

Case Report

Primary cutaneous small cell carcinoma; a case report with differential diagnosis

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Abstract: Primary cutaneous small cell carcinoma (PC-SmCC) is extremely rare; only two cases have been reported in the world literatures. A 79-year-old woman presented a small cutaneous tumor in the face. Physical examination showed a tumor measuring 1.0x.08x0.6 cm in the shallow skin of the face. Excisional skin biopsy was performed. The biopsy showed complete excision of the tumor. The tumor was located in the shallow dermis and no connections to epidermis were seen. The tumor was invasive into subcutaneous tissue and surrounding dermis. The tumor was very hypercellular tumor composed of small cells with scant cytoplasm, hyperchromatic nuclei, negative nucleoli, and molded nuclei. The shapes of tumor cells are round, ovoid or spindle. The histological appearances fulfilled the criteria of SmCC of WHO. Immunohistochemically, the tumor cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK34BE12, CD5, CD6, CK8, p63, NSE, NCAM, synaptophysin (focal), chromogranin (focal), p53, KIT, PDGFRA and Ki-67 (labeling index (LI)=86%). They were negative for CK7, CK19, CK20, EMA, vimentin, CEA, S100 protein, CA19-9, TTF-1, MUC1, MUC2, MUC5AC and MUC6. Mucin histochemistry revealed no mucins. A molecular genetic analysis of PCR-direct sequencing identified no mutations of *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) genes. The author diagnosed this cutaneous tumor as SmCC. Post-diagnosis whole body examination using various imaging and endoscopic techniques revealed no tumors. This may confirm that the skin tumor was primary. The cutaneous tumor was completely resected with wide margins. The patient is now followed up without therapy 8 months after the diagnosis. No recurrence or metastasis is seen. The differential diagnosis from Merkel cell carcinoma and basal cell carcinoma is very difficult and herein discussed.

Keywords: Skin, small cell carcinoma, basal cell carcinoma, Merkel cell carcinoma

Introduction

Primary cutaneous small cell carcinoma (PC-SmCC) is an extremely rare tumor; only two cases have been reported in the English literature [1, 2]. Like small cell lung carcinoma (SCLC), PC-SmCC shows aggressive biological behaviors and the prognosis was poor [1, 2]. However, the clinicopathological data and patient outcome are not established because of its extreme rarity.

The author reports herein a case of PC-SmCC. The pathological diagnosis was very difficult because of the rarity of PC-SmCC and also because the concept of PC-SmCC is not established. It is not listed in WHO blue book of skin tumors. In addition, the author felt difficulties in the differential diagnosis from basal cell carcinoma (BCC) and Merkel cell carcinoma (MCC).

Case report

A 79-year-old woman presented a small cutaneous tumor of the face. Physical examination showed a tumor measuring 1.0x.08x0.6 cm in the shallow skin of the face. Excisional cutaneous biopsy was performed. The biopsy showed complete excision of the tumor.

The tumor was located in the shallow dermis and no connections to epidermis were seen (**Figure 1A**). The tumor was very hypercellular tumor composed of small cells with scant cytoplasm, hyperchromatic nuclei, negative nucleoli, and molded nuclei (**Figure 1A-F**). The tumor cells were round or spindle in shape. The borders of cell nests were ragged. No palisading nuclei and cleft formations as seen in basal cell carcinoma (BCC) were seen. No characteristic vesicular nuclei as seen in Merkel cell carcinoma

Skin small cell carcinoma

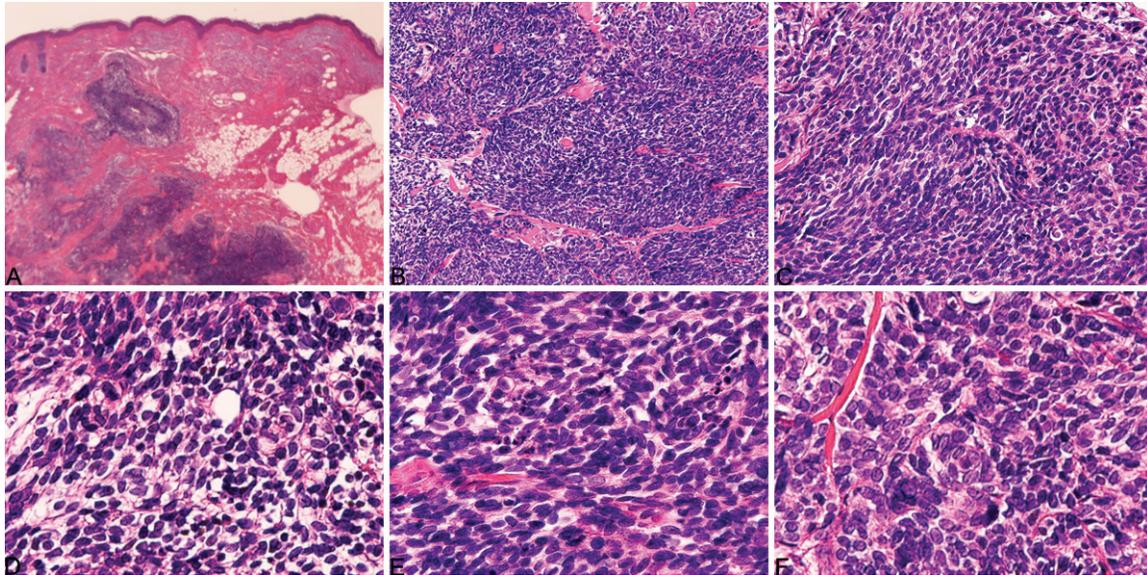


Figure 1. Histology of the tumor. The tumor cells are located in the shallow dermis. The tumor cells form cellular irregular clusters, where the periphery shows invasive features. The tumor itself is also invasive into the subcutis and surrounding dermis. The cellular clusters are highly cellular. No nuclear palisading or cleft formations as seen in basal cell carcinoma are seen. The tumor cells characteristically very small and ovoid and spindle shaped. There are many mitotic and apoptotic bodies. The cytoplasm of the tumor cells is very scant. The nuclei are characteristically molded and very hyperchromatic. No nucleoli are seen. No differentiation is seen. The shape of the tumor cells fulfills the criteria of small cell carcinoma of EHO, but it also resembles embryonic stem cells in human embryo. All HE: A: x20. B: x100, C: x200. D: x400. E: x400.

ma (MCC) were noted. No differentiations were seen, including squamous cell carcinoma (SCC) differentiation. The histological appearances fulfilled the criteria of SmCC of WHO [3].

Immunohistochemically, the tumor cells were positive for cytokeratin (CK) AE1/3 (**Figure 2A**), CK CAM5.2, CK34BE12 (**Figure 2B**), CD5, CD6, CK8, p63 (**Figure 2C**), NSE (**Figure 2D**), NCAM (**Figure 2E**), synaptophysin (focal) (**Figure 2F**), chromogranin (focal) (**Figure 2G**), p53 (**Figure 2H**), KIT (**Figure 2I**), PDGFRA (**Figure 2J**) and Ki-67 (labeling index (LI)=86%) (**Figure 2K**). They were negative for CK7, CK19, CK20, EMA, vimentin, CEA, S100 protein, CA19-9, TTF-1, MUC1, MUC2, MUC5AC and MUC6. Mucin histochemistry revealed no mucins.

A molecular genetic analysis of *KIT* gene (exons 9, 11, 13, and 17) and *PDGFRA* gene (exons 12 and 18) was performed by the PCR direct sequencing method, as previously reported. This was performed because the tumor cells were positive for KIT and PDGFRA. The author always investigates the mutational status of these two genes when the author encounters tumors positive for KIT and PDGFRA. This is because, if activating mutations were found,

imatinib mesylate, a gene targeting drug, may be effective. The exons of both genes were selected because they are frequent mutation sites. The primers were used as previously reported, and were shown in **Table 1**. In brief, the genomic DNA was extracted from the paraffin sections containing the SmCC cells with proteinase K digestion and phenol/chloroform extraction, and subjected to PCR for 40 cycles (94°C for one minute, 52°C for one minute, 72°C for one minute), using a thermal cycler (GeneAmp PCR system 9700, Applied Biosystems, ABI, CA). The annealing temperature was 53°C. PCR products were extracted, and subjected to a computed automatic DNA sequencer (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems, ABI, CA). Two cases of gastric GIST and two cases of uterine leiomyoma were used as positive controls and negative controls, respectively.

The molecular analysis revealed no mutations of genes of *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) genes in this cutaneous tumor, Imatinib may be ineffective.

The post-diagnosis whole body examinations using various imaging and endoscopic tech-

Skin small cell carcinoma

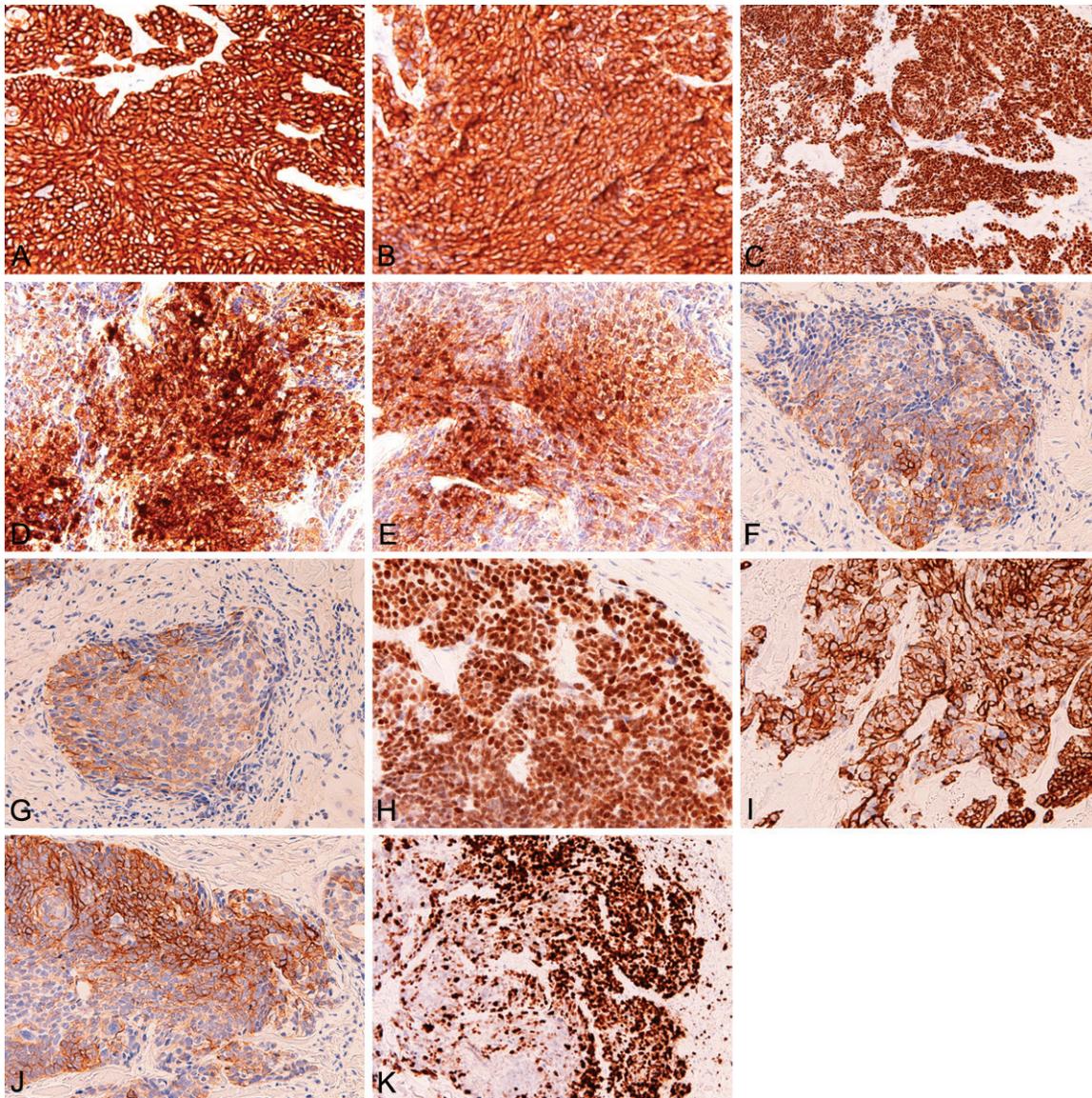


Figure 2. Immunohistochemical findings of the tumor. The tumor cells were positive for cytokeratin (CK) AE1/3 (A), CK CAM5.2, CK34BE12 (B), CD5, CD6, CK8, p63 (C), NSE (D), NCAM (E), synaptophysin (focal) (F), chromogranin (focal) (G), p53 (H), KIT (I), PDGFRA (J) and Ki-67 (labeling index (LI)=86%) (K). They were negative for CK7, CK19, CK20, EMA, vimentin, CEA, S100 protein, CA19-9, TTF-1, MUC1, MUC2, MUC5AC and MUC6. Mucin histochemistry revealed no mucins.

niques revealed no tumors. This confirmed that the skin tumor was primary. The cutaneous tumor was completely resection, and the margins were negative for tumor cells. The patient is now followed up without chemoradiation therapy 8 months after the diagnosis. No recurrence or metastasis is seen.

Discussion

The present tumor was composed of small round and spindle cells. The tumor cells had

very scant cytoplasm, molded nuclei, hyperchromatic nuclei, and inconspicuous or absent nucleoli. These histological features are those of SmCC. SmCC is defined only by histologically findings. That is, SmCC of any locations is defined as epithelial malignant neoplasm consisting of very small cells with scant cytoplasm, hyperchromatic nuclei, molded nuclei, and absent nucleoli [3]. SmCC may frequently shows spindle shaped nuclei and frequently shows characteristic degeneration in biopsy, surgical and autopsy specimens. More than 90% of

Skin small cell carcinoma

Table 1. Primer sequence

Forward	Reverse
<i>KIT</i> exon 9	
5'-TCC TAG AGT AAG CCA GGG CTT-3'	5'-TGG TAG ACA GAG CCT AAA CAT CC-3'
<i>KIT</i> exon11	
5'-GAT CTA TTT TTC CCT TTC TC-3'	5'-AGC CCC TGT TTC ATA CTG AC-3'
<i>KIT</i> exon 13	
5'-GCT TGA CAT CAG TTT GCC AG -3'	5'-AAA GGC AGC TTG GAC ACG GCT TTA-3'
<i>KIT</i> exon 17	
5'-CTC CTC CAA CCT AAT AGT GT-3'	5'-GTC AAG CAG AGA ATG GGT AC-3'
<i>PDGFRA</i> exon12	
5'-TTG GAT ATT CAC CAG TTA CCT GTC-3'	5'-CAA GGG AAA AGC TCT TGG-3'
<i>PDGFRA</i> exon 18	
5'-ACC ATG GAT CAG CCA GTC TT-3'	5'-TGA AGG AGG ATG AGC CTG ACC-3'

SmCC shows neuroendocrine features. In the present case, apparent neuroendocrine features were seen; the tumor cells were positive for NCAM, NSE, synaptophysin, chromogranin, KIT and PDGFRA. Thus, it appears that the diagnosis SmCC is correct. With regard to small cell carcinoma, please refer to the author's numerous papers.

However, the immunohistochemical findings of positive high molecular weight CK including CK 34BE12, CK5, and CK6 and p63 are findings of basal cell carcinoma (BCC). BCC may show neuroendocrine differentiations and may express KIT and PDGFRA. Although no typical features of BCC such as cleft formations and peripheral nuclear palisading were seen, the tumor cells can be regarded as basaloid. However, the tumor cells of the present case had much more atypia and much more resembled SmCC cells than basaloid cells of BCC. Thus, it is possible that BCC be denied completely. The high molecular weight CK and p63 are markers of BCC, SCC, urothelial carcinoma (UC) and basal cells or any organs, myoepithelial cells of any organs and myoepithelial carcinoma. Therefore, it can be concluded that PC-SmCC may express p63 and high molecular weight CK.

The second differential diagnosis is from Merkel cell carcinoma (MCC). The only neuroendocrine carcinoma (NEC) and neuroendocrine tumor (NET) of the skin is MCC in the WHO blue book. The neuroendocrine features (NEF) are very difficult to define. A significant percentage of carcinomas of any organs show NEF. In the skin, BCC and SCC frequently show NEF. Thus,

the distinction between carcinoma with NEF and NEC became obscure. In general, it was unwritten consensus that a certain carcinoma with > 50% NEF is regarded as NEC, and that with < 50% NEF as carcinoma with NEF. In the present study, the NSE and NCAM apparently exceeded 50% of

tumor cells, although those of the synaptophysin and chromogranin were around 50%. It should be kept in mind that now KIT and PDGFRA are regarded as neuroendocrine antigens or markers. Thus, the present case is certainly NEC. Please refer to the author's numerous papers in these aspects.

The most important point of the present study is differentiation from MCC. The nuclei of MCC are characteristic. It shows very hyperchromatic vesicular nuclei. In MCC, nuclei may be present, while nucleoli is usually absent in SmCC, This absence of nucleoli is one of the most characteristic feature of SmCC. In the present tumor, nucleoli are basically absent. Another characteristic of MCC is its positive reaction to CK20. CK20 in MCC shows very characteristic perinuclear dotted pattern, which is the most sensitive and specific findings of MCC. The present tumor was negative for CK20. Thus, the present tumor is not MCC. Because no description of primary cutaneous SmCC is now listed in the WHO blue book and it was extremely rare, meticulous differential diagnoses are mandatory in making the diagnosis of primary cutaneous SmCC.

The present cutaneous tumor must be differentiated from cutaneous metastasis of SCLC and SmCC of extrapulmonary organs. The present tumor was negative for TTF-1, which are almost always positive in SCLC. In the present patient, various imaging modalities and endoscopies identified no tumors in the body. These findings suggest that the present tumor is not metastatic SCLC. TTF-1 is negative in extrapulmonary

SmCC. However, no tumors were clinically found in the body, highly suggesting that the present tumor is primary cutaneous SmCC.

The present tumor was positive for NCAM, KIT, PDGFRA, NSE, synaptophysin, chromogranin, all are antigens or markers of stem cells (SC). Histologically, the present tumor cells very well resemble embryonic stem cells (ESC). Taken together, it is conceivable that the present tumor is SC carcinoma. The concept that SmCC is a kind of SC carcinoma is unclear, but the author, who investigated profoundly the embryonic SC, strongly feels that the SmCC cells closely resemble embryonic SC. This concept is a future problem. In the dynamics of SC in developmental biology, please refer to the author's many references.

SCLC and SmCC of the extrapulmonary organs very frequently express KIT and PDGFRA. For these, please refer to the author's numerous publications. In the present study also, the author investigated the gene status of *KIT* and *PDGFRA*. It was found that no mutations were seen in the hot spots. *KIT* and *PDGFRA*, both mapped to 4q12, encode transmembranous receptor tyrosine kinase oncoproteins called KIT (CD117) and PDGFRA, respectively. Both molecules are transmembranous oncoproteins involved in tumorigenesis, particularly in gastrointestinal stromal tumor. It is famous that SCLC and SmCC of extrapulmonary organs express KIT and PDGFRA, but no mutations at the hot spots of GIST; namely *KIT* gene (exons 9, 11, 13, and 17) and *PDGFRA* gene (exons 12 and 18). In future, mutations of other exons and all introns should be examined in SCLC and SmCC. In GIST, imatinib mesylate, a gene targeting drug, is relatively very effective. However, imatinib has little effect in SCLC. In GIST, many kinds of gain-of-function mutations are seen in

KIT and *PDGFRA* genes. Imatinib appears effective in cases with mutations of *KIT* and *PDGFRA*. Because the *KIT* and *PDGFRA* expression is very characteristics of SCLC and extrapulmonary SmCC, analyses of all exons of introns of the both genes are mandatory. If mutations would be found, creating new molecular targeting drugs are possible. Please refer to numerous excellent papers of Drs. Hirota S, Sihto H, and Miettinen M in this important research field. Also, please refer to the author's numerous papers in this field. This area is very important.

Declaration

The author has no conflict of interest.

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