Sporadic ganglioneuromatosis of esophagogastric junction in a patient with gastro-esophageal reflux disorder and intestinal metaplasia

Richard Siderits, Iman Hanna, Zahid Baig, Janusz J Godyn

Abstract

A 58-year-old female with a recurrent history of upper abdominal pain and intermittent dysphagia underwent endoscopic evaluation that demonstrated an irregular and nodular esophago-gastric (EG) junction and grade I erosive esophagitis. Biopsies showed prominent intestinal metaplasia of Barrett’s type without dysplasia, chronic inflammation and multiple aggregates of large cells within the mucosal lamina propria, some with spindle shaped nuclei. Immunohistochemistry stains for keratins AE-1/AE-3 were negative, while S-100 and NSE were positive. This, together with routine stains, was diagnostic for mucosal ganglioneuromatosis. The background of chronic inflammation with intestinal type metaplasia was consistent with long-term reflux esophagitis. No evidence of achalasia was seen. Biopsies of gastric antrum and fundus were unremarkable, without ganglioneuronal proliferation. Colonoscopy was unremarkable. No genetic syndromes were identified in the patient including familial adenomatous polyposis and multiple endocrine neoplasia type II b (MEN II b). Iansoprazole (Prevacid) was started by oral administration each day with partial relief of symptoms. Subsequent esophagogastroduodenoscopy repeated at 4 mo showed normal appearing EG junction. Esophageal manometry revealed a mild non-specific lower esophageal motility disorder. Mild motor dysfunction is seen with gastro-esophageal reflux disease (GERD) and we feel that the demonstration of localized ganglioneuromatosis was not likely related etiologically. In the absence of findings that might suggest neural hypertrophy, such as achalasia, the nodular mucosal irregularity seen with this instance of ganglioneuromatosis may, however, have exacerbated the patient’s reflux.

© 2006 The WJG Press. All rights reserved.
fusion and celiac axis stenting. Medications prior to endoscopic biopsy of esophagogastric EG junction included the following: Atorvastatin, pioglitazone HCl, diphenhydramine, Glipizide, Pyridoxine, isosobide and dihydrocodeinone.

**Endoscopic and microscopic findings**

Endoscopy showed a somewhat nodular and irregular appearing EG junction with non-erosive mucosa (Figure 1). The antrum showed mild non-erosive gastritis. The pylorus and duodenum were unremarkable. Biopsies of the EG junction, antrum and duodenum were obtained. Hematoxylin and Eosin stained histologic sections from the EG junction showed aggregates of tangled fascicles of large cells mixed with Schwann-like spindle cells expanding lamina propria (Figure 2). At low magnification this gave a pseudo granuloma appearance with distortion of the adjacent gland architecture. Higher magnification revealed a fibrillar cytoplasmic matrix with monomorphic bland nuclei without mitotic activity. Differential diagnosis for these features included ganglioneuroma, neurofibroma and schwannoma[1]. Immunohistochemical staining for S100 demonstrated a nerve sheath component. Focal positivity for Synaptophysin confirmed the presence of a ganglioneuronal tissue (Figure 3). The glandular epithelial component showed frequent goblet cells with no evidence of dysplasia. Chronic inflammatory cells were scattered in mucosal stroma. The biopsy diagnosis based on both HE and immunophenotypic characterization was of localized ganglioneuromatosis of EG junction within a background of mild chronic inflammation and prominent intestinal metaplasia without dysplasia.

**Treatment and follow-up**

Clinical correlation excluded the presence of achalasia or MEN- II B. Treatment following this diagnosis of localized ganglioneuroma associated with esophagitis included prevacid 30 mg daily. Neurontin had been considered if symptoms would have progressed; however, this was not the case. A follow-up observation with repeat endoscopic evaluation at 4 mo was performed and showed mild gastritis with mild chronic inflammation in an unremarkable EG junction without ulceration or nodularity. Early recognition of symptomatology that might suggest either lower esophageal sphincter (LES) dysfunction or esophageal dysmotility was reviewed with the patient. No other family members were symptomatic or presented a history that might suggest hereditary or familial factors. Colonoscopy showed no discrete lesions. Except for occasional bouts of mild non-specific abdominal pain and mild dysphagia, the patient remained well for a year. There was no complaint, odynophagia or nausea. Esophageal manometry was performed for persistent dysphagia at one year following the initial biopsy. This demonstrated a distal esophageal amplitude of 106 mm mercury with a duration of 3.5 s, peristaltic contraction 90% with 10% simultaneous contractions. Detailed review of the manometric data suggested a mild non-specific lower esophageal motility disorder.

In the absence of changes that might suggest neural hypertrophy, occasionally seen with achalasia, the mild motor dysfunction in this patient may be related to GERD. The demonstration of localized ganglioneuromatosis was most likely fortuitous and not etiologically related to the gastroesophageal reflux. However, the patient’s insulin dependant diabetes might have affected esophageal motility possibly associated with an increased incidence of reflux.

It is most likely that the generous biopsy sampling of the nodular EG may have removed a significant portion of the lesion; therefore, it was not overtly visible on the subsequent endoscopy.
DISCUSSION

Primary esophageal tumors that show neuroid differentiation in addition to ganglieneuromata, include gastro-intestinal autonomic nerve tumor (GAN)\(^1\)\(^\text{[2,3]}\), schwannoma\(^1\)\(^\text{[4,5]}\) (some occasionally showing melanocytic differentiation)\(^6\), and neurofibromas\(^7\). The innervation of the lower esophagus includes parasympathetic supply from the vagi and sympathetic innervation from the greater splanchnic and thoracic ganglia\(^8\). Histologically the neural components are seen within the muscle layer as myenteric plexus and in the submucosal neural plexus with branches entering the lamina propria\(^9\).

Solitary or disseminated Schwann cell and ganglion cell proliferation anywhere in the gastrointestinal tract may appear as small intramucosal nodular lesions\(^10\), exophytic polypoid lesions, or poorly demarcated transmural proliferations\(^11\). Ganglioneuroma, a fully differentiated tumor with no immature components\(^12\), may occur as a solitary lesion (sporadic) or as multiple lesions called ganglioneuromatosis and may be associated with other diseases (syndromic).

Sporadic ganglioneuroma has been unknown to be associated with genetic syndromes and has been detected in patients of all ages with a mean age of 50 years. The majority of the solitary lesions are asymptomatic and, therefore, found incidentally, most frequently in the left colon\(^13\).

Among the cases of multiple lesions, ganglioneuromatosis of an exophytic polypid type (ganglioneuromatous polyposis) is characterized by interposition of neural proliferations with glandular components and is usually associated with familial adenomatous polyposis and multiple cutaneous lipomas. Ganglioneuromatosis of transmural proliferation type arising from the neural plexus in the bowel wall is frequently associated with other tumors, including MEN IIb (medullary carcinoma thyroid, pheochromocytoma, oral-mucosal neuromas and skeletal deformities)\(^14\), multiple ganglioneuromas and neurofibromas of the gastrointestinal tract, von Recklinghausen's disease, and neurogenic sarcoma\(^15\). Florid hyperplasia of submucosal or myenteric plexus is distinct for intramural ganglioneuromatosis and occurs with type I neurofibromatosis\(^16\). Patients with syndromic ganglioneuromatosis present with symptoms, and the lesions are found much earlier in life, with a mean age approximately 35 years. There is no gender predominance in the incidence of this disease.

Non neoplastic neural proliferations involving the esophagus include achalasia, which is an esophageal motor disorder associated with a loss of myenteric ganglion cells with inflammation and secondary changes including neural proliferation, which closely mimics ganglioneuromatosis\(^17\). Neoplastic neural tumors that can involve the esophagus include ganglioneuroma, GAN, schwannoma, neurofibroma and other less prevalent forms like granular cell tumor with large eosinophilic cells\(^18\); gangliocytic paraganglioma showing predominantly spindle shaped cells with both ganglion and neuroendocrine features (more often seen in duodenum)\(^19\). Ganglioneuromatosis is visibly present throughout the gut showing predominantly spindle shaped neural proliferations with frequent ganglion type cells.

Ganglioneuroma is a benign tumor and the solitary variant may be cured by excision of the nodular lesion or complete polypectomy. Lesions in syndromic ganglioneuromatosis may require surgery, but the patient may die from the associated syndromes.

In summary, this case illustrates an instance of sporadic ganglioneuromatosis involving EG junction in a 58-year old female with a recurrent history of upper abdominal pain. Background of chronic inflammation and intestinal type metaplasia suggested that the symptoms were related to reflux esophagitis, possibly exacerbated by the nodular growth of the ganglioneuromatosis, which involved the gastro-esophageal junction. The attendant mild lower esophageal motility disorder (demonstrated by manometry) may reflect nonspecific reflux disorder. The patient was initially treated with lansoprazole (Prevacid), which resulted in a partial relief of symptoms. This was followed by esomeprazole (Nexium) with additional relief of symptoms. The patient continued to experience mild intermittent dysphagia without odynophagia or nausea. Repeat EG endoscopy at 4 mo showed unremarkable GE junction. The importance of recognizing symptomatology indicative of lower esophageal sphincter dysfunction was reviewed with this patient with a discussion of follow-up studies over time\(^20\). It appears that the initial generous biopsy sampling removed the EG tumor nodularity, and this, together with the anti-acid treatment, decreased the intensity of the reflux esophagitis. Following the manometric study the patient was advised to swallow slowly with at least 30 s intervals, avoid beverages with extreme temperatures and was maintained on her current medications. We believe that although not etiologically associated, localized esophageal ganglioneuromatosis may exacerbate aspects of gastro-esophageal reflux disorder.

REFERENCES

1. Burger PC, Scheithaur BW, Vogel FS. Surgical Pathology of the Nervous System and its Coverings. 4th ed. New York: Churchill Livingston, 2002: 515-519, 620-623
2. Lam KY, Law SY, Chu KM, Ma LT. Gastrointestinal autonomic nerve tumor of the esophagus. A clinicopathologic, immunohistochemical, ultrastructural study of a case and review of the literature. Cancer 1996; 78: 1651-1659
3. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 1999; 30: 1213-1220
4. Hsu SD, Cheng YL, Chen A, Lee SC. Esophageal schwannoma. J Formos Med Assoc 2013; 102: 346-348
5. Prévot S, Bienvenu L, Vaillant JC, de Saint-Maur PP. Benign schwannoma of the digestive tract: a clinicopathologic and immunohistochemical study of five cases, including a case of esophageal tumor. Am J Surg Pathol 1999; 23: 431-436
6. Brown RM, Darnton SJ, Papadaki L, Antonakopoulos GN, Newman J. A primary tumour of the oesophagus with both melanocytic and schwannian differentiation. Melanocytic schwannoma or malignant melanoma? J Clin Pathol 2002; 55: 318-320
7. Lee R, Williamson WA. Neurofibroma of the esophagus. Ann Thorac Surg 1997; 64: 1173-1174
8. Clemente CD. Crainial nerves. In: Gray’s Anatomy. 13th ed. Philadelphia: Lea & Febiger, 1985: 1174-1187
9. Young B, Heath JW. Gastrointestinal tract structure. In: Wheeler’s Functional Histology a text and color atlas. 4th ed. Philadelphia: Churchill Livingston, 2000: 250-251
Siderits R et al. Sporadic localized esophageal ganglioneuromatosis of esophageal junction

10 Rosai J. Gastrointestinal tract tumors. In: Rosai and Ackerman’s Surgical Pathology. 9th ed. New York: Mosby, 2004: 824-825
11 Kwon MS, Lee SS, Ahn GH. Schwannomas of the gastrointestinal tract: clinicopathological features of 12 cases including a case of esophageal tumor compared with those of gastrointestinal stromal tumors and leiomyomas of the gastrointestinal tract. Pathol Res Pract 2002; 198: 605-613
12 Weis WW, Goldblum JR. Primitive Neuroectodermal Tumors and Related Lesions. In: Enzinger and Weiss’s Soft Tissue Tumors. 4th ed. Philadelphia: Mosby, 2001: 1284-1285
13 Iacobuzio-Donahue CA, Montgomery E, Goldblum JR. Gastrointestinal Mesenchymal Tumors Ch. 7, edited by Montgomery E, Fisher C. In: Gastrointestinal and Liver Pathology. Philadelphia: Churchill Livingstone, 2005: 204-234
14 Cuthbert JA, Gallagher ND, Turtle JR. Colonic and oesophageal disturbance in a patient with multiple endocrine neoplasia, type 2b. Aust N Z J Med 1978; 8: 518-520
15 Lewin KJ, Appelman HD. Mesenchymal tumors and tumor-like proliferations. In: Atlas of Tumor Pathology Tumors of the Esophagus and Stomach. Washington DC: AFIP Press, 1996: 441-444
16 Weidner N, Cote R, Suster S, Weiss L. Gastrointestinal tract; Large Intestine. In: Modern Surgical Pathology. Philadelphia: Saunders, 2003: 792-795
17 Mills SE, Carter D, Greenson JK, Oberman HA, Reuter V, Stoler MH. Inestinal Neoplasms Ch. 34. In: Sternberg’s Diagnostic Surgical Pathology. Vol. 2, 4th edition. Philadelphia: Lipincott Williams & Wilkins, 2004: 1549-1550, (achalasia) 1413
18 Gershwind ME, Chiat H, Addei KA, Ferraro LR. Granular cell tumors of the esophagus. Gastrointest Radiol 1978; 2: 327-330
19 Odze R, Goldblum J, Crawford J. Mesenchymal Tumors of the GI tract Ch. 22. In: Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas. Philadelphia: Saunders, 2004; 518-519
20 Fauci AS, Braunwald E, Isselbacher K, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL. Diseases of the Esophagus Ch. 283. In: Harrison’s Principles of Internal Medicine. 14th edition. New York: McGraw-Hill, 1998: 1588-1596

S- Editor Wang GP  L- Editor Zhu LH  E- Editor Liu WF

www.wjgnet.com