

First Report of a Gangliocytic Paraganglioma Arising in a Tailgut Cyst

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Here we present the first report of a gangliocytic paraganglioma arising in a tailgut cyst; it occurred in a 56-year-old man. Tailgut cysts are uncommon congenital hamartomatous lesions that arise in the retrorectal presacral space in infants or adults. Benign or malignant tumors associated with tailgut cysts are rarely described; the most common tumors are adenocarcinomas and carcinoid tumors. A gangliocytic paraganglioma is a rare benign tumor that occurs nearly exclusively in the second portion of the duodenum. Rare cases have been reported at other locations, but a tailgut cyst has never been described. In our case, a resected $3.9 \times 3.3 \times 3$ cm mass was composed predominantly of a solid yellow white neuroendocrine tumor within the area of a tailgut cyst. The neuroendocrine component of this tumor was different from previously described carcinoid tumors with respect to the histologic findings of neural differentiation as well as the intermixed typical gangliocytic features highlighted by immunohistochemical stains for S-100 protein and neurofilament. Although an intermixed area of the tailgut cyst and gangliocytic paraganglioma were found in some areas, the pathogenesis of this tumor remains to be elucidated.

Key Words : Hamartoma; Cyst; Paraganglioma

Tailgut cysts are uncommon congenital hamartomatous lesions that arise in the retrorectal presacral space in infants or adults. As the term itself indicates, these tumors are considered to arise from the remnants of the post-anal gut. Tumors associated with these lesions are even rarer, most of them being adenocarcinomas and carcinoid tumors that are thought to arise in the epithelial component of tailgut cysts. A gangliocytic paraganglioma is a rare benign tumor, which occurs almost exclusively in the second portion of the duodenum. Although rare cases have been described at other sites including the appendix,^{1,2} lungs,³ nasopharynx,⁴ bronchus,⁵ mediastinum,⁶ and even ovarian cystic teratoma,⁷ it has never been described in a tailgut cyst. Histologically, these tumors are characterized by the presence of three different cell types: neuroendocrine cells, Schwann cell-like spindle cells, and scattered ganglion cells. However, the origin and the etiology of these tumors have not yet been established.

Here we report the first case of a gangliocytic paraganglioma arising in a tailgut cyst. It occurred in a 56-year-old man. We also review previous reports in the literature of tumors arising in tailgut cysts.

CASE REPORT

A 56-year-old male patient presented with an intermittent melena of several months duration. He had undergone surgery for an anal fistula 20 years prior to his admission and an appendectomy for acute appendicitis a few years prior to his admission. He had a past history of pulmonary tuberculosis and had achieved complete remission after six months of anti-tuberculosis medication. Endoscopic findings showed a round protruding bulging mass of the submucosal type just above the anus with normal-appearing overlying mucosa (Fig. 1A). On abdominal computed tomography and magnetic resonance imaging, the tumor was shown to be a relatively well-demarcated round mass located in the retrorectal and presacral space without a connection into the rectal mucosa and muscle layer (Fig. 1B). The results of laboratory tests were within normal limits for all tumor markers (carcinoembryonic antigen [CEA], CA19-9, CA-72-4, squamous cell carcinoma antigen). The tumor was resected carefully through a transcoccygeal approach.

Grossly, the tumor measured $3.9 \times 3.3 \times 3$ cm and showed a partly smooth and a partly irregular outer surface (Fig. 1C). The irregular part showed small ruptured cystic lesions. On the

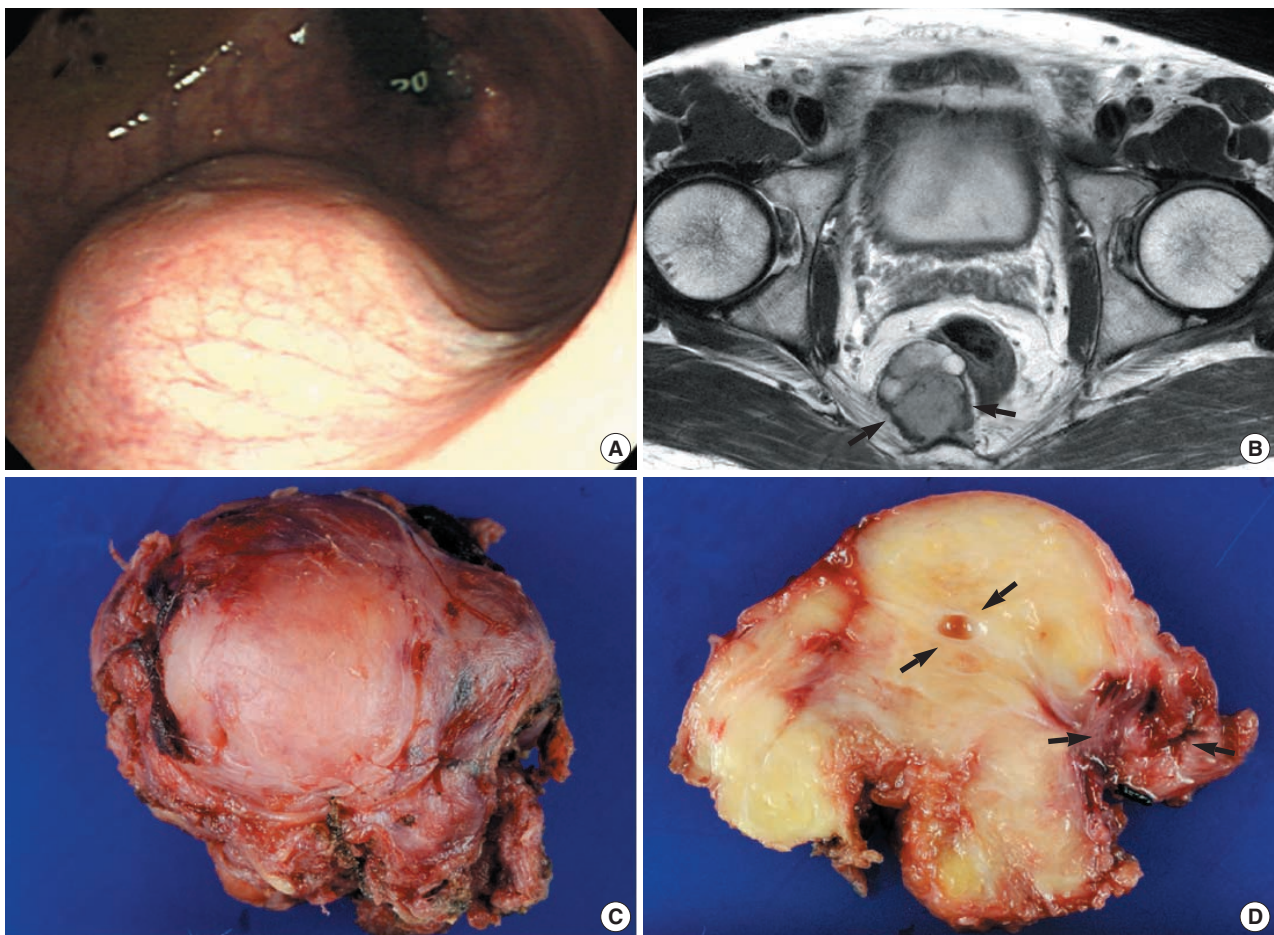


Fig. 1. Colonoscopy shows a round protruding submucosal tumor with a smooth unremarkable overlying mucosa just above the anal sphincter (A). A magnetic resonance imaging scan reveals a relatively well-demarcated multinodular mass in the presacral and retrorectal space (arrows) (B). There is no connection between the mass and the rectal mucosa or the anal sphincter muscle. The external surface of the resected mass is partly smooth and partly irregular (C). The cut surface shows a predominantly yellow white, myxoid and solid appearance with scattered cystic lesions mainly in the right lower part of the picture (arrows) (D).

cut section, the tumor revealed a predominantly yellow white solid and slightly myxoid appearance intermixed with small cysts scattered mainly in the periphery of the tumor (Fig. 1D). There were no specific structures suggesting a teratoma, such as hair, cartilage, or bone tissue. No obvious necrosis or hemorrhage was identified. Microscopically, the tumor was composed of a mostly solid area and a focal cystic area (Fig. 2A). The multilocular cysts were lined by various kinds of epithelia, such as squamous, intestinal, and transitional epithelia (Fig. 2B). Many scattered irregular and discontinuous thick bundles of smooth muscle were observed around the cystic spaces. The tumor cells of the solid area showed various kinds of organoid (neuroendocrine) growth patterns, such as trabeculae or cell nests (Fig. 2C). Some areas revealed admixed features of neural and organoid (neuroendocrine) differentiations (Fig. 2D), while other area

showed admixed features of neural and gangliocytic differentiations (Fig. 2D). No mitoses were identified. The tumor cells showing organoid (neuroendocrine) differentiation were cuboidal with a slightly granular eosinophilic cytoplasm and centrally located uniform round nuclei with speckled chromatin and inconspicuous nucleoli. The tumor cells constituting the area of neural differentiation were spindly and wavy with inconspicuous sharply tapered cytoplasmic borders and with elongated nuclei. The tumor cells intermingled with neural differentiation showed typical gangliocytic features such as a large abundant eosinophilic polygonal cytoplasm with eccentrically located round nuclei with prominent nucleoli.

On immunohistochemical staining, the tumor cells showed strong positivity for CAM 5.2 (1 : 50, Cell Marque, Hot Springs, AR, USA) and other neuroendocrine markers such as neuron-

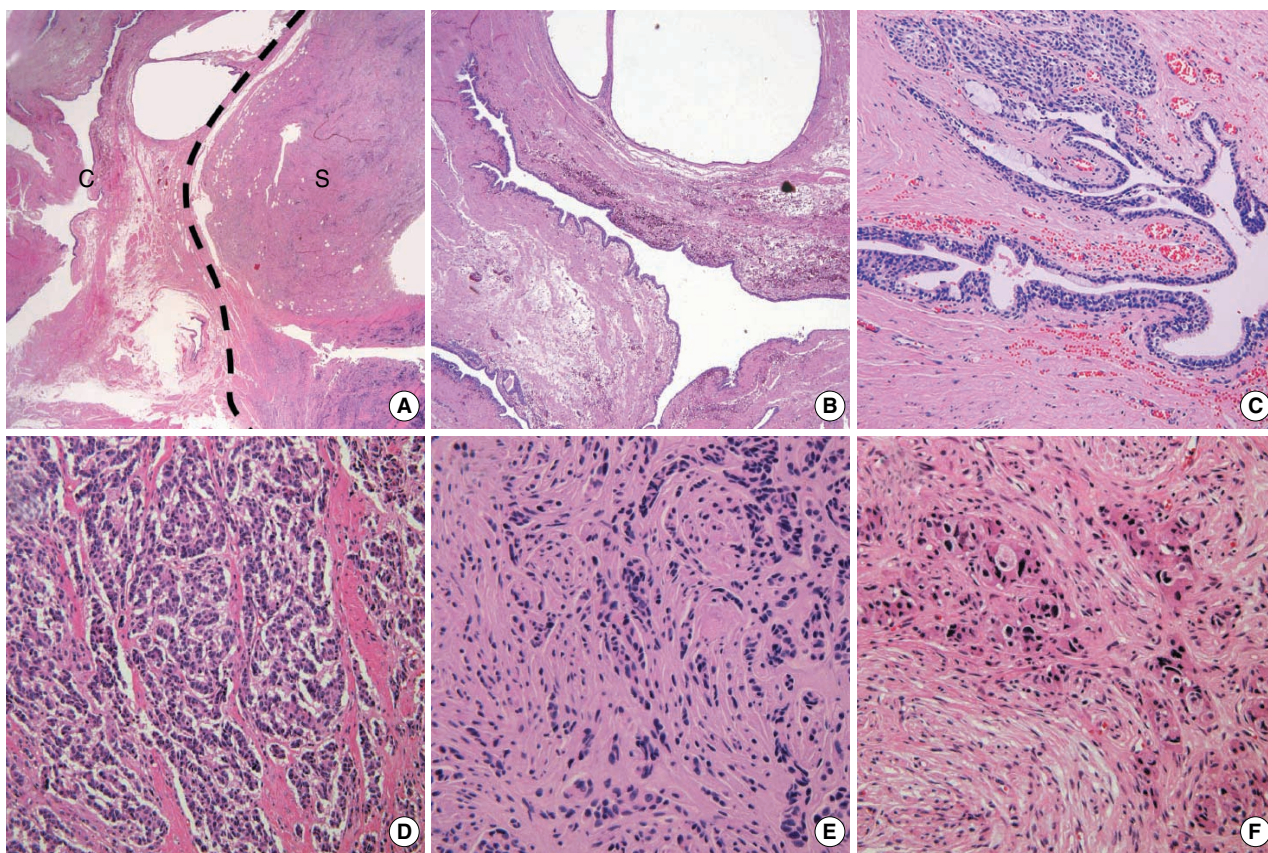


Fig. 2. Microscopically, the low power view reveals solid tumor cell infiltration (designated as S) and cystic part (designated as C) (A). The cystic lesions are surrounded by disorganized smooth muscle bundles (B). These are lined by mucinous, columnar, and transitional epithelia (C). The solid area of organoid (neuroendocrine) pattern shows solid sheets of cuboidal tumor cells arranged in typical trabeculae, ribbons, festoons, and cell nests with intervening thick smooth muscle bundles, which seem to be the components of a tailgut cyst (D). In some area, the neuroendocrine tumor cells are admixed with tumor cells with neural differentiation (E). In another area, a few tumor cells with abundant eosinophilic cytoplasm and large round nuclei, similar to ganglion cells, are admixed with tumor cells with neural differentiation (F).

specific enolase (1 : 300, Dako, Glostrup, Denmark), CD56 (1 : 100, Zymed, San Francisco, CA, USA), synaptophysin (1 : 100, Dako), chromogranin A (1 : 500, Dako); they showed negativity for cytokeratin (1 : 50, Zymed), vimentin (1 : 500, Dako), smooth muscle actin (1 : 1,000, Neomarkers, Fremont, CA, USA), and CEA (1 : 500, Dako). While immunohistochemical staining for S-100 protein (1 : 200, Dako) revealed negativity in tumor cells and positivity in sustentacular elements in the area of neuroendocrine differentiation, it revealed weak and strong positivity in the tumor and sustentacular cells in the area of neural differentiation (Fig. 3A, B). Immunohistochemical staining for neurofilaments (1 : 50, Dako) revealed strong positivity in a few scattered tumor cells showing gangliocytic differentiation (Fig. 3D). On electron microscopy, several clusters of 80-400 nm spherical neurosecretory granules were seen in the cytoplasm. On follow-up computed tomography (CT) scanning carried out

four months after the operation, there was no definite evidence of tumor recurrence or metastasis.

DISCUSSION

Tailgut cysts, also known as retrorectal cystic hamartomas, are congenital hamartomatous lesions present in the retrorectal and presacral space. According to the largest series of Hjerbstad and Helwig⁸ which collected 53 cases of tailgut cysts at the Armed Forces Institute of Pathology, the tumors occur in all age groups, with ages ranging from 4 days to 73 years (average, 35 years), and are more commonly found in females (female : male = 3.1 : 1). About half of the patients were symptomatic, with the most common symptoms being pain of the perirectal or low back area and symptoms of mass effects such as rectal

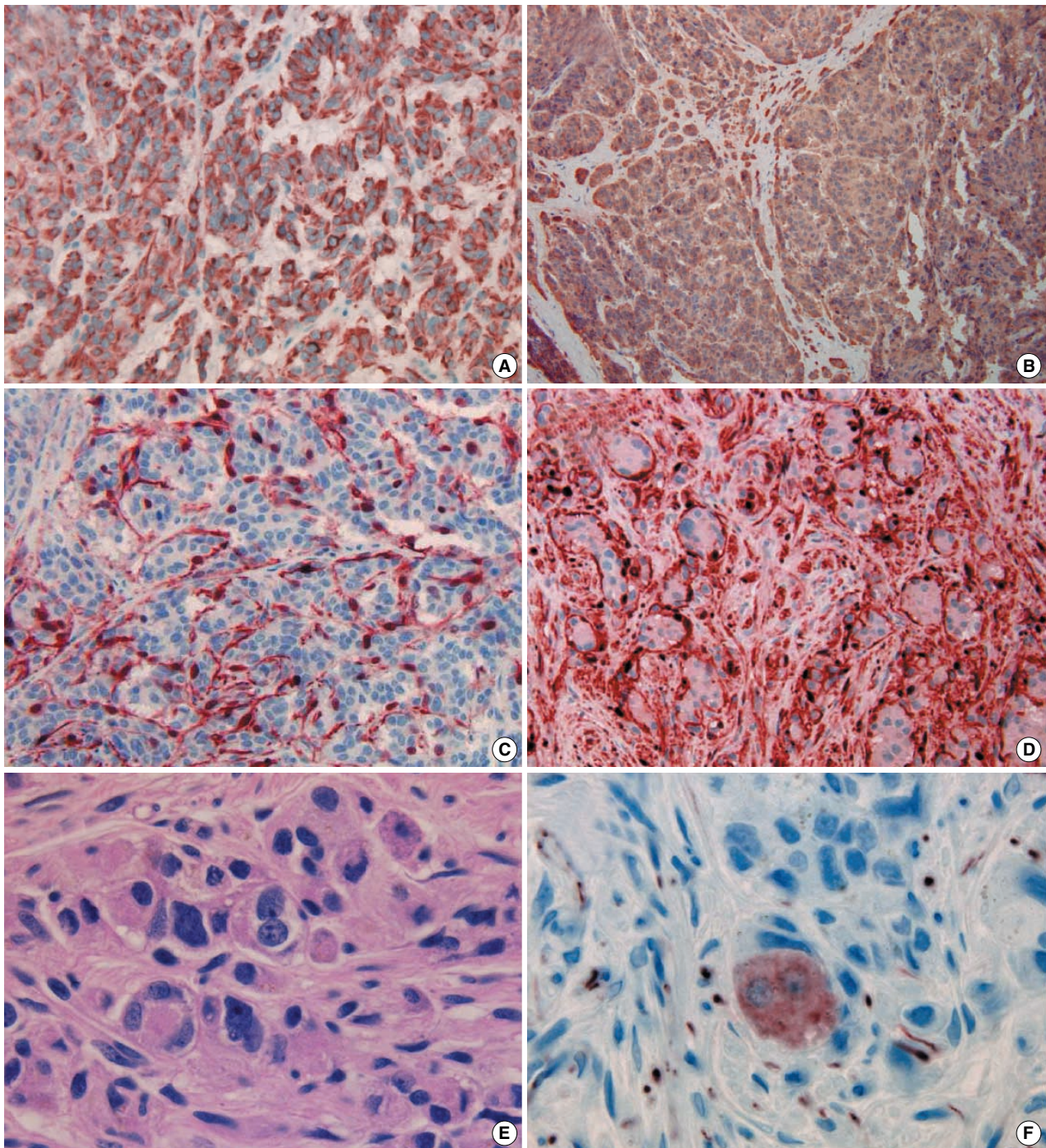


Fig. 3. Immunohistochemically, the tumor cells showing neuroendocrine differentiation are positive for chromogranin (A) and CAM 5.2 (B) and negative for S-100 protein (C). In the area of neuroendocrine differentiation, the cells surrounding tumor cells show positivity for S-100 protein, resembling the sustentacular elements of a paraganglioma (C). In the area of neural differentiation, both tumor cells and sustentacular elements are positive for S-100 protein (D). The tumor cells with abundant eosinophilic cytoplasm and large round nuclei (E) demonstrate focal positivity for neurofilaments (F), verifying gangliocytic differentiation.

fullness, constipation, painless rectal bleeding, and change in the caliber of stool or urinary frequency.

Histologically, tailgut cysts are predominantly multicystic

and can contain a variety of epithelia: squamous, transitional, mucinous or ciliated columnar and cuboidal mucus secreting. The surrounding cystic wall demonstrates various amounts of

disorganized smooth muscle bundles without a neural plexus. With this histologic evidence and its unique location, the anterior sacrococcygeal or retrorectal cystic masses were thought to arise from the tailgut if their lining consisted of an intestinal-type epithelium and they lacked a definite muscular or serous coat. In our case, the cystic part of the tumor was not clearly identified on gross examination because the cysts had previously been ruptured and compressed by the coexisting solid part. However, on microscopic examination, multiple cystic lesions lined by various kinds of epithelia, and surrounded by a disorganized smooth muscle bundle without a neural plexus were clearly identified in the center and the periphery of the tumor.

The differential diagnoses for a retrorectal cystic mass include teratoma, epidermal/dermoid cyst, rectal duplication cyst, müllerian cyst, and anal gland cyst. A diagnosis of these masses can be made on the basis of the anatomical location and the histological components of the cyst. In contrast to the tailgut cysts showing various kinds of epithelia, teratomas and dermoid cysts show mostly squamous epithelia with keratin or dermal appendages. Rectal duplication cysts show mostly columnar epithelia of the rectum, and müllerian cysts do not show transitional epithelia. While tailgut cysts are characterized by disorganized and dispersed smooth muscle bundles, epidermal/dermoid cysts do not show any smooth muscle. Teratomas contain various kinds of mesenchymal elements such as nervous, cartilaginous, and bony structures. In rectal duplication cysts, the muscle layers are well-developed with a nerve plexus between them instead of the disorganized muscle bundles seen in our case. A lack of connection between the anal mucosa and the sphincter muscle and a deep location in the retrorectal space can rule out the possibility of an anal gland cyst.

Regarding the solid part of the tumor, there have been several reports of tumors associated with tailgut cysts, with most tumors being adenocarcinomas,⁹ and neuroendocrine tumors.¹⁰⁻¹³ Cases of squamous cell carcinoma,¹⁴ sarcoma,¹⁵ and endometrioid adenocarcinoma¹⁶ have also been documented. Most adenocarcinomas arising in the intestinal epithelium of the tailgut cyst are considered incidental findings without any specific pathogenetic mechanism other than that of usual rectal adenocarcinomas.

Carcinoid tumors arising in tailgut cysts are thought to be derived from enterochromaffin cells of remnant colonic epithelium in tailgut cysts. Patients with carcinoid tumors, including neuroendocrine carcinoma arising in tailgut cysts, were mainly middle-aged women (6 women and 3 men), ranging in age from 18 to 69 years old.¹³ All cases had symptoms related to local mass effects. No kind of carcinoid syndrome principally related

to an excess of serotonin was found, suggesting that these tumors are mostly non-functional. All cases that were available for a review of microscopic findings showed classical microscopic features of carcinoid tumors such as trabecular, insular, ribbons and festoons, cell nests, and acinar patterns. Gangliocytic differentiation, as seen in our case, was not described in previous cases. Immunohistochemically, they revealed positivity for cytokeratin, CAM 5.2, and one or more neuroendocrine markers such as chromogranin, synaptophysin, or neuron specific enolase.

On the other hand, gangliocytic paragangliomas (paraganglioneuromas) are another kind of rare tumor occurring almost exclusively in the second portion of the duodenum, usually in proximity to the ampulla of Vater. However, a few cases have been reported at other locations, including the appendix,^{1,2} esophagus,⁶ jejunum,¹⁷ pancreas,¹⁸ lung,³ nasopharynx,⁴ bronchus,⁵ mediastinum⁶ and even ovarian cystic teratoma.⁷ Histologically, the microscopic findings of these tumors are apparent and distinctive, with no exact counterpart elsewhere in the body. Three cell components are present: 1) epithelial and endocrine cells with a carcinoid-like appearance arranged in cell nests or trabeculae; 2) intermingled ganglion cells, showing immunoreactivity for neuron-specific enolase, S-100 protein, and neurofilament; and 3) spindle-shaped Schwann cells and/or sustentacular cells immunoreactive for S-100 protein. Our case also showed definite gangliocytic differentiations with immunoreactivity for neurofilaments as well as neuroendocrine and neural differentiations.

The histogenesis of gangliocytic paragangliomas is still a matter of debate. Some authors consider gangliocytic paragangliomas to be true neoplasms of neuroendocrine origin.¹⁹ However, others believe that these tumors are hamartomatous lesions developing in misplaced embryonic pancreatic tissue, which is described as 'sympathetico-insular complexes,' because most of these tumors are located in the proximity of pancreatic tissue and occasionally express pancreatic enzymes.^{2,20,21} Although the first theory seems to be consistent with the origin of our case, the pathogenetic mechanism remains unclear.

As for the prognosis of our case, a differential diagnosis of the solid portion of this tumor is very important. If the tumor is considered a carcinoid tumor, it is classified into a category of well-differentiated neuroendocrine carcinomas (malignant carcinoid tumor) according to the 2000 World Health Organization classification of gastrointestinal neuroendocrine tumors.²² This means that the tumor can develop into metastases or recur even if the tumor was totally resected, and the follow-up CT of this patient revealed unremarkable findings. However, if the

tumor is considered a gangliocytic paraganglioma, it may have a benign clinical course, although in a few cases metastases to regional lymph nodes have been described.²⁰ The fact that the normal rectal mucosa contains neuroendocrine cells that could be the origin of carcinoid tumors might be used to support the theory that a gangliocytic paraganglioma is a neoplasm of neuroendocrine origin like a carcinoid tumor, but such a theory does not explain the presence of the three distinctive different cell types in the tumor. After an extensive review of the literature about carcinoid tumors with neural or gangliocytic differentiation, we found an interesting original description of a 'neurocarcinoïde' in the appendix written by Masson¹ in 1956, which described similar histological features to those of a gangliocytic paraganglioma. Since, there was definite gangliocytic differentiation with immunoreactivity for neurofilament, we think the diagnosis of a gangliocytic paraganglioma might be more suitable for this case.

In summary, we report a very interesting case of a gangliocytic paraganglioma arising in a tailgut cyst in a 56-year-old man. The differential diagnosis of the tumor was essential for predicting the patient's prognosis. A study of tumors associated with tailgut cysts is warranted to clarify the pathogenesis of these tumors.

REFERENCES

1. Masson P. Human tumors: histology, diagnosis and technique. 2nd ed. Paris: Librairie Maloine, 1956.
2. van Eeden S, Offerhaus GJ, Peterse HL, Dingemans KP, Blaauwgeers HL. Gangliocytic paraganglioma of the appendix. *Histopathology* 2000; 36: 47-9.
3. Hironaka M, Fukayama M, Takayashiki N, Saito K, Sohara Y, Funata N. Pulmonary gangliocytic paraganglioma: case report and comparative immunohistochemical study of related neuroendocrine neoplasms. *Am J Surg Pathol* 2001; 25: 688-93.
4. Sinkre P, Lindberg G, Albores-Saavedra J. Nasopharyngeal gangliocytic paraganglioma. *Arch Pathol Lab Med* 2001; 125: 1098-100.
5. Kee AR, Forrest CH, Brennan BA, Papadimitriou JM, Glancy RJ. Gangliocytic paraganglioma of the bronchus: a case report with follow-up and ultrastructural assessment. *Am J Surg Pathol* 2003; 27: 1380-5.
6. Weinrach DM, Wang KL, Blum MG, Yeldandi AV, Laskin WB. Multifocal presentation of gangliocytic paraganglioma in the mediastinum and esophagus. *Hum Pathol* 2004; 35: 1288-91.
7. Mahdavi A, Silberberg B, Malviya VK, Braunstein AH, Shapiro J. Gangliocytic paraganglioma arising from mature cystic teratoma of the ovary. *Gynecol Oncol* 2003; 90: 482-5.
8. Hjermstad BM, Helwig EB. Tailgut cysts: report of 53 cases. *Am J Clin Pathol* 1988; 89: 139-47.
9. Tampi C, Lotwala V, Lakdawala M, Coelho K. Retrorectal cyst hamartoma (tailgut cyst) with malignant transformation. *Gynecol Oncol* 2007; 105: 266-8.
10. Prasad AR, Amin MB, Randolph TL, Lee CS, Ma CK. Retrorectal cystic hamartoma: report of 5 cases with malignancy arising in 2. *Arch Pathol Lab Med* 2000; 124: 725-9.
11. Mourra N, Caplin S, Parc R, Flejou JF. Presacral neuroendocrine carcinoma developed in a tailgut cyst: report of a case. *Dis Colon Rectum* 2003; 46: 411-3.
12. Song DE, Park JK, Hur B, Ro JY. Carcinoid tumor arising in a tailgut cyst of the anorectal junction with distant metastasis: a case report and review of the literature. *Arch Pathol Lab Med* 2004; 128: 578-80.
13. Mathieu A, Chamblou R, Le Moine F, Maris C, Van de Stadt J, Salmon I. Tailgut cyst associated with a carcinoid tumor: case report and review of the literature. *Histol Histopathol* 2005; 20: 1065-9.
14. Umar T, Mikel JJ, Poller DN. Carcinoma arising in a tailgut cyst diagnosed on fine needle aspiration (FNA) cytology. *Cytopathology* 2000; 11: 129-32.
15. Mouloupoulos LA, Karvouni E, Kehagias D, Dimopoulos MA, Gouliamos A, Vlahos L. MR imaging of complex tail-gut cysts. *Clin Radiol* 1999; 54: 118-22.
16. Kanthan SC, Kanthan R. Unusual retrorectal lesion. *Asian J Surg* 2004; 27: 144-6.
17. Grouls V, Pickartz H, Reis HE. Pedunculated polypoid gangliocytic paraganglioma of the afferent jejunal loop of a Billroth II stomach. *Leber Magen Darm* 1987; 17: 327-33.
18. Henry C, Ghalel-Méchaoui H, Bottero N, Pradier T, Moindrot H. Gangliocytic paraganglioma of the pancreas with bone metastasis. *Ann Chir* 2003; 128: 336-8.
19. Collina G, Maiorana A, Trentini GP. Duodenal gangliocytic paraganglioma: case report with immunohistochemical study on the expression of keratin polypeptides. *Histopathology* 1991; 19: 476-8.
20. Burke AP, Helwig EB. Gangliocytic paraganglioma. *Am J Clin Pathol* 1989; 92: 1-9.
21. Perrone T, Sibley RK, Rosai J. Duodenal gangliocytic paraganglioma: an immunohistochemical and ultrastructural study and a hypothesis concerning its origin. *Am J Surg Pathol* 1985; 9: 31-41.
22. Hamilton SR, Aaltonen LA. World Health Organization classification of tumours: pathology and genetics of tumours of the digestive systems. Lyon: IARC Press, 2000.