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Primary Extrapulmonary Small Cell Carcinoma of the Appendix
– A Case Report –

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Primary extrapulmonary small cell carcinoma (EPSCC) of the appendix is an extremely rare entity, and there has been only one previous report on this in the English medical literature. We report here on the first Korean case of EPSCC of the appendix in a 55-year-old woman. The patient had no history of an identified pulmonary tumor, and she presented with constipation and lower abdominal pain. The patient underwent right hemicolectomy with regional lymph node dissection and bilateral salphigo-oophorectomy. The histology of the entire appendiceal tumor revealed pure EPSCC with diffuse immunoreactivity for pancytokeratin, cytokeratin 7, cytokeratin 20, CD56, thyroid transcription factor 1, c-kit and carcinoembryonic antigen, and there was focal weak immunoreactivity for chromogranin A and synaptophysin. After the second cycle of chemotherapy, the condition of the patient gradually deteriorated due to cancer peritonei and the patient died 7 months later. EPSCC of the appendix is a distinctive clinicopathological entity that displays highly aggressive behavior and an unfavorable outcome.

Key Words : Appendix; Carcinoma, small cell

Primary extrapulmonary small cell carcinoma (EPSCC) of the appendix is an extremely rare entity. Although one case of mixed EPSCC associated with an intestinal-type adenocarcinoma has been previously reported,[1] pure EPSCC of the appendix has been reported only once in the English medical literature.[2] We report here on a case of 55-year-old Korean woman with a primary pure EPSCC arising from the appendix. In particular, we performed immunohistochemical staining by using a large panel of antibodies to characterize this tumor and to compare it with the two previously reported cases.[1,2] To the best of our knowledge, this is the first case of a pure EPSCC of the appendix in Korea and it is only the second reported case of a pure EPSCC of the appendix in the English medical literature.

CASE REPORT

A 55-year-old woman presented with constipation and intermittent lower abdominal pain of an insidious onset and progressive course, and she'd suffered from these symptoms for the previous year. She had experienced 3-4 kg weight loss during the previous 3 months. Her past medical history was unremarkable and there was no history of tobacco or alcohol use. The abdominal examination revealed right upper quadrant tenderness. A computed tomography (CT) scan of the abdomen and pelvis revealed an appendiceal cancer with multiple metastatic regional lymphadenopathies and pelvic seeding. The patient underwent right hemicolectomy with regional lymph node dissection and bilateral salphigo-oophorectomy. Macroscopic examination of the right hemicolectomy specimen revealed a markedly enlarged appendix that measured 8 cm in length and 2.8 cm in diameter. The serosal surfaces of the resected specimen were markedly hemorrhagic and they were adhered to each other. Multiple enlarged lymph nodes that measured up to 1.5 cm were dissected from the pericolic adipose tissue. On the tissue sections, the appendiceal wall was totally replaced by the mass and the appen-

diceal lumen was entirely obliterated and filled with a grayish granular mass. The mass extended to the periappendiceal fat tissue (Fig. 1). The mucosa of the resected small and large intestines was unremarkable. Both resected ovaries (3.0 × 1.5 cm and 2.0 × 1.8 cm in size, respectively) showed a dirty outer surface. Both salpinges were grossly unremarkable, and each of them measured 4 cm in length. The entire appendiceal mass was submitted for histologic processing and 22 hematoxylin and eosin (H&E) stained slides were reviewed to determine whether this tumor was pure or mixed. The postoperative histological examination revealed a small cell carcinoma composed of sheets of small round, ovoid or fusiform cells with hyperchromatic nuclei, dispersed chromatin, no or inconspicuous nucleoli and scanty amphophilic cytoplasm. The tumors also exhibited brisk mitotic activity, apoptosis and individual cell necrosis. The tumor had infiltrated the entire thickness of the muscularis wall up to the serosal surface (Fig. 2A). Extensive lymphovascular invasion was identified, and 6 of the 19 dissected lymph nodes contained metastatic carcinoma. Despite that several H&E serial sections were performed on the cecal surgical margins at the base of the appendix, no residual tumor was found. Both the ovaries also revealed multifocal metastatic deposits of tumor at the surface (Fig. 2B). Immunohistochemical stains were performed to characterize the tumor. The characteristics of the antibodies used in this study and the results are presented in the Table 1 and Fig. 3. Briefly, the tumors showed a diffuse positivity for pancytokeratin, cytokeratin (CK) 7, CK20, CD56, thyroid transcription factor 1 (TTF-1), c-kit and carcinoembryonic antigen. Focal weak immunopositivity was observed for chromogranin A, synaptophysin and CD99. The tumors showed negativity for p53 and CDX2. The labeling index by Ki-67 was very low with less than 1% positive staining. The patient had a normal chest radiograph and CT scan of the chest, and negative sputum cytology and negative bronchoscopy examination. A diagnosis of primary appendiceal EPSCC was made in the absence of any identified pulmonary tumor. She had an uneventful surgical recovery and was transferred to the oncology department for palliative chemotherapy. After the second cycle of chemotherapy, the condition of the patient gradually deteriorated due to cancer peritonei and the patient died 7 months later.

Fig. 1. The cut surface of the right hemicolectomy specimen shows the appendiceal wall, which is totally replaced by the mass and the lumen is entirely obliterated and filled with grayish granular mass. The mass extends to the periappendiceal fat tissue without cecal involvement.

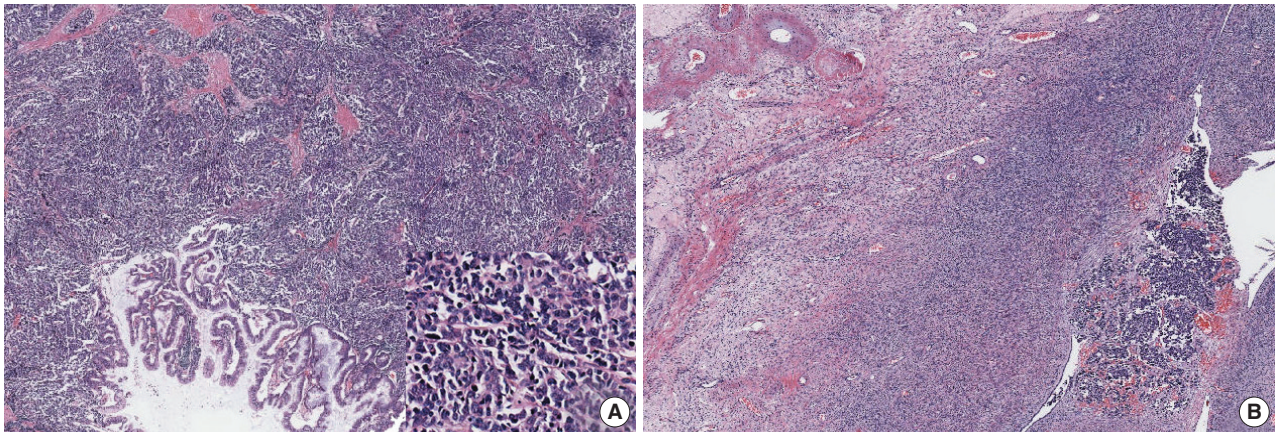

Fig. 2. The postoperative histological examination reveals a small cell carcinoma infiltrating the entire thickness of the muscularis wall up to the serosal surface (A). The tumor is composed of sheets of small round, ovoid or fusiform cells with hyperchromatic nuclei, dispersed chromatin, no or inconspicous nucleoli and scanty amphophilic cytoplasm. The tumor also exhibits brisk mitotic activity, apoptosis and individual cell necrosis (A, inset). The ovary also reveals metastatic deposits of small cell carcinoma at the surface (B).

Table 1. The results of the immunohistochemistry for the extrapulmonary small cell carcinoma of the appendix as compared with the two previously reported cases

Immunohisto -chemical markers	Antibody used in our case			Results		
	Source	Clone	Dilution	Our case	O'Kane *et al.*[2]	Rossi *et al.*[1, a]
Pancytokeratin	Dako	MNF116	1 : 200	+	+	+
Cytokeratin 7	Dako	OV-TL12/30	1 : 200	+	-	-
Cytokeratin 20	Dako	Ks20.8	1 : 200	+	-	-
CD56	Zymed	123C3	1 : 50	+	-	Focal +
Chromogranin A	Dako	DAK-A3	1 : 100	Focal +	-	+
Synaptophysin	Dako	Polyclonal	1 : 200	Focal +	+	+
TTF-1	NeoMarkers	8G7G3/1	1 : 50	+	+	-
c-kit	Dako	Polyclonal	1 : 200	+	x	-
CD99	Zymed	O13	1 : 100	Focal +	-	x
CDX2	Biogenex	7C7/D4	1 : 200	-	x	-
CEA	Dako	11-7	1 : 5,000	+	x	-
p53	Dako	DO-7	1 : 50	-	x	-
Ki-67	Dako	MIB-1	1 : 100	< 1%	90%	90%

+, positive immunoreactivity; –, negative immunoreactivity; x, not done.
[a]Immunohistochemical results for only small cell carcinoma component.
TTF-1, thyroid transcription factor 1; CEA, carcinoembryonic antigen.

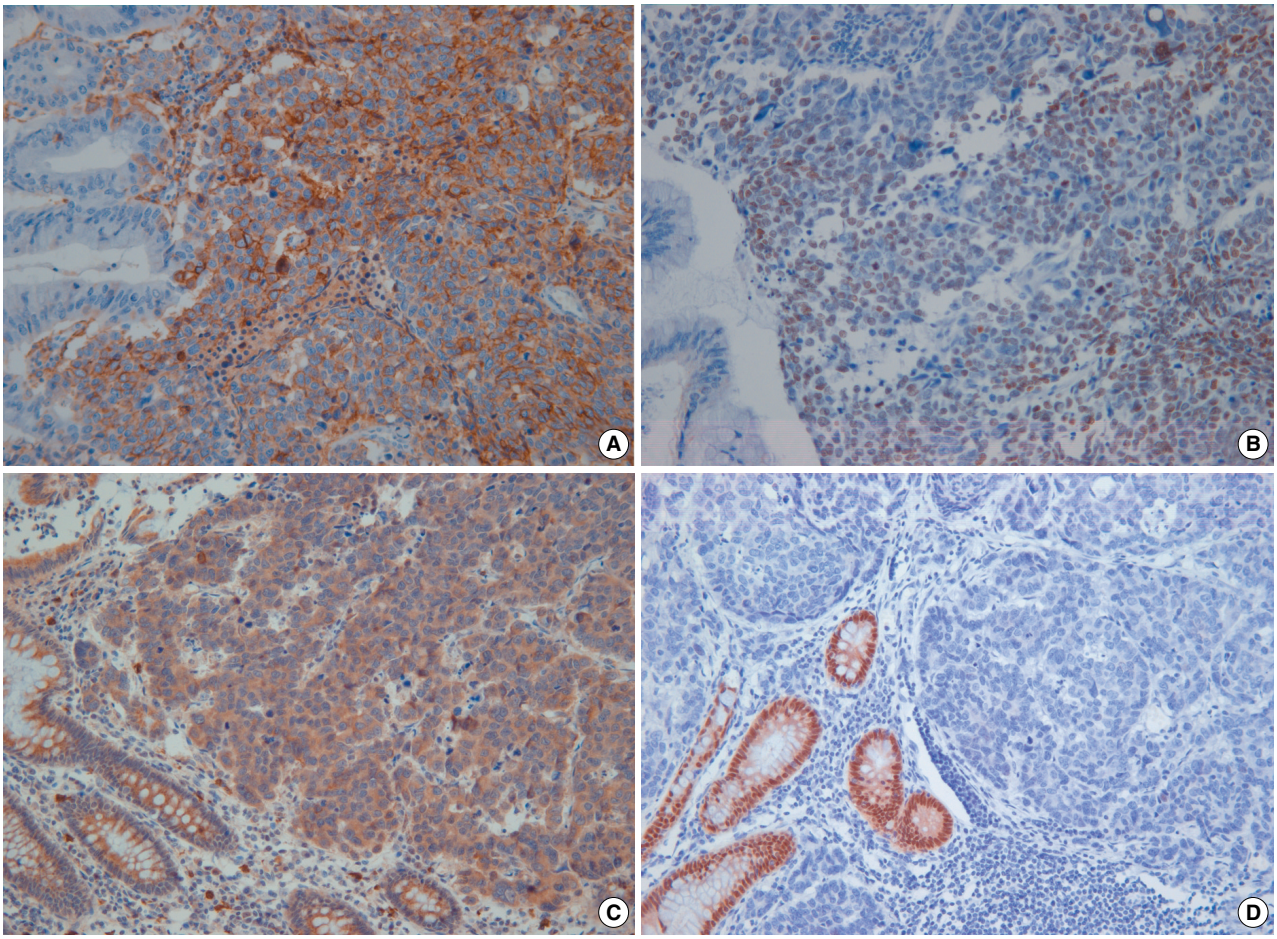

Fig. 3. Immunohistocehmically, the tumor cells show positive reactivity for CD56 (A), thyroid transcription factor 1 (B) and c-kit (C), but the tumor cells were negative for CDX2 (D).

DISCUSSION

Tumors of the appendix are very rare, with the majority of them being primary appendiceal malignancies such as carcinoid or adenocarcinoma.[3] However, pure EPSCC of the appendix is extremely rare and there has been only one such case previously reported in the English medical literature.[2] To the best of our knowledge, this is the first Korean case of a pure EPSCC of the appendix and it is only the second reported case of a pure EPSCC arising from the appendix in the English medical literature.

Since the first report on an EPSCC in 1930,[4] this histological subtype has been recognized at all sites of the body except the central nervous system. However, SCC is uncommon with an overall incidence of approximately 0.1% to 0.4% in nonpulmonary sites.[5] The most common primary sites have been the gastrointestinal (GI) tract and uterine cervix in two reports of a single-center study.[5,6] The clinical behavior of these tumors has been found to be aggressive, with early dissemination and frequent recurrence, and this is similar to their pulmonary counterparts. The patients with GI primary EPSCC have a poorer prognosis than do those patients with primary EPSCC tumors at other location. The patients with colorectal EPSCC have shown an aggressive clinical course with a median overall survival of 10.4 months[7] and a 5-year survival rate of 13%.[8] Our patient died 7 months after surgery and the patient in a previously reported case passed away 2 months after surgery.[2] Although there has been no comparative study in the medical literature, it is consistent that appendiceal EPSCC has an aggressive clinical course. However, the patient with mixed SCC and adenocarcinoma was disease free 65 months after surgery.[1] Thus, it is worthwhile to emphasize that the biologic behavior of pure EPSCC is poorer than that of mixed SCC.

The histogenesis of appendiceal EPSCC is controversial because there are far too few cases in the literature to answer this question. Furthermore, the results of the immunohistochemistry were inconsistent between our case and the other two cases,[1,2] as is shown in Table 1. On immunohistochemistry, both the pure EPSCC of the present case and that of O'Kane *et al.*[2] stained for TTF-1, as was also shown in the EPSCC of other sites, whereas the SCC component of the mixed case of Rossi *et al.*[1] was unstained for TTF-1. It has been reported that EPSCC of the colon may be associated with an adenocarcinomatous component within the same tumor or with a synchronous, but separate colonic adenocarcinoma.[9] Rossi *et al.*[1] reported that the SCC appeared to be a poorly differentiated endocrine component that was likely derived from secondary genetic alterations during the progression of adenocarcinoma. However, it has been suggested that EPSCC of the GI tract probably arises from pluripotential stem cells of the endoderm.[10] CDX2 expression characterizes the normal GI epithelium including that of the appendix and is also strongly maintained in exocrine and/or endocrine intestinal tumors,[11] but our case was unstained for CDX2. The marker c-kit must be taken into account because the tumor cells of the present case were found to express c-kit, which is in contrast to that of the case of Rossi *et al.*[1] Therefore, the stem cell factor-c-kit system may contribute to tumor development and the neuroendocrine differentiation from the stem cell theory should also be considered, and especially for pure EPSCC like our case.[12] Furthermore, c-kit may be considered as a potential target for novel therapeutic approaches because there is presently no consensus regarding the optimal treatment strategy for appendiceal EPSCC.

Despite the fact that this type of tumor is extremely rare, it is important that pathologists and clinicians be aware the appendix may be a potential site of EPSCC and the appendix must be considered as a primary site for an unknown origin of SCC. However, using investigative modalities such as a CT scan and bronchoscopy are mandatory to exclude the possibility of a pulmonary origin. This awareness could also help to prevent a misdiagnosis of EPSCC as poorly differentiated adenocarcinoma, which is crucial because EPSCC has been shown to carry a particularly poor prognosis, and these EPSCC patients may benefit from treatment with alternative chemotherapeutic agents.

REFERENCES

1. Rossi G, Bertolini F, Sartori G, *et al.* Primary mixed adenocarcinoma and small cell carcinoma of the appendix: a clinicopathologic, immunohistochemical, and molecular study of a hitherto unreported tumor. Am J Surg Pathol 2004; 28: 1233-9.
2. O'Kane AM, O'Donnell ME, Shah R, Carey DP, Lee J. Small cell carcinoma of the appendix. World J Surg Oncol 2008; 6: 1-4.
3. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer 2002; 94: 3307-12.
4. Duguid JB, Kennedy AM. Oat-cell tumors of mediastinal glands. J Pathol Bacteriol 1930; 33: 93-9.
5. Cicin I, Karagol H, Uzunoglu S, *et al.* Extrapulmonary small-cell carcinoma compared with small-cell lung carcinoma: a retrospective single-center study. Cancer 2007; 110: 1068-76.
6. Lee SS, Lee JL, Ryu MH, *et al.* Extrapulmonary small cell carcino-

ma: single center experience with 61 patients. Acta Oncol 2007; 46: 846-51.
7. Bernick PE, Klimstra DS, Shia J, *et al.* Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum 2004; 47: 163-9.
8. Demellawy DE, Samkari A, Sur M, Denardi F, Alowami S. Primary small cell carcinoma of the cecum. Ann Diagn Pathol 2006; 10: 162-5.
9. Vortmeyer AO, Lubensky IA, Merino MJ, *et al.* Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas. J Natl Cancer Inst 1997; 89: 1448-53.
10. de Bruin NC, de Groot R, den Hollander JC, Agoston SI, van Dongen JJ, Neijens HJ. Small-cell undifferentiated (neuroendocrine) carcinoma of the cecum in a child with common variable immunodeficiency. Am J Pediatr Hematol Oncol 1993; 15: 258-61.
11. Werling RW, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol 2003; 27: 303-10.
12. Kurt E, Sezgin C, Evrensel T, *et al.* Therapy, outcome and analysis of c-kit expression in patients with extrapulmonary small cell carcinoma. Int J Clin Pract 2005; 59: 537-43.