

Case Report

Pseudomyxoma cutis; a new entity

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Abstract: Pseudomyxoma (PM) implies an accumulation of a large amount of mucins which show myxomatous appearances. PM Peritonei (PMP) is famous and the only example of PM. PMP means excessive accumulation of mucins and mucin-secreting cells in the peritoneal cavity. The causes of PMP are mostly mucinous tumors, both benign and malignant, of ovaries and vermiform appendix. The author experienced excessive accumulation of mucins and mucin-producing cells in the subcutis and deep soft tissue. This situation very resembled PMP. Thus, the author termed the lesion as PM cutis (PMC). A 57-year-old man admitted to our hospital because of multiple subcutaneous large tumors in the perianal skin. The tumors were deeply seated and soft. No biopsy was performed. Very large skin and subcutis resection of the perianal region was done. Grossly, the material was skin and soft tissue flap measuring 25x25x5cm. The subcutis and deep soft tissue were resected. On cut surface, the tumor was slimy liquid. Microscopical examination revealed a large amount of mucins pools and mucin-producing intestinal epithelium with mild atypia. The author diagnosed it metastatic extremely well differentiated adenocarcinoma producing mucins, and pointed out anorectal primary. Thus, Miles operation was performed, which showed tumor formation in the anus. The tumor was located from the submucosa to adventitia, and composed of mucin pools and mucins producing intestinal-type epithelium with atypia. Mucins histochemistry showed that the mucin pools and epithelial cytoplasm contained neutral, carboxylated, and sulfated mucins. Immunohistochemically, the tumor cells were positive for CKAE1/3, CKCAM5.2, CK7, CK8, CK19, CK20, CEA, CA19-9, CD68, MET, p53, MUC2, MUC5AC, KIT, PDGFRA, chromogranin, and Ki-67 (76%). They were negative for CK34BE12, CK5/6, CK14, CK18, EMA, vimentin, desmin, smooth muscle actin, p63, CD34, ER, PgR, CA125, MUC1, MUC6, CD45, CD10, synaptophysin, surfactant Apo-A, TTF-1, NCAM, bcl-2, CDX-2. Although the atypia is mild, the author diagnosed primary anorectal extremely well differentiated adenocarcinoma with excessive production of mucins. The author considers the cutaneous mucins and tumor cells are metastatic or directly invading lesions of the anal tumor. Thus, the author termed pseudomyxoma cutis (PMC) for the cutaneous lesion.

Keywords: Pseudomyxoma, skin, anal, mucins, mucin producing tumor, immunohistochemistry

Introduction

Pseudomyxoma (PM) is a condition of excessive accumulation of a large amount of mucins and mucin-producing epithelial cells [1-3]. The excessive mucins assume features of myxomatous appearances. PM Peritonei (PMP) is the most famous and the only example of PM [1-3]. PMP means excessive accumulation of mucins and mucin-secreting cells in the peritoneal cavity. The causes of PMP are mostly mucinous tumors, both benign and malignant, of ovaries and vermiform appendix. The treatment of PMP is difficult. When excessive amount of mucins accumulated in the peritoneal cavity, the treatment becomes impossible. The mucins of PM

are produced by ovarian and appendiceal epithelial tumors, but the epithelial tumor's morphologies are not definitive [1-3]. Most of the mucin producing tumor showed intermediate morphology between benignity and malignancy. Some are apparently benign, while others are malignancy. However, patients with malignant tumor will die before PMP emerges.

The author experienced excessive accumulation of mucins and mucin-producing cells in the cutaneous tissue of subcutaneous and deep soft tissues. This situation very resembled or was identical with pseudomyxoma peritonei (PMP). Thus, the author termed the cutaneous lesion as pseudomyxoma cutis (PMC).

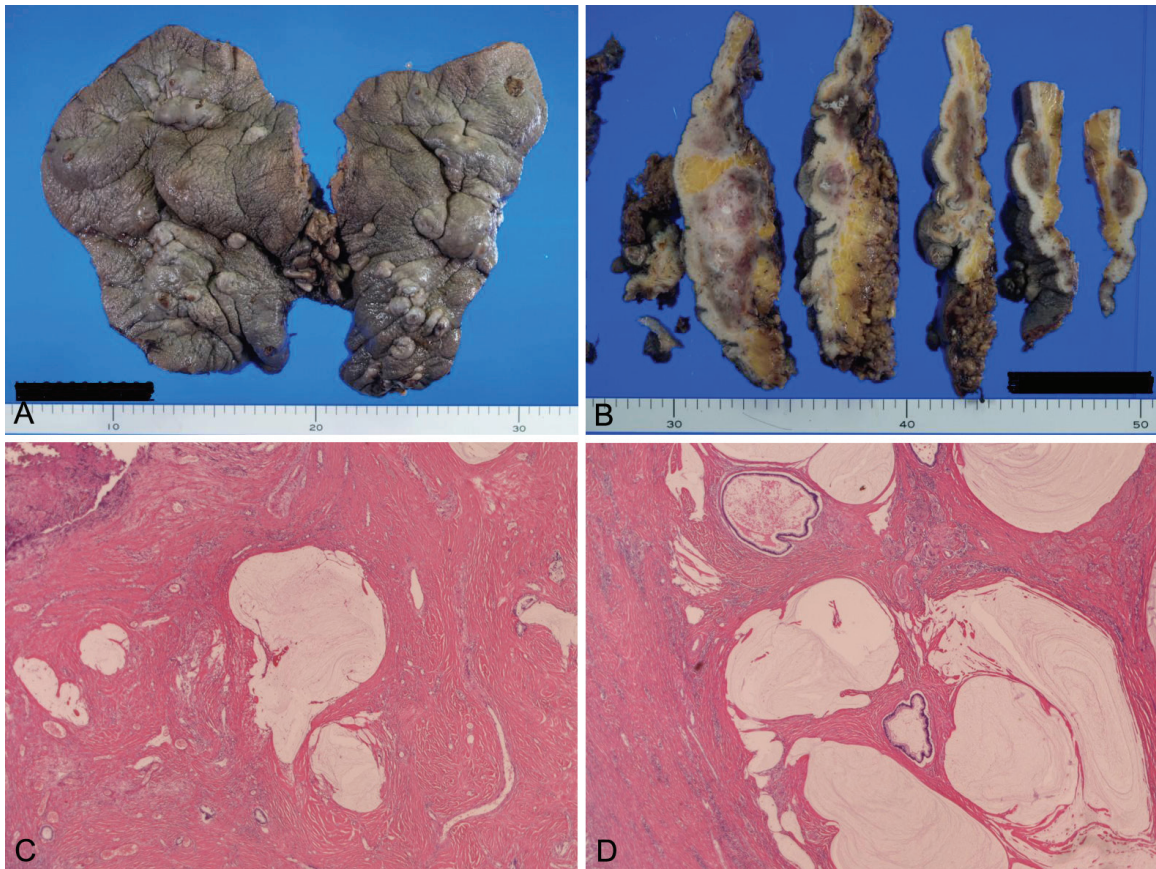


Figure 1. Histology of skin lesions. A: Macroscopically, the large skin flap measuring 25cm have numerous subcutaneous soft tumor. B: The cut surface of the skin flap shows that the skin tumors are mucinous lake. C, D: The subcutaneous tissue of the skin shows mucin lakes and mucin-producing epithelial tumor cells. C, D: x150.

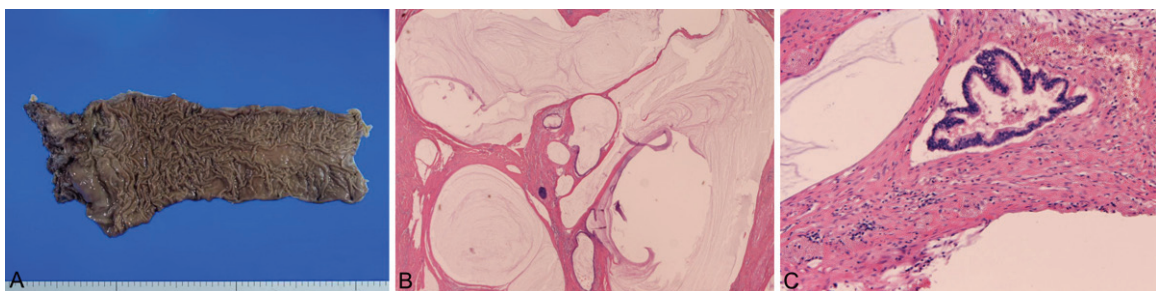


Figure 2. Pathology of anorectum lesions. A: The resected anorectum. The anus (left) shows multiple polypoid tumors. B: The anus tumors are composed of mucins lakes and mucin-secreting glandular epithelium. HE, x100. C: Findings similar to B. However, the epithelium shows moderate atypia in the mucins-producing tumor cells. HE, x200.

Case report

A 57-year-old man admitted to our hospital because of multiple subcutaneous large tumors in the perianal skin. The tumors were relatively deeply seated and soft. No biopsy was performed. Very large skin and subcutis resection of the perianal region was performed.

Grossly, the material was skin and soft tissue flap measuring 25x25x5cm. The subcutis and deep soft tissue were resected. Numerous subcutaneous soft tumor were recognized (**Figure 1A**). On cut surface, the tumor was slimy liquid (**Figure 1B**). Microscopical examination revealed a large amount of mucins pools and mucin-producing intestinal-type epithelium

Pseudomyxoma cutis

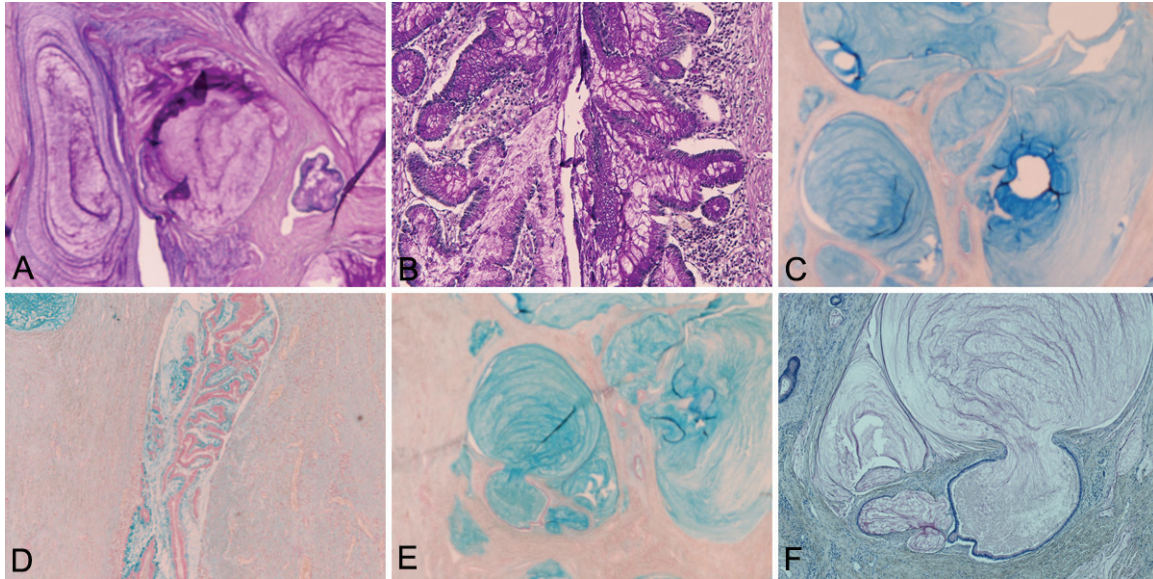


Figure 3. Mucin histochemistry in anal lesions. A: The mucins lakes show neutral mucins. d-PAS stain, x100. B: The tumor cells also showed large amounts of neutral mucin. d-PAS, x100. C: The mucins lakes show carboxylated mucins. AB pH 2.5 stain, x100. D: The tumor cells also showed large amounts of carboxylated mucins. AB pH 2.5 stain, x100. E: The mucins lakes show sulfated mucins. AB pH 1.0 stain, x100. F: The mucins lakes and tumor cells are stained with mucicarmine stain. Mucicarmine stain, x100.

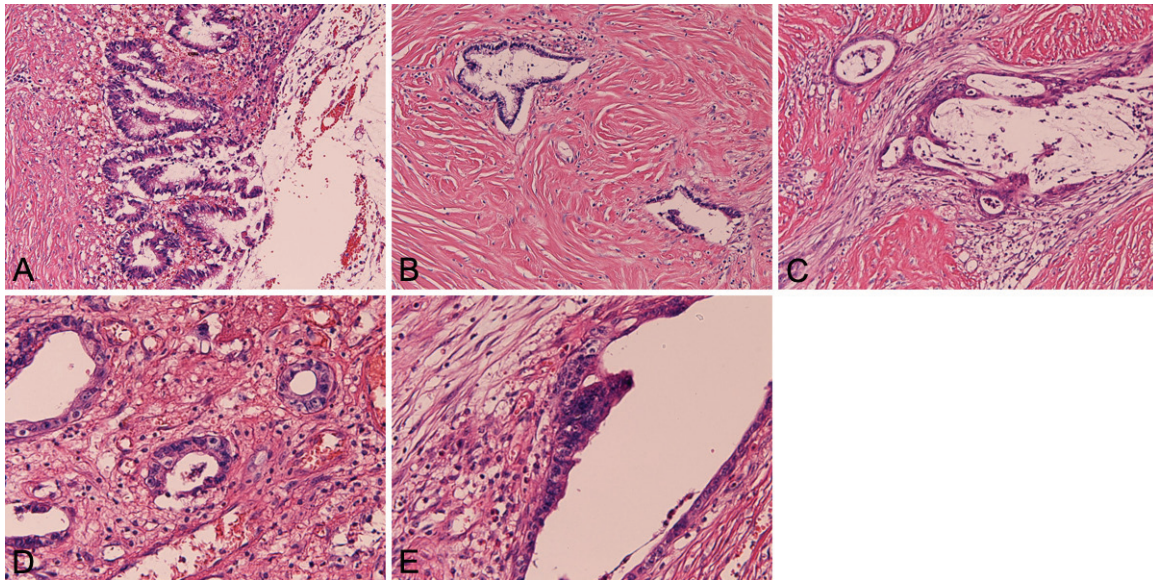


Figure 4. Morphology of anal and skin tumors. A, B: The mucins-secreting epithelium forms well developed tubules. However, they show mild nuclear atypia such as hyperchromasias and nuclear dipolarity. The cytoplasm is very clear due to accumulation of mucins. A, B: x100. C: The tumor cells shows significant atypia and glands in glands pattern. These features only can lead to well differentiated adenocarcinoma. HE, x100. D: The some tubular structures have significant cellular atypia highly suggestive for well differentiated adenocarcinoma. HE, x200. E: Some tubules show piling up or stratification of lining cells, highly suggestive of well differentiated adenocarcinoma. HE, x200.

with mild atypia (**Figure 1C** and **1D**). The author diagnosed it as metastatic extremely well differentiated adenocarcinoma producing mucins, and pointed out anorectal primary.

Thus, Miles operation was performed, which showed tumor formation in the anus (**Figure 2A**). The tumor was located from the submucosa to adventitia, and composed of mucin pools

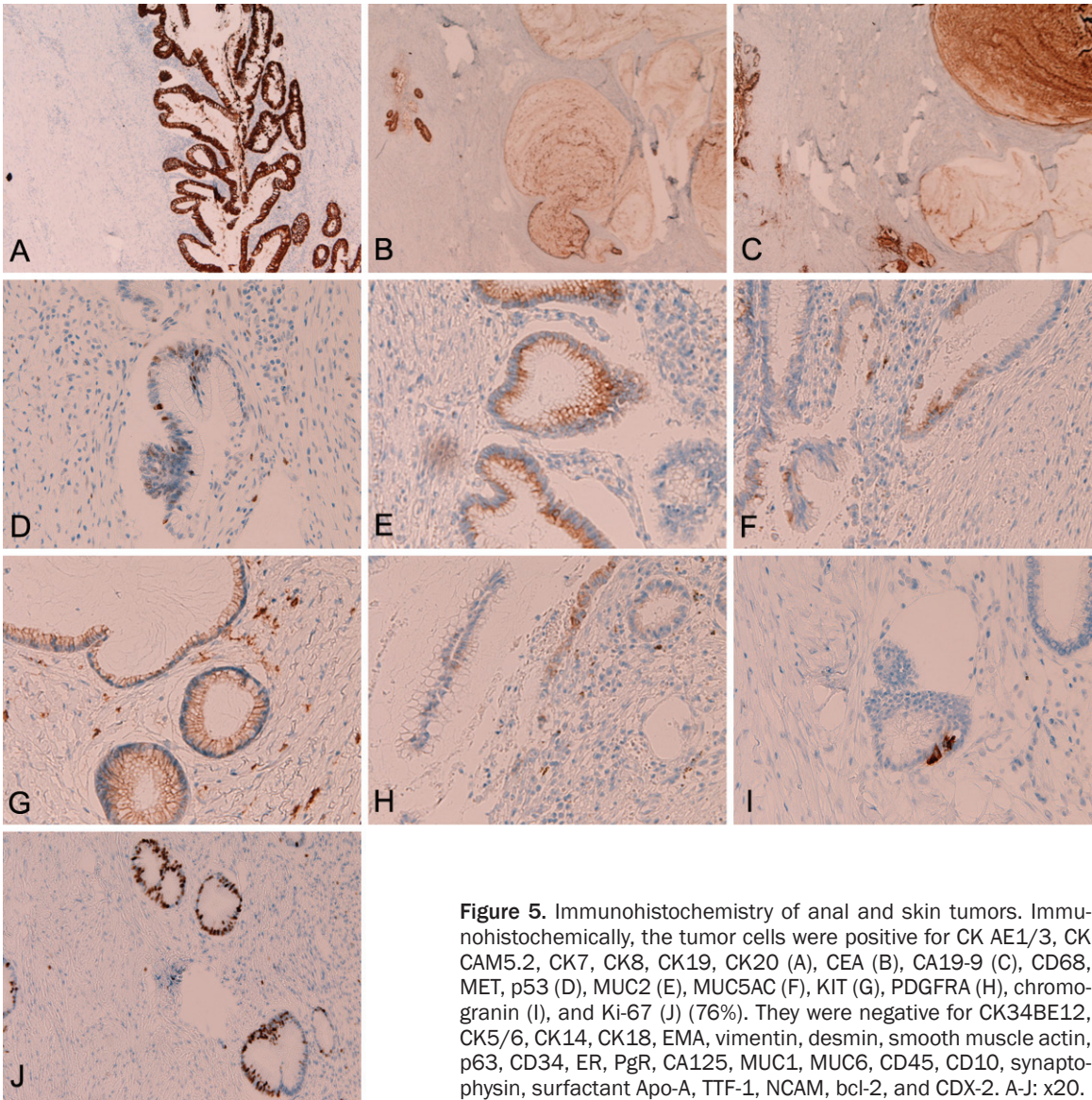


Figure 5. Immunohistochemistry of anal and skin tumors. Immunohistochemically, the tumor cells were positive for CK AE1/3, CK CAM5.2, CK7, CK8, CK19, CK20 (A), CEA (B), CA19-9 (C), CD68, MET, p53 (D), MUC2 (E), MUC5AC (F), KIT (G), PDGFRA (H), chromogranin (I), and Ki-67 (J) (76%). They were negative for CK34BE12, CK5/6, CK14, CK18, EMA, vimentin, desmin, smooth muscle actin, p63, CD34, ER, PgR, CA125, MUC1, MUC6, CD45, CD10, synaptophysin, surfactant Apo-A, TTF-1, NCAM, bcl-2, and CDX-2. A-J: x20.

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'

and mucins producing intestinal-type epithelium with atypia (**Figure 2B** and **2C**).

Mucins histochemistry was performed, as previously reported [4-8]. It consisted of mucicarmine, colloidal iron, periodic acid-Schiff (PAS), diastase-predigested PAS

(d-PAS), Alcian blue (AB) at pH2.5, AB at pH1.0, and combined d-PAS/AB at 2.5 and at 1.0. The mucins pools and the cytoplasm of mucins-producing tumor cells of both skin and anal lesions were positively stained by colloidal iron, PAS, d-PAS (**Figure 3A** and **3B**), AB at pH2.5 (**Figure 3C** and **3D**), AB at pH1.0 (**Figure 3E**), mucicarmine stain (**Figure 3F**), and combined d-PAS/AB techniques. Please refer to the author's numerous works on mucins histochemistry.

The morphology and immunohistochemistry of the skin and anal lesions were the same. The mucins-producing tumor epithelial cells showed columnar shape, thus they were intestinal-type epithelium (**Figure 4A** and **4B**). The cytoplasm was clear due to excessive mucins as described above. The epithelial tumor cells are located adjacent to the mucins pool, and it was obvious that the epithelial tumor cells were producing mucins pools. The nuclei were hyperchromatic. These cells formed tubular structures. The atypia was mild. In some areas, nuclear atypia, nuclear crowding and piling up and the glands in glands pattern suggesting of malignancy were seen (**Figure 4C-E**). However, obvious carcinoma cells were not seen. However, the tumor cells were located in the submucosa, muscle layer, adventitia and extra-adventitial areas; so that it was certain that the tumor had invasive, malignant potentials. No apparent lymphovascular permeations were seen. The surgical margins of both the skin flap and anorectum were negative for tumor cells. The author thought that the mucins-producing tumor cells and mucins pools were completely resected.

An immunohistochemistry was performed with the use of Dako Envision method, as previously reported [9-15]. Immunohistochemically, the tumor cells were positive for CK AE1/3, CK CAM5.2, CK7, CK8, CK19, CK20 (**Figure 5A**), CEA (**Figure 5B**), CA19-9 (**Figure 5C**), CD68, MET, p53 (**Figure 5D**), MUC2 (**Figure 5E**), MUC5AC (**Figure 5F**), KIT (**Figure 5G**), PDGFRA (**Figure 5H**), chromogranin (**Figure 5I**), and Ki-67 (**Figure 5J**) (76%). They were negative for CK34BE12, CK5/6, CK14, CK18, EMA, vimentin, desmin, smooth muscle actin, p63, CD34, ER, PgR, CA125, MUC1, MUC6, CD45, CD10, synaptophysin, surfactant Apo-A, TTF-1, NCAM, bcl-2, and CDX-2.

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 [16-32]. 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 mucins-producing tumor. Imatinib may be ineffective.

Although the atypia is mild, the author diagnosed this tumor as primary anorectal extremely well differentiated adenocarcinoma with excessive production of mucins. The author thought the cutaneous mucins and tumor cells are metastatic or directly invading lesions of the anal tumor. Thus, the author termed pseudomyxoma cutis (PMC) for the cutaneous lesion. The terminology seems quite logical and the situations are very similar or identical with pseudomyxoma peritonei.

Discussion

The present patient presented as multiple many cutaneous soft tumors. The histology of them was mucins pools with embedded or adjacent mucins-producing intestinal-type

tumor cells. These appearances are identical with pseudomyxoma peritonei (PMP) [1-3]. Thus, the term pseudomyxoma cutis (PMC) in the present case is quite natural and logical.

The pathology of the multiple skin tumors showed intestinal-type tumor epithelial cells with columnar shape. Therefore, the author suggested anorectal malignancy near the skin tumors. The anorectum obtained by Miles operation shows multiple tumors consisting of mucins pools and intestinal-type tumor cells identical with those of the skin tumor. Thus, the author diagnosed it as primary extremely well differentiated adenocarcinoma of the anus producing large amounts of mucins. The author considered that the primary is anus and the skin tumors are metastatic or directly invasive tumors from the anal primary. Please refer to the author's numerous articles of GI cancers.

The differential diagnoses are primary mucinous carcinoma of the skin and primary mucinous adenocarcinoma of the anus. The present tumor is not primary cutaneous mucinous carcinoma. This tumor occurs in the dermis and consisted of lobulated appearance of mucins production. In addition, the cellular atypia is much severe and is easily regarded as apparent carcinoma. The present anal tumors are not anorectal mucinous carcinoma, in which the mucin accumulations are not so large. The atypia in mucinous carcinoma is marked and the tumor cells are easily labeled as carcinoma cells. Please consult the author's several articles of cutaneous mucinous carcinoma and mucinous carcinoma of colorectum.

The primary site of the present study is definitely anus. The CK7+/CK20+ or CK20+ strongly suggests the anorectal primary. In addition, MUC apomucin profile (MUC1-, MUC2+++, MUC5AC+, MUC6-) in the present tumor strongly suggests anorectal primary. MUC1 is transmembranous non-secretory mucins mainly seen in pancreatic ducts. MUC2 is secretory mucins mainly seen in goblet cells of the intestine, and MUC5AC and MUC6 are secretory mucins present in the foveolar and pyloric glands epithelium. The present case had strong MUC2 apomucin, almost indicating the anorectal primary. The mild expression MUC5AC may suggest that this primary anorectal carcinoma may contain gastric foveolar differentiation.

Please consult the author's numerous papers of MUC and CK profiling.

In the present study, the atypical features of mucins-secreting tumor cells were mild. However, the tumor cells had hyperchromatic nuclei. Occasionally, atypical features suggestive of adenocarcinoma such as piling up or stratification of nuclei, cellular atypia including hyperchromasia, increased nucleocytoplasmic ratio and nucleoli, structural atypia including glands in glands pattern, nuclear dipolarities were seen. However, the overall appearance of HE histology is intermediate or extremely well differentiated adenocarcinoma. The immunohistochemical findings of positive p53 and high Ki-67 labeling index (76%) are also highly suggestive of malignant potential of the present tumor. The immunohistochemical findings of positive CEA and CA19-9 also strongly suggest that the tumor cells are adenocarcinoma cells. However, most important is that the anal tumors are located in the submucosa, muscular layer, adventitia, and extra-adventitia tissue strongly suggests the invasiveness of the tumor. The skin tumors are histologically and immunohistochemically certainly secondary. The absence of tumor cells and mucin pools in the dermis where skin appendage is absent strongly suggests that the skin tumors are secondary tumor.

The present study used broad immunohistochemical study. The cytokeratin profiles show that the present tumor has mainly low molecular weight cytokeratin. CD68 was positive, significant number of histiocytes accumulated in the lesion, where the cells show macrophages for mucins. MET was positive, suggesting that HGF/MET signaling play an important role of tumorigenesis and tumor progression. P53 was positive, suggesting p53 mutations and malignant potentials. Chromogranin was mildly positive, suggesting mild neuroendocrine differentiation in the present tumor. CK34BE12, CK5/6, CK14, CK18 and EMA were negative, suggesting that the present tumor lack these epithelial antigens. Vimentin was negative, suggesting that the tumor is not mesenchymal tumor. Desmin and smooth muscle actin were negative, suggesting that the present tumor is not myogenic tumor. p63 was negative, suggesting that the present tumor is not squamous cell carcinoma, basal cell carcinoma and myoepithelial carcinoma. CD34 was negative, suggest-

ing that the present tumor is not vascular tumor, solitary fibrous tumor, GIST, or stem cell cancers. ER and PgR were negative, suggesting that the present tumor is not dependent of female hormones and not endometriosis-related lesions. CA125 was negative, suggesting no associated with female genital organs. CD45 and CD10 were negative, suggesting that the tumor is not lymphoma or granulocytic sarcoma. Synaptophysin and NCAM were negative, suggesting that the tumor does not show neuroendocrine features. Surfactant Apo-A and TTF-1 were negative, suggesting that the present tumor is not primary pulmonary or thyroid carcinomas. Bcl-2 is negative, suggesting the tumor is not follicular lymphoma, certain mesenchymal tumor or stem cell cancers. Finally, it was mysterious that the present tumor cells were negative for CDX-2, a nuclear antigen present in gastrointestinal tracts. This negativity of CDX-2 is only the weak point of the author's opinion. However, it is well known that CDX-2 is not expressed in all anorectal tumors. There are many CDX-2 negative anorectal carcinomas. Thus, the negativity of CDX-2 only seems not to deny the author's suggestions.

In the present case, KIT and PDGFRA were expressed in tumor cells. The expressions of these molecules in anorectal carcinoma have not been reported. Since the author always investigates gene mutational status in tumors positive for KIT and PDGFRA. The present genetics are such examples. It was found that there were no mutations in *KIT* and *PDGFRA* in their hot spots. Many tumors express KIT, but tumors with gene mutations of *KIT* and *PDGFRA* are limited. The high frequency group for positive mutations includes GIST, e-GIST, melanoma, and germ cell tumors. More studies investigating all exons and introns of *KIT* and *PDGFRA* are needed. Please refer to the author's numerous articles on KIT and PDFRA.

In conclusion, the author demonstrated unique tumors of the skin and anus composed of mucins pools and atypical glandular epithelium that appeared primary anorectal extremely well differentiated adenocarcinoma with excessive mucins productions. The histology of cutaneous many tumors is identical with much more common pseudomyxoma peritonei. Therefore, the author termed the secondary cutaneous tumors as pseudomyxoma cutis.

Declaration

The author has no conflict of interest.

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