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Case Report

Benign Hybrid Schwannoma-Perineurioma of the Gastric Wall: A Report of Three Cases

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Abstract

We present three cases of benign hybrid peripheral nerve sheath tumors of the stomach. Endoscopy revealed a gastric mass in all cases; thus, a partial gastrectomy was performed. Gross examination revealed gastric masses extending through the wall. Histologically, the tumor cells were bland, spindled, with tapered and often wavy nuclei in a loose fibromyxoid stroma formation. On the basis of hematoxylin-eosin (H&E) stain analysis, the differential diagnosis included schwannomas, perineuriomas, leiomyomas, and gastrointestinal stromal tumors. Immunohistochemistry revealed diffuse immunostaining for S-100 protein and multifocal positivity for epithelial membrane antigen, Glut-1, and Claudin-1 in all three cases. CD117, DOG1, actin and neurofilament protein were uniformly negative. Based on the histopathology and immunophenotype, these tumors are classified as benign hybrid schwannoma-perineuriomas. They cases presented herein, complete five cases in the English language literature of hybrid peripheral nerve sheath tumors affecting the stomach.

Keywords: Hybrid peripheral nerve sheath tumors, Schwannoma, Perineurioma

Introduction

The spectrum of benign peripheral nerve sheath tumors (PNSTs) include neurofibromas, schwannomas, and perineuriomas, primarily presenting as distinct lesions [1,2]. PNSTs showing features of more than one histologic type are increasingly recognized as hybrid PNSTs [3-5]. Originally described by Feany et al., the majority of hybrid PNSTs arise in peripheral nerves of the extremities and trunk, and are rarely documented in the gastrointestinal tract [6-8]. We discuss three additional cases of hybrid PNSTs of the stomach, and emphasize immunohistochemistry in order to reach an accurate diagnosis.

Materials and Methods

We identified three cases of hybrid PNSTs from the files of the Anatomical Pathology Department of the Medica Sur Hospital in Mexico City. These cases were submitted for consultation from January 2010 to September 2020. None were previously published. Basic clinical details were obtained from requisition forms and clinic notes.

Moreover, 4μm sections were cut from paraffin blocks in these cases and stained with hematoxylin and eosin (H&E). Additional paraffin sections were procured for immunohistochemical studies, which were performed on formalin-fixed, paraffin-embedded material using a standard avidin-biotin immunoperoxidase technique.

Immunohistochemistry included antibodies directed against S-100 protein (Bio SB; dilution 1:200), smooth muscle actin (Bio SB; dilution 1:500), epithelial membrane antigen (EMA) (BioCare; dilution 1:100), glucose transporter 1 (Glut-1) (BioCare; dilution 1:100), CD117 (Bio SB; dilution 1:250), discovered on GIST 1 (DOG-1) (BioCare; dilution 1:100), neurofilament protein (Cell Marque; dilution 1:500), GFAP (Bio SB; dilution 1:500), CD34 (Bio SB; dilution 1:100) and Ki-67 (Bio SB; dilution 1:50).

Results

Clinical features of the three cases are summarized in Table 1. The patients included one female and two males, with a mean age of 49.6 years (range, 37 to 58 years). Patients presented with abdominal discomfort, while patient two presented with diarrhea

Table 1: Clinicopatholgical features of published gastric hybrid peripheral nerve sheath tumors.

Case	Age (y)/ Sex	Site	Size (cm)	Clinical Diagnosis	Immunohistochemical Findings	Reference
1	76/F	Greater curvature	7.0	Mesenchymal tumor	**(+) S100, EMA, Glut-1** **(-) CD34, Smooth muscle actin, Desmin, DOG-1, CD-117.**	# 8
2	50/F	Body	1.2		**(+) S100, GFAP, CD56, EMA, Glut-1, Claudin-1, CD34** **(-) CD-117, DOG1, PDGFα**	# 9
3	58/M	Fundus	3.0	GIST	**(+) S100, EMA, Glut-1, Claudin-1, Neurofilament protein** **(-) Smooth muscle actin, CD-117, DOG1**	Present case
4	37/F	Body	6.5	Leiomyoma	**(+) S100, EMA, Glut-1, Claudin-1, Neurofilament protein** **(-) Smooth muscle actin, CD-117, DOG1**	Present case
5	54/M	Body	4.6	GIST	**(+) S100, EMA, Glut-1, Claudin-1, Neurofilament protein** **(-) Smooth muscle actin, CD-117, DOG1**	Present case

and hematemesis (Table 1). None of the patients had a history of neurofibromatosis, schwannomatosis, or multiple endocrine neoplasm syndrome. The endoscopic diagnoses before excision included gastrointestinal stromal tumor (GIST) and leiomyoma, so a partial gastrectomy was performed in all cases. Clinical follow-up was available without evidence of recurrence or metastatic disease (mean follow-up two years). Gross examination showed a relatively well-circumscribed submucosal nodular mass that macroscopically was suggestive GIST or leiomyoma. The tumors range from 5.0 to 9.0 cm in maximal diameter (Table 1).

The mucosal surface overlying the mass of two cases was ulcerated and focally hemorrhagic (Figures 1A, 2A). The cut surface was tan-white/yellow, with a firm consistency (Figures 2B, 3A). The surrounding gastric mucosa was focally congested and the serosal surface was intact. The histopathologic study revealed similar morphology in all three tumors. They were well-circumscribed and the tumor cellular proliferation consisted of fascicles of bland spindle cells with elongated tapering ends, often wavy nuclei, and a pale or slightly eosinophilic cytoplasm, set in a variable collagenous stroma (Figures 2C, 3B). There were focal areas with lymphoid infiltrate with lymphoid follicles in the periphery of the lesion (Figure 2D). There were no Verocay bodies or Antoni B areas. In addition, there were no significant nuclear atypia, mitotic activity, or necrosis to suggest malignancy. Case two (37-year-old patient) also showed a focal lace-like/reticular /microcystic pattern with delicate anastomosing and intersecting strands with focal myxoid stroma (Figure 1B). Based exclusively on the H&E section, the differential diagnoses included schwannoma, perineurioma, leiomyoma, and GIST.

Immunohistochemical studies revealed that the cellular proliferation of all three cases showed diffuse positivity for S100, while EMA (epithelial membrane antigen), Glut-1, and Claudin-1 were

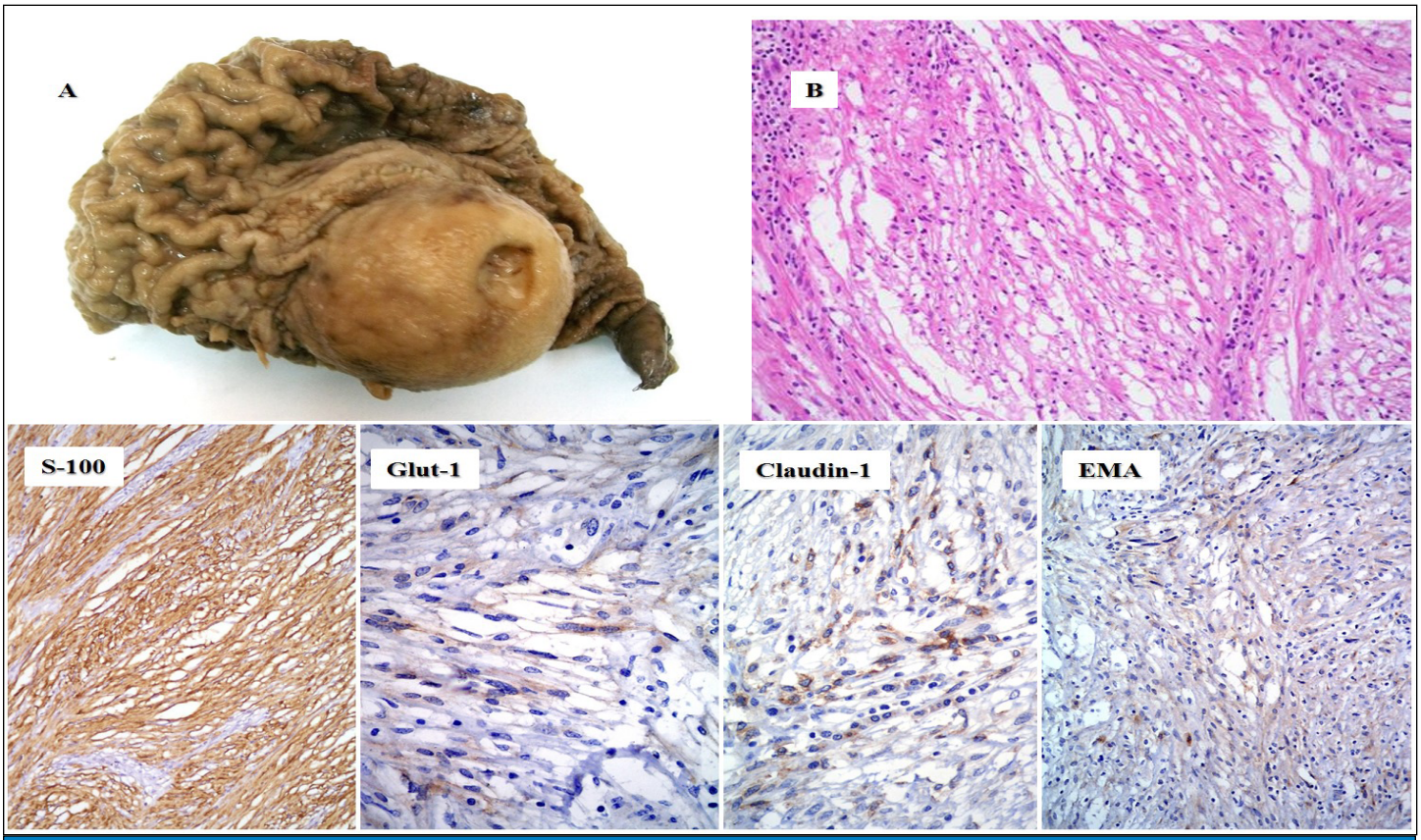

Figure 1: Case #1: 37-year-old female. A) The tumor mass was ulcerated and focally hemorrhagic; B) The tumor cells showed a reticular growth pattern in a fibromyxoid stroma. Strong diffuse S100 protein expression. Glut-1, Claudin-1, and EMA highlighted fascicles of perineurial cells. EMA = epithelial membrane antigen.

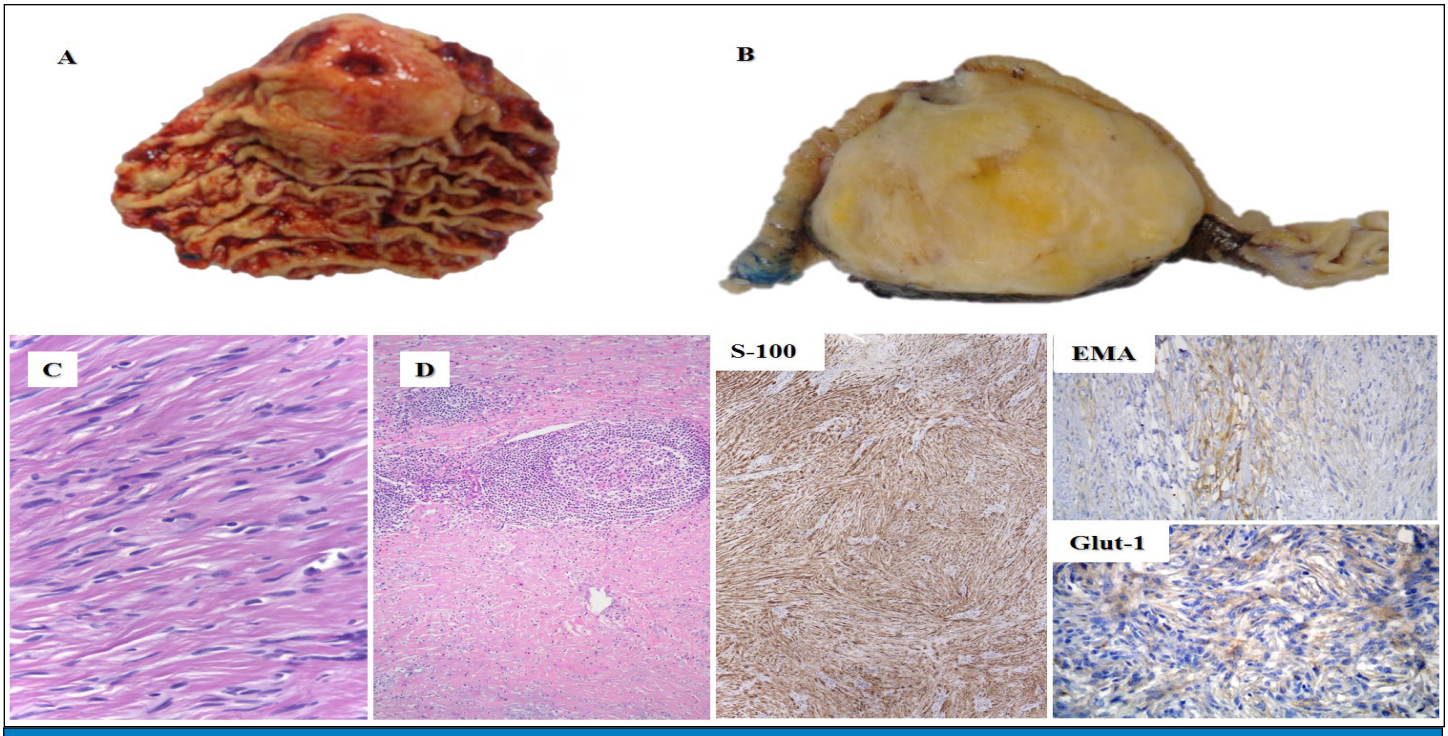

Figure 2: Case #2: 54-year-old male. A) The tumor mass was ulcerated and hemorrhagic; B) The cut surface was a tan-yellow with a firm consistency; C) Most neoplastic cells show oval or plump spindle cells with wavy nuclei. No significant nuclear atypia, mitotic activity, or necrosis was present. D) Areas with lymphoid infiltrate with focal lymphoid follicles. Strong diffuse S100 protein expression. EMA and Glut-1 highlighted fascicles of perineurial cells. EMA = epithelial membrane antigen.

positive in multiple areas. GFAP was focally positive in cases one and two, and negative in case three. All other markers, including smooth muscle actin, DOG-1, CD117, and neurofilament protein were uniformly negative. CD34 expression was focal and thus limited to the stromal component between tumor cell fascicles, with Ki67 expressed in less than 5% of tumor cells in the three cases. A diagnosis of hybrid nerve sheath tumor was rendered; case one represented schwannoma/reticular perineurioma while cases two and three represented cellular schwannoma/perineurioma.

Discussion

The diagnosis of schwannoma, perineurioma and neurofibroma is usually uncomplicated, given the unique morphological and immunohistochemical characteristics of each tumor type [1,2]. PNSTs demonstrating morphologic overlap of these entities have been named hybrid PNSTs. These tumors exhibit an abrupt transition of cell types with overlapping immunohistochemical positivity between S-100 (schwanninan) and EMA, Glut-1, and Claudin-1 (perineurial). Extraneural occurrence of benign PNSTs with distinct schwannomas and perineurioma features is infrequent, and those involving the gastrointestinal tract are extremely rare [9]. To the best of our knowledge, our three cases summarize five reported cases in the English language literature of hybrid PNSTs, affecting the stomach, and are summarized in table 1 [8-10]. Tumors in the gastrointestinal tract can be diagnostically challenging, as differential diagnoses include other benign PNSTs, GISTs, and leiomyomas [3].

Histologically, the presence of storiform, lamellar, and whorled patterns (perineurioma-like architecture), combined with a neural-like schwannian differentiation, suggest the possibility of hybrid schwannoma-perineurioma. Yet, immunohistochemical analysis is crucial to confirm the diagnosis. It is possible to determine the biphasic composition only by combining S-100, EMA, Glut-1, and Claudin-1 [3]. Hybrid schwannoma-perineuriomas usually lack Antoni A and B areas, Verocay bodies, and hyalinized blood vessels, which are characteristically seen in schwannomas. On the other hand, the perineurial component of hybrid schwan-

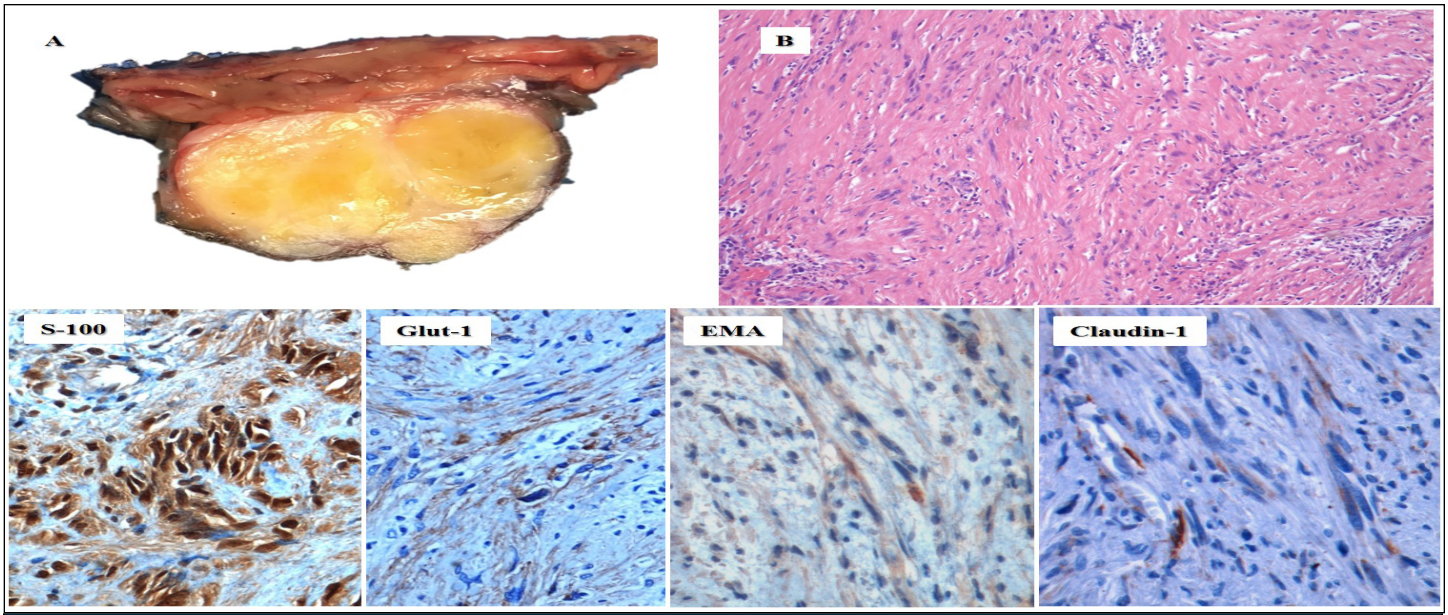

Figure 3: Case #: 58-year-old male. A) The cut surface of the tumor was well-circumscribed, yellow with a firm consistency; B) Spindle-shaped and fascicularly-arranged cells in fibrous stroma, with scattered lymphoid infiltrate. Strong diffuse S100 protein expression. Glut-1, EMA, and Claudin-1 immunostains highlighted fascicles of perineurial cells. EMA = epithelial membrane antigen.

noma-perineuriomas tend to be inconspicuous on H&E sections; therefore, it is likely that hybrid tumors are underrecognized. In fact, the routine use of IHC including S-100, EMA, Glut-1, and Claudin-1 has been suggested to increase the frequency of hybrid PNST detection. GIST and leiomyoma must be considered as a differential diagnosis in any patient presenting with a spindle cell neoplasm in the stomach.

In our three cases, the clinical diagnosis was of GIST (2 cases) and leiomyoma (1), possibly due to the fact that these neoplasms are the most frequently mesenchymal tumors present at this anatomical site. Unfortunately, there is no clinical, endoscopic, CT, MRI or PET-CT characteristics to suggest the diagnosis of a hybrid tumor, and histopathological examination with appropriate immunohistochemistry is needed. The negative expression of CD117 and DOG1 will exclude the diagnosis of GIST, whereas negativity to actin and desmin excludes the diagnosis of leiomyoma.

Concerning treatment, complete surgical excision is curative, since the behavior of such tumors is usually benign; however, one recurrence after incomplete resection of two cases of malignant transformations have been reported [11].

In summary, hybrid PNSTs occurring in the gastrointestinal tract may be easily overlooked; therefore, a high degree of suspicion is necessary. Immunohistochemical analysis is crucial in order to endorse the hybrid proliferation of these tumors. Routine use of immunohistochemistry in spindle cell neoplasms of the stomach, including S-100. Glut-1 and claudin-1, will surely increase their frequency.

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