Case Report

Perivascular Epithelioid Cell Tumor of the Rectum: Differential Diagnosis of a Rare Case

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Perivascular epithelioid cell tumors are a group of mesenchymal tumors that typically occur in soft tissue. These tumors have been reported in various organs but rarely in the gastrointestinal tract. Most of them are considered low-grade malignant tumors; however, some cases of high-grade malignancy have been described. We report a case with long-term follow-up of a rectal tumor in a 57-year-old woman presenting with bloody stool. Colonoscopic examination revealed a 1.5-cm submucosal tumor in the rectum, and the patient underwent endoscopic snaring polypectomy. Tumor histology showed large polygonal cells with clear to slightly eosinophilic cytoplasm arranged in an organoid pattern. Immunohistochemical studies of the tumor cells revealed positive reactivity for HMB-45 and negative staining for smooth muscle actin, desmin, cytokeratin, synaptophysin, chromogranin A, CD34, CD117, S100 proteins, and TFE3. Thus, a colorectal perivascular epithelioid cell tumor was diagnosed. A definite diagnosis of a gastrointestinal perivascular epithelioid cell tumor is difficult because of its rarity and variable morphology. The biological characteristics, clinical behaviors, and definitive treatment of the tumors are not completely understood owing to limited case reports and studies. The differential diagnosis, malignant potential, and clinical expression and treatment of these tumors are discussed after a review of the literature. Patients should be carefully followed owing to the malignant potential of these tumors.
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Perivascular epithelioid cell tumors (PEComas) are a family of rare mesenchymal tumors with distinct histological and immunohistochemical characteristics of myomelanocytic differentiation. These tumors were first reported by Bonetti et al. in 1992.[1] This group includes angiomyolipomas, clear cell "sugar" tumor of the lung, lymphangiomyomatosis, and genetic PEComas in various sites. In 2002, the World Health Organization (WHO) recognized this family of neoplasms as rare soft tissue tumors.[2] PEComas have been recently reported in the kidney, liver, lung, uterus, and adnexa[3,4] but rarely in the gastrointestinal (GI) tract. According to our review of relevant literature, to date only a few cases have been reported and one serial study has been published.[5,6] Because of their rarity, PEComas are typically misdiagnosed in the initial biopsy specimen. Their clinical behavior as well as prognostic factors and treatment remain unclear. Most cases have relatively short follow-up periods. PEComas are typical low-grade malignancies; however, some

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cases have shown more aggressive behaviors.[5] We present a female patient with a rectal PEComa presenting with bloody stool; she was disease-free 50 months postoperatively. Moreover, we have reviewed previously reported cases of GI PEComas.

Case Report

A 57-year-old Taiwanese woman experienced epigastrial pain and passed bloody stool for months. She did not have fever, vomiting, or diarrhea. Colonoscopic examination revealed a 1.5-cm submucosal tumor, with ulceration of the overlying mucosa (Fig. 1). The patient had no medical complications and no significant family history of malignancy. Her chest radiography was normal, and the preoperative carcinoembryonic antigen level was within the normal limit. The patient underwent colonoscopic snaring polypectomy for removing the supposedly carcinoid tumor.

Gross examination revealed that the tumor measuring 1.5 × 1.2 × 1.0 cm was covered by mucosa, with focal ulceration. The cut surface was solid, tan, and elastic without necrosis. Microscopic examination showed a well-defined submucosal tumor (Fig. 2A) composed of large polygonal cells arranged in organoid or trabecular patterns and surrounded by delicate fibrovascular bands (Fig. 2B). The tumor cells had ovoid nuclei, small nucleoli, and abundant clear to slightly eosinophilic cytoplasm (Fig. 2C). No definite mitoses or necrosis were observed. The tumor was completely removed with free margins.

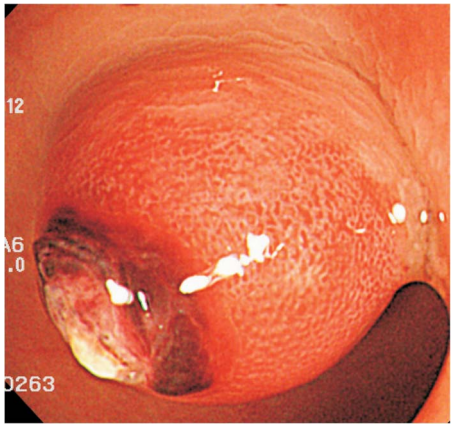

Fig. 1. Colonoscopic examination shows a 1.5 cm submucosal tumor covered by ulcerated mucosa.

The initial differential diagnoses included a carcinoid tumor and an epithelioid-type GI stromal tumor (GIST). Paraffin sections were used for conduct-

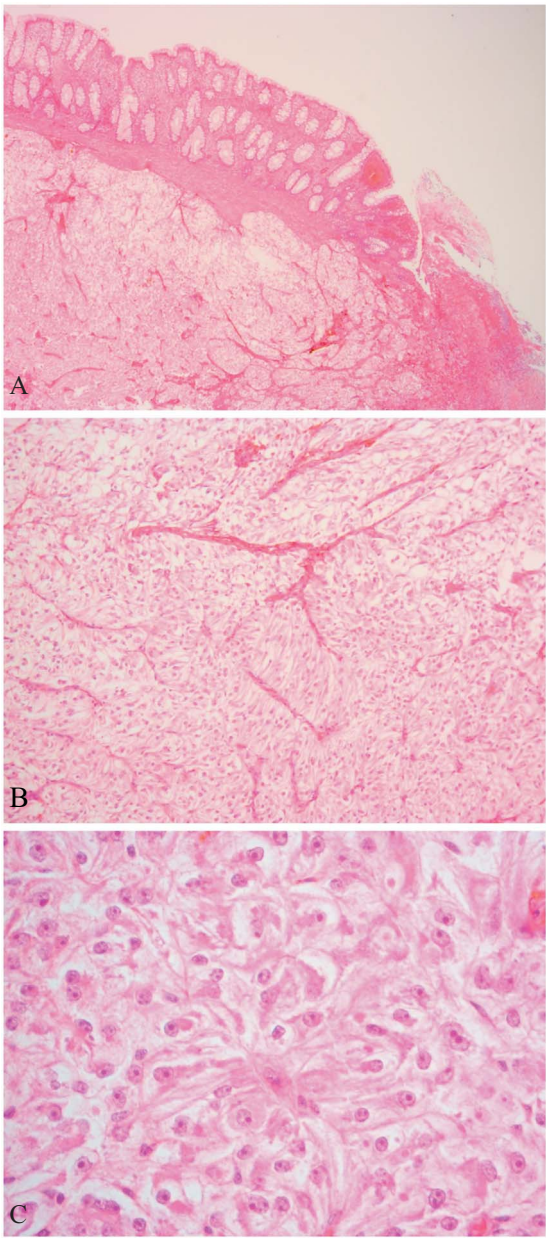

Fig. 2. Photomicrographs of the rectal tumor. (A) A well-defined tumor in submucosal region. The surface is ulcerated (H&E, 25x). (B) The tumor cells are arranged as variable sheets or organoid structures in delicate fibrovascular stroma (H&E, 100x). (C) The neoplastic cells show ovoid nuclei, distinct nucleoli and abundant clear to eosinophilic granular cytoplasm. Mitoses are not found (H&E, 400x).

ing immunoperoxidase studies with the avidin-biotin-peroxidase method. Immunohistochemical staining was performed using standard reagents and techniques on an Autostainer of Ventana BenchMark ULTRA. The following antibodies were used: cytokeratin, synaptophysin, chromogranin-A, CD56, smooth muscle actin, desmin, S-100, CD34, and CD117. However, the tumor cells stained negative for all these markers. Further differentiation of rare tumors of PEComa and metastatic renal cell carcinoma is suggested. The primary antibodies of HMB-45, TFE3, CD10, and renal cell carcinoma marker (RCC) were applied. The tumor cells revealed positive reactivity for HMB-45 (Fig. 3) and stained negative for the remaining antibodies (Table 1); thus, a colorectal PEComa was diagnosed.

The patient subsequently underwent endoscopic examination and biopsy 3 months after the initial operation. No residual tumor was observed in the biopsied specimen. The patient was regularly followed up at the GI and surgical outpatient department and showed no evidence of recurrent disease or metastatic lesions 50 months postoperatively.

Discussion

PEComa is recognized by the WHO as a very rare soft tissue tumor in 2002.[2] However, it has not been established in the GI tumors of WHO classification owing to it's extreme rarity. PEComas are tumors resulting from the proliferation of plumed perivascular epithelioid cells. They have been reported in the kidney, lung, soft tissue, gynecologic sites,[3,4] and rarely in the GI tract.[5,6] Only a few case reports and a series study, total number of 70 cases, on GI PEComas have been reported in the English medical literature in PubMed.

To date, GI PEComas[5,6] have been reported in 43 women and 27 men. The average age of patients was 5.5-71 years. The frequently observed symptoms included abdominal pain, GI bleeding, vomiting, diar-

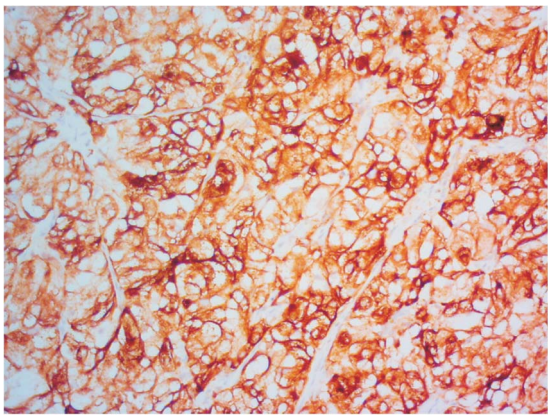

Fig. 3. Immunohistochemical staining. Tumor cells show diffuse cytoplasmic staining with HMB-45 (400x).

Table 1. Primary antibodies used for differential diagnosis in this case

Antibodies	Source	Major reactivity[a]	Result
Cytokeratin	Dako, CA, U.S.A.	Epithelial cells	-
Synaptophysin	Ventana Roche, AZ, U.S.A.	Neuroendocrine cells	-
Chromogranin-A	Ventana Roche, AZ, U.S.A.	Neuroendocrine cells	-
CD56	Cell Marque, CA, U.S.A	Neuroendocrine cells	-
CD34	Ventana Roche, AZ, U.S.A.	GIST[b], endothelial cells	-
CD117	Thermo, MA, U.S.A	GIST[b]	-
Smooth muscle actin	Ventana Roche, AZ, U.S.A	Smooth muscle cells	-
S-100	Ventana Roche, AZ, U.S.A.	Peripheral nerve sheath cells, melanocytes	-
CD10	Ventana Roche, AZ, U.S.A	Renal cell carcinoma	-
RCC	Ventana Roche, AZ, U.S.A	Renal cell carcinoma	-
HMB-45	Ventana Roche, AZ, U.S.A.	Melanocytes	+
TFE3	Cell Marque, CA, U.S.A	Alveolar soft part sarcoma	-
Ki-67[c]	Ventana Roche, AZ, U.S.A	Proliferative index	2%

[a] Most antibodies have multiple applications, but only the major activity associated with the differential diagnosis of this case is listed. [b] GIST: gastrointestinal stromal tumor. [c] Ki-67 was performed in some case reports, but no significant cut-off value was established.

rhea, and rarely constipation and peritonitis. Unlike patients with PEComas in other organs, PEComa of the GI tract was associated with tuberculous sclerosis in only one patient. The most common location was the colon (n = 36), followed by the small intestine (n = 20), rectum (n = 7), and stomach (n = 4). The other rare lesion sites included the appendix,[7] gallbladder, and mesentery.[6] The tumor size was 0.8-22.0 cm. PEComas in 22 patients (30.1%) exhibited malignant behaviors, with 4 cases of local recurrence and 19 cases of metastasis. The most common metastatic site was the liver (77%), followed by the lung (23%). Seven patients died of diseases within 2-48 postoperative months.

The typical cytological observations of PEComas include polygonal cells with ovoid nuclei, distinct nucleoli, and abundant clear to slightly eosinophilic granular cytoplasm. They are typically arranged as nests or sheets surrounded by a delicate fibrovascular network. Variable nuclear pleomorphism and mitotic figures are a characteristic aggressive finding. The differential diagnoses included a carcinoid tumor, an epithelioid GIST, a melanoma, a clear cell sarcoma of the soft part (CCS), and an alveolar soft part sarcoma (ASPS). Rarely, spindle or pleomorphic cells are also observed in PEComas, and the diagnosis of leiomyosarcoma and GIST should be differentiated. Immunohistochemical studies facilitate the differential diagnosis in daily practice. Table 1 shows the primary antibodies used in this study. PEComas are neoplasms with perivascular epithelioid cell differentiation; they typically express a melanocytic marker (HMB-45 or melan-A) and variable smooth muscle markers (smooth muscle actin or desmin). A melanoma and CCS reveal positive reactivity for melanocytic markers; however, they typically have a high nuclear grade and react with S-100 protein, which is not expressed in PEComas. An ASPS shows prominent nuclear staining for the carboxy-terminal protein of TFE3 and yields histological pictures similar to those PEComas. However, in contrast to PEComas, an ASPS stains negative for HMB-45.[2] A carcinoid tumor is the most commonly observed low-grade epithelioid cell tumor in the GI tract; it may first be considered when the tumor cells show abundant granular cytoplasm and are arranged in a trabecular pattern. However, a carcinoid tumor is easily eliminated through positive reactivity for cytokeratin and neuroendocrine markers, such as synaptophysin, chromogranin A, and CD56. If a tumor is mainly composed of spindle cells, the possibility of a GIST or leiomyosarcoma should be considered. GISTs are typically reactive for c-KIT (CD117) or DOG-1, phenotypically consistent with Cajal-cell differentiation. The aforementioned antibodies are not expressed in PEComas. The tumor cells of leiomyosarcomas stain positively for smooth muscle markers (actin and desmin) and negatively for melanocytic markers. Table 2 lists the most likely differential diagnosis of rare epithelial tumors of the GI tract. In our case, the tumor cells showed an epithelioid pattern and a clear to

Table 2. Differential diagnosis of GI PEComa using immunohistochemical studies

Tumors / Antibodies	Our case	PCOma[a]	CCS[b]/Melanoma	ASPS[c]	GIST[d]	Carcinoid
Cytokeratin	-	-	-	-	-	+
Synaptophysin	-	-	-	-	-	+
Chromogranin-A	-	-	-	-	-	+
CD56	-	-	-	-	-	+
CD34	-	-	-	-	+	-
CD117	-	-	-	-	+	-
Actin	-	V[e]	-	-	V	-
S-100	-	-	+	V	V	-
HMB-45	+	+	+	-	-	-
TFE3	-	V	-	+	-	-

[a] PEComa: perivascular epithelioid cell tumor; [b] CCS: clear cell sarcoma of soft tissue (melanoma of soft parts); [c] ASPS: alveolar soft part sarcoma; [d] GIST: gastrointestinal stromal tumor; [e] V: variable staining.

granular cytoplasm. A carcinoid tumor and an epithelioid GIST were suspected because of their frequent incidence in the GI tract. Finally, serial immunohistochemical studies revealed a PEComa. PEComas are typically underdiagnosed, particularly in immunohistochemical studies with an inadequate budget owing to the rarity of PEComas in the GI tract. They have some characteristic morphology considering the entity.

GI PEComas have variable clinical behaviors, ranging from benign to high-grade sarcomas. Definite diagnosis is crucial for further treatment and follow-up. In the limited cases reported to date, 5.7% local recurrence and 27.1% metastasis were recorded.[5] The previously described malignant histological observations of PEComas included tumor size > 5 cm, an infiltrating border, necrosis, vascular invasion, and nuclear pleomorphism.[8] Recently, the only serial study of GI PEComas reported some significant observations, including diffuse and marked nuclear pleomorphism and mitoses > 2/10 high-power field, were associated with a clinically malignant behavior.[6] In addition, ki-67, the p53 protein, and cyclin-D1 were detected in some cases aimed at detecting the malignant potential.[5,9,10] Only cyclin-D1 is suggested as a marker of the aggressive phenotype but requires further investigation.

The follow-up period for GI PEComas was typically short, and the therapeutic and outcome data were limited. Therapy for GI PEComas has not been standardized; however, complete excision with a safe margin is considered the mainstay treatment. 19 patients developed metastatic disease; 10 of them received chemotherapy and one also underwent radiotherapy.[6] However, the benefits of chemotherapy and radiotherapy have not been established. In our patient, the tumor did not show mitotic feature, and only mild nuclear pleomorphism was noted. The tumor cells showed low proliferative index of ki-67 and negative reactivity of cyclin-D1 and p53 protein. No unfavorable histological characteristics were observed. The patient underwent endoscopic snaring polypectomy and was disease-free 50 months postoperatively.

Although PEComas typically show typical histological features, they have been under-recognized until recently, particularly when they occur in the GI tract. Awareness of the characteristic morphological features and application of myomelanocytic markers in any suspected, unusual-appearing tumors may result in the correct diagnosis of PEComas, which have variable malignant potential. A regular follow-up of at least 48 months is recommended for the patients displaying malignant pathological features.

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病例報告

直腸之血管旁類上皮細胞瘤：一罕見病例及其鑑別診斷

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血管旁類上皮細胞瘤 (perivascular epithelioid cell tumor) 是一群具有肌細胞及黑色素細胞分化 (myomelanocytic) 的特殊細胞所形成的罕見腫瘤。此類腫瘤多發生於軟組織，世界衛生組織於 2002 年將之列於軟組織腫瘤的正式分類之一。之後開始有一些病例被報告發生於腎臟、肝臟、子宮等臟器中，但發生於腸胃道的病例則少之又少，近年來只有一些零星病例報告，因此尚未列入世界衛生組織之腸胃道腫瘤分類中。此類腫瘤的臨床表現差異極大，從良性到高惡性轉移及致死病例都有可能。由於病例稀少，此類腫瘤尚無法規劃出標準治療方針與準確地預測病人臨床表現。也因為此腫瘤罕見，導致確切診斷警覺度低，使鑑別診斷困難，常需經歷一系列病理及免疫化學染色檢查，方能獲得正確診斷。而其臨床處置方法與預後和腫瘤的病理表現息息相關，因此正確的診斷與詳細的病理表現描述，對臨床醫師決定如何給予病人術後的處置與追蹤是很重要的。我們報告這例位於直腸的病例，起初被臆測為類癌 (carcinoid tumor) 或腸胃基質腫瘤 (gastrointestinal stromal tumor)，經過病理切片及免疫染色多種抗體檢查後確診是血管旁類上皮細胞瘤。我們報告這位罕見病例，並收集發生於腸胃道之此類腫瘤的相關文獻，使讀者能進一步了解腸胃道血管旁類上皮細胞瘤的特性，以期增加診斷率及給予病人更適當的處置與追蹤。

關鍵詞　血管旁類上皮細胞瘤、腸胃道的、免疫化學、HMB-45。