceous carcinoma, Skin, Histopathology, KIT, Platelet-derived growth factor-alpha, Immunohistochemistry

1. INTRODUCTION

Sebaceous carcinoma (SC) of skin is defined as a cytologically and/or architecturally malignant neoplasm demonstrating exclusively sebaceous differentiations.^[1] Patients with SC are usually old adults with a mean age of 62 years.^[1] Female is more often affected with male, to female ratio of 1:2.^[1] The preferential sites of locations are ocular tissues and eyelid, followed in order by skins of head and neck, trunk, genitalia, and extremities.^[1] Rare cases were reported in mouth, salivary glands, lungs and breast.^[1]

The protein of KIT (aka SCFR and CD117) and platelet-derived growth factor-alpha (PDGFRA) are transmembranous receptor tyrosine kinases involved in signal transduction. KIT is the name of KIT gene, and it is not an abbreviation. They are encoded by KIT and PDGFRA genes, both mapped on the chromosome site 4q12, both of which are involved in tumorigenesis of various tumors including gastrointestinal stromal tumor (GIST), malignant melanoma, germ cell tumors, and hematopoietic malignancies.^[2-5]

The expressions of KIT and PDGFRA and their genes' status

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in SC of skin have rarely been investigated.^[6-9] Goto^[8] reported recently that KIT is upregulated in 12/13 (92.3%) of sebaceous skin tumors. Hussein^[9] showed normal expression of KIT protein; its expression was present in keratinocytes (stratum basale), melanocytes, mast cells, sebaceous glands, and sweat glands. In contrast, KIT expression was absent in stratum spinosum, stratum granulosum, stratum corneum, blood vessels and arrector pili muscle.^[9] Herein reported is a rare case of SC of the skin face with expression of KIT and PDGFRA.

2. CASE REPORT

An 82-year-old woman had rapidly growing tumor of the cheek skin and consulted our hospital. Physical examination revealed a polypoid tumor measuring 0.8 cm × 0.7 cm × 0.7 cm with reddish ulcerations. A biopsy was taken, and the

biopsy was diagnosed as basal cell carcinoma (BCC) with sebaceous differentiation by the pathologist. Further excision of the tumor with wide margins was performed.

Histologically the tumor was located in the dermis, and was polypoid (see Figure 1A). The epidermis showed ulceration; thus, the relationship between the tumor and epidermis was not clear. The tumor was composed of solid nests of atypical cells regarded as malignant (see Figure 1B). Invasive features into the dermis were seen in some places (see Figure 1C). The margins were negative for tumor cells, and no lymphovascular invasion were noted. Numerous islands of bubbly sebaceous atypical cells were recognized within the solid carcinoma cells with hyperchromasia and nucleoli (see Figures 1A-D). Numerous mitotic figures, including atypical mitosis were present. Focal areas showed trichilemmal keratinization (see Figure 1D).

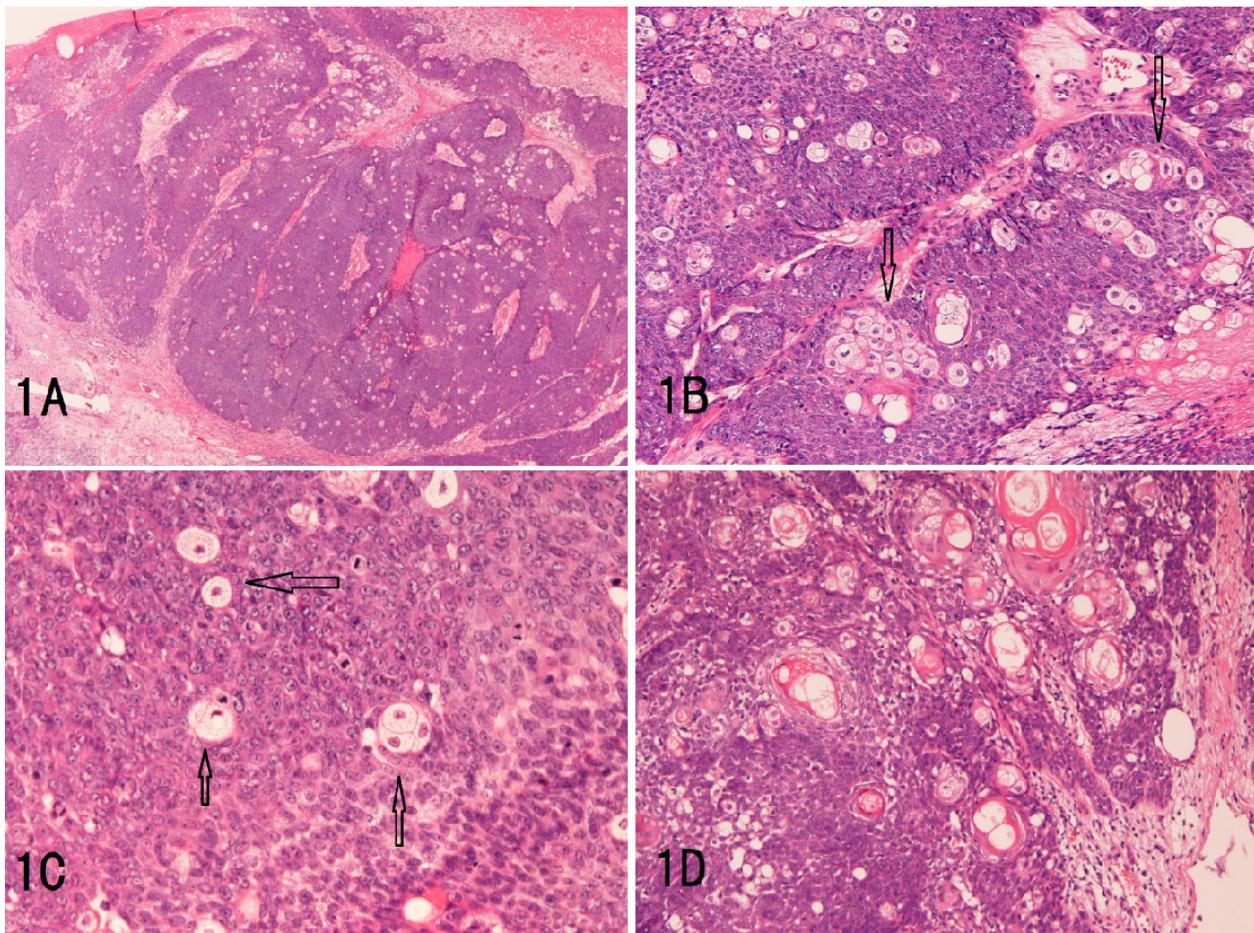


Figure 1. Histologic features sebaceous carcinoma of the skin

A: A very low power view. The cutaneous tumor is composed of medullary malignant tumor arranged in solid sheets. The epidermis is erosive and desquamated. A: HE staining, ×20 magnification; B and C: The tumor is composed of solid sheet of malignant cells with hyperchromatic nuclei and nucleoli. The apparent sebaceous differentiation is seen (bubbly cells) (arrows). The bubbly cells also show strong atypical features. Numerous mitotic figures, including atypical ones are seen. Focal areas show small keratinizations. HE staining, B: ×100 magnification. C: ×200 magnification; D: Trichilemmal keratinization is seen in focal areas. HE staining, ×200 magnification.

A histochemical study was performed, as previously reported. No mucins or argyrophilic and argentaffin cells were present. Glycogens were present in tumor cells. An immunohistochemical study was performed with the use of EnVision System method (Dako®), which consist in a two-step visualization systems of very high sensitivity, based on a unique enzyme-conjugated polymer backbone, which, in addition, also carries secondary antibody molecules, as previously reported in other literatures.^[2-5] Tumor cells were positive for cytokeratin (CK) AE1/3, CK 34BE12 (see Figure 2A), CK5, CK6, CK14, p63 (see Figure 2B), KIT (see Figure 2C), PDGFRA (see Figure 2D), MET (see Figure 2E), ErbB2 (see Figure 2F), p53, and Ki-67 (labeling index = 82%). The tumor cells were negative for CK CAM5.2, CK7,

CK8, CK18, CK19, CK19, synaptophysin, chromogranin, NSE, NCAM, S100 protein, vimentin, α -smooth muscle actin, CD34, D31, HMB45, CEA, CA19-9, MUC1, MUC2, MUC5AC, and MUC6. Immunostainings seemed important for SC such as epithelial membrane antigen (EMA), BerEP4, androgen receptor (AR), gross-cystic fluid-15 (GCDFP-15), BRST-1^[10,11] were not done simply because of the author did not have the antibodies. The molecular genetic analysis, which was done by PCR-direct sequencing as previously reported^[2-5] identified no mutations of *KIT* and *PDGFRA* gene. The author diagnosed the lesion as SC of face skin. The patient is well and has no tumor 18 months after the operation.

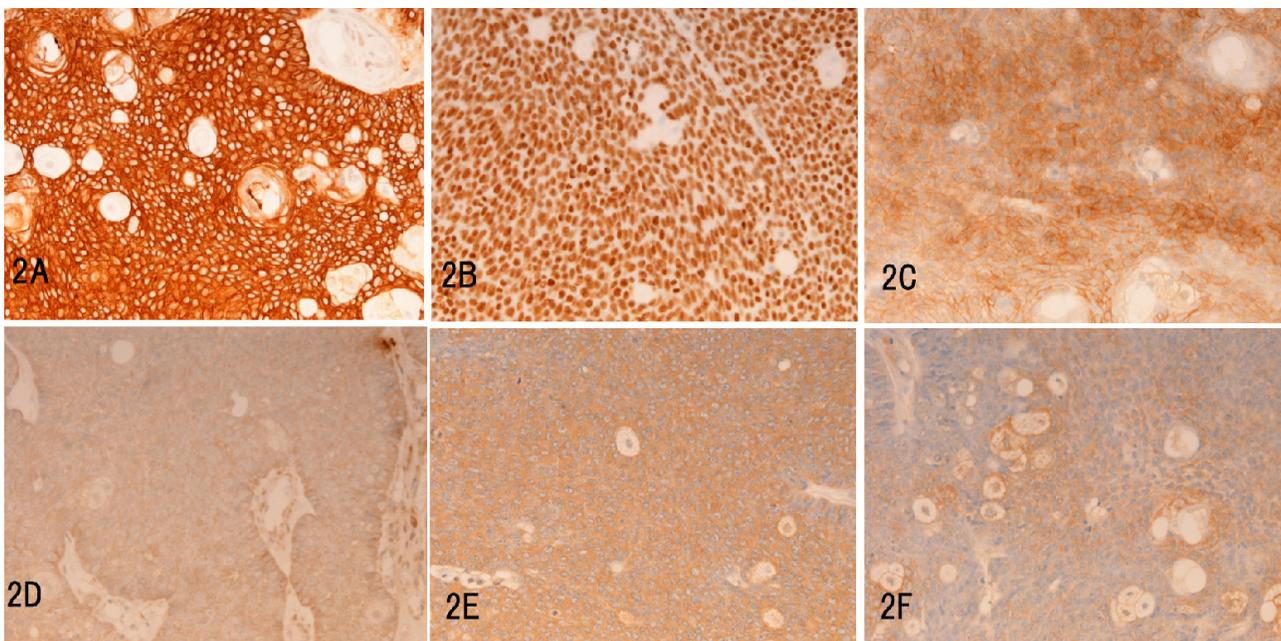


Figure 2. Immunohistochemical features of sebaceous carcinoma of the skin. The tumor cells are positive for CK34BE12 (A), p63 (B), KIT (C), PDGFRA (D), MET (E), and ErbB2 (F). A-F: $\times 200$.

3. DISCUSSION

The present skin tumor fulfills the criteria of SC of WHO.^[1] The first biopsy diagnosis was BCC with sebaceous differentiation, and the second diagnosis of resected skin was SC, reflecting the difficulty in biopsy diagnosis of SC. SC must be differentiated from BCC with sebaceous differentiation and sebaceoma. The present study showed significant atypia regarded as malignancy, and numerous mitotic figures were seen. In addition, the present tumor showed microinvasive features. Immunohistochemically, p53 was positive and Ki-67 showed very high labeling index. Thus, the present case is malignant and is not sebaceoma or sebaceous adenoma. The present tumor is not squamous cell carcinoma (SCC) because of lack in keratinization and intercellular

bridges. It is not BCC because of the presence of bubbly cells, though immunostaining of Ber-EP4 was not done.

The author diagnosed the present tumor as SC; however, differential diagnosis from BCC with sebaceous differentiation (SD) is very difficult and may be controversial among pathologists.^[12] The author prefers the diagnosis of SC. Apparently, the present tumor is a malignant tumor with sebaceous differentiation. However, all tumor cells are not composed of “bubbly” cells. “Bubbly” cells were seen in islands of solid tumor nests. The areas other than “bubbly” cells showed no apparent differentiation. Regarding this aspect, the case does not fulfill criteria of SC completely and other immunohistochemical data are not fully compatible

with SC. However, the non-bubbly cells are larger and have more severe atypia than basaloma cells of BCC. In addition, the tumor lacked peripheral nuclear palisadings and cleft formations, characteristics of BCC. In addition, the tumor showed micro-invasion which is usually not seen in BCC except invasive variant of BCC. From these reasons, a diagnosis of SC was made. Focal keratinizations characterized as trichilemmal keratinizations were seen in the tumor. This does not reflect SCC differentiation but shows trichilemmal differentiation. Because the hair and sebaceous glands are closely associated with each other in location, morphology and development of normal anatomy, this finding supports the diagnosis of SC.

The present tumor showed no mucins, argentaffin cells, or argerophylic cells, suggesting no differentiation into appendage and into endocrine lineages. Immunohistochemically, the tumor cells showed predominant expression of high molecular weight cytokeratins. No low-molecular weight cytokeratins (CK CAM5.2, CK7, CK8, CK18, and CK19) were seen. Although there have been a few comprehensive studies of CKs in SC,^[13-15] it seems possible that SC largely expresses high-molecular-weight CKs.^[13,14] The present findings suggested that SC is composed of only high molecular weight CK (CK AE1/3, CD34BE12, CD5, CD6, and CD14) in the CK profile, being compatible with those of studies.^[13,14] P63 was positive; this p53-related molecule is expressed in BCC, SCC, SC, and myoepithelial carcinoma. Namely, p63 is expressed in epithelial cells with high molecular weight cytokeratins. In the case presented here, synaptophysin, chromogranin, NSE, NCAM, and S100 protein were negative; therefore there were no neuroendocrine differentiation. In the present tumor, S100 protein, vimentin, α -smooth muscle actin, CD34, D31 and HMB45 were negative, implying that it is not melanoma and has no smooth muscle, vascular, and mesenchymal differentiations. In the case report described here, CEA, CA19-9, MUC1, MUC2, MUC5AC, and MUC6 were negative, indicating that the tumor does not display features of adenocarcinoma or skin appendage (apocrine and eccrine glands) lineages.

The most important findings are the positive expressions of KIT, PDGFRA, ErbB2, and MET in the tumor. In the skin, KIT is basically expressed in basal cells, mast cells, BCC, and adenoid cystic carcinoma.^[9,16] The present case may raise the possibility that SC is listed in KIT-positive tumors. Similar situations are conceivable in PDGFRA. The tumor revealed no mutations of KIT and PDGFRA genes. Positive expressions of KIT and PDGFRA proteins and negative gene mutations of KIT and PDGFRA in the present SC is the first

case report. Description of more case reports, systematic studies of KIT and PDGFRA protein functions, and molecular studies of KIT and PDGFRA genes in SC are needed.

As is well known, KIT, PDGFRA, MET, and ErbB2 are transmembranous receptor tyrosine kinases, whose ligands are stem cell factor (SCF), platelet-derived growth factor- α (PDGF α), hepatocyte growth factor (HGF), and epidermal growth factor (EGF), respectively.^[17-27] The positive immune-expressions of these kinases may suggest malignant nature of the present tumor because the enzyme activities of these kinases are high in malignant tumor and developmental organs.^[17-27] In addition, they are frequently expressed in stem cells and cancer stem cells,^[17-27] pausing the possibility that the present tumor may contain cancer stem cells or that it may be a stem cell cancer. Tumor growth and progression requires these signaling molecules of growth factors and their receptors.^[17-27] Therefore, in this case also, the signaling pathways of SCF/KIT, PDGF α /PDGFRA, HGF/MET and EGF/ErbB2 seem to play roles in the oncogenesis and tumor progression.

Recently, molecular targeting or antibody drugs have been developed against various signal transduction molecules, and they may be effective in some malignancies. The molecular targeting agents of KIT is imatinib (Gleevec), which is effective in GIST, acute myeloid leukemia and chronic myeloid leukemia.^[28] The molecular targeting of ErbB2 is trastuzumab (Herceptin) and is now being used in patients with breast cancers positive for HER2/neu.^[28] There are tendencies that these drugs are more effective in cases with activating mutations of the genes than cases without gene mutations.^[28] In this report, proteins of KIT and ErbB2 were detected in tumor cells, raising the possibility that SC in the present patients can be treated by imatinib and trastuzumab, though general confirmation of the effectiveness await further studies. Finally, p53 was strongly positive, indicating the p53 gene mutations and malignant potentials.^[29] The high Ki-67 labeling index (82%) indicates that the present tumor has rapid cell proliferation and malignant natures.

In conclusion, a rare case of SC is reported and its differential diagnosis was discussed. The tumor had only high molecular weight CKs and has no low molecular weight CKs. The SC has no neuroendocrine features. p53 was positive, suggesting p53 gene mutations in this tumor. The SC expressed receptor tyrosine kinases of KIT, PDGFRA, MET and ErbB2. No mutations at genomic level of KIT and PDGFRA were noted. These receptor tyrosine kinases seems to play roles in initiation and progression of the present cases of SC.

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