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Case 5

Clinical history:

Man, asymptomatic, with a family history of gastric cancer. In his family, the proband was a 23-year old female who presented epigastric pain. Multiple endoscopic biopsies revealed the presence of diffuse carcinoma (signet ring cell type). Upon total gastrectomy, a large tumour was observed in the body of the stomach with lymph node metastases. The patient died 9 months after surgery. Mutation screening revealed the presence of a germline mutation of E-cadherin gene (*CDH1*) leading to an aminoacid substitution for an Ala to Val at position 1901 (C>T) in codon 634. The proband had an older brother who had died with diffuse gastric carcinoma at the age of 26. The proband had also six asymptomatic siblings who were tested after informed consent, and one (the present case) harbored the same Ala634Val germline alteration.

This individual was informed, during genetic counseling, he was a carrier of the *CDH1* germline mutation that was identified in the proband. He was recommended to undergo a program of endoscopic screening and both gastroscopy and random biopsies were negative for malignancy. The early death of two siblings and the putative pathogenic potential of the *CDH1* mutation were the main factors leading to the decision of prophylactic gastrectomy, albeit no alterations were revealed by gastroscopy and random biopsies. Elective total prophylactic gastrectomy was carried out on June 7, 2005.

Pathologic features:

The surgical specimen (total gastrectomy) was grossly normal both in appearance and by palpation. The stomach was opened along the greater curvature, pinned onto wax board, and fixed in 10% formalin. The specimen was sectioned in its entirety, with the source of each section noted on a corresponding map (the number of blocks was 197, each containing one or more tissue fragments).

In the microscopic evaluation of the surgical specimen, 14 *foci* of intramucosal diffuse carcinoma (signet ring cell type) were identified. Neoplastic cells displayed a pure signet ring cell phenotype, those in the deepest levels of invasion were smaller than neoplastic cells present in the superficial zone of the mucosa. Vascular (lymphatic or venous) invasion and nodal metastases were not observed. Surgical resection margins (oesophageal and duodenal) were free of neoplasia.

Additionally, *in situ* signet ring cell carcinomas (2 lesions) were identified in the surgical specimen, characterized by the lining of foveolae and glands by signet ring cells with hyperchromatic nuclei and lack of polarity with respect to the basement membrane. Furthermore, three glands/foveolae displayed a two-layer structure, an inner layer composed of benign mucous cells and an outer layer of continuous or discontinuous tumour signet ring cells, displaying the features of the so-called pagetoid spread.

Background changes identified in the gastric mucosa encompassed mild chronic gastritis, foveolar hyperplasia and tufting of surface epithelium (focally with globoid change). Intestinal metaplasia was not found and *Helicobacter pylori* infection was not detected.

Diagnosis: Signet ring cell/diffuse carcinoma in the setting of Hereditary Diffuse Gastric Cancer (HDGC).

Discussion:

The syndrome of HDGC was defined after Parry Guilford and colleagues described germline truncating E-cadherin gene (*CDH1*) mutations in three Maori families with autosomal dominant diffuse gastric cancer (1,2). In 1999, the International Gastric Cancer Linkage Consortium

(IGCLC) was constituted with the aim to develop common terminology for this disease, and to produce evidence-based guidelines for the management of patients (3). The IGCLC defined the syndrome of Hereditary Diffuse Gastric Cancer (HDGC) (OMIM #137215) as any family fulfilling one of the following criteria: (1) two or more documented cases of diffuse gastric cancer in first/second degree relatives, with at least one diagnosed before the age of 50; or (2) three or more cases of documented diffuse gastric cancer in first/second degree relatives, independently of age. Families with aggregation of gastric cancer and an index case with diffuse gastric cancer, but not fulfilling the IGCLC criteria for HDGC, are termed familial diffuse gastric cancer (FDGC).

Once *CDHI* mutations are identified in asymptomatic individuals, they are presented with the options of intensive endoscopic surveillance or prophylactic gastrectomy (3). The aim of surveillance is to identify an early curable lesion but the value of endoscopy is unproven due to the difficulty of detecting intramucosal lesions (4). Antral predominance of early cancers was reported by some authors (5) but not confirmed by others (6). In an effort to improve the diagnostic yield of surveillance endoscopy in the upper gastrointestinal tract, techniques such as chromoendoscopy have been recommended (7).

Several prophylactic gastrectomies have been performed in carriers of *CDHI* germline mutations. To date, it has been demonstrated that resected stomachs from different families all carried multifocal signet ring cell carcinoma (6,8).

The systematic study of the prophylactic gastrectomies led to the proposal of a model of the early development of Hereditary Diffuse Gastric Cancer (9) encompassing the following lesions: *in situ* signet ring cell carcinoma, pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae, and early invasive intramucosal signet ring cell carcinoma. The discrepancy between the numerous invasive carcinoma *foci* identified in some gastrectomy specimens and the low number of *in situ* carcinoma lesions suggests that invasion of the lamina propria by signet ring cells may occur without a morphologically detectable *in situ* carcinoma (9).

The prophylactic gastrectomy specimen here described displayed the different lesions that have been reported in the setting of HDGC. Noteworthy, the present family was identified after the histopathologic evaluation of the surgical specimen obtained from the proband. In this stomach, besides a widely invasive signet ring cell carcinoma, we identified *in situ* carcinoma and pagetoid spread of signet ring cells in the adjacent gastric mucosa. These findings raised the possibility of HDGC and led to the search of *CDHI* mutation that was performed in non-neoplastic mucosa of the surgical specimen from the proband (10). A *CDHI* germline mutation was identified and genetic screening was offered to other family members leading to the identification of the asymptomatic individual herein reported, who was submitted to prophylactic surgery. This study highlights the role of pathology in the identification of Hereditary Diffuse Gastric Cancer (10).

Data on screening of germline *CDHI* mutations were recently reviewed (11). A large number of families with aggregation of gastric cancer, from distinct geographic backgrounds, have been analyzed to date and 56/439 (12.8%) families have been found to carry *CDHI* germline mutations. Families fulfilling the IGCLC criteria for HDGC are now 118 (26.9% of 439 families) and 43/118 (36.4%) were shown to carry germline mutations, which are spread along all *CDHI* gene sequence.

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Case 6

Clinical history:

Man, 35-year-old, with long lasting dyspepsia.

In January 2005 the patient was submitted to gastric endoscopies on two occasions at the Hospitais da Universidade de Coimbra in Portugal. He was found to have multiple, non-healing, gastric ulcers that failed to respond to Proton Pump Inhibitors (PPIs) therapy. *Helicobacter pylori* infection was not diagnosed and no antibiotic therapy was prescribed. Consecutively, diffuse gastric mucosal thickening was observed raising suspicion for a neoplastic process. A distal gastrectomy was performed on the patient at the same hospital.

Clinicopathologic features:

The surgical specimen was constituted by distal stomach (GC-24cm; LC-12-cm; duodenal segment- 1.5cm); lymph nodes (n=26) were isolated from both curvatures (the largest with 1.5cm in diameter); lymph nodes from the hepatic- and celiac-chain were sent also for examination.

The antral mucosa appeared erythematous and edematous with irregular nodular masses. The body mucosa, however, had a normal appearance.

By histology, no evidence of neoplasia was found but rather a diffuse inflammatory destructive gastritis. Notably, no parasite, viral inclusions or *H. pylori* were found on initial microscopic evaluation. Lymph nodes displayed reactive changes. The case was sent for consultation, initially to the University Hospital S.João, Porto, Portugal and later to the Gastrointestinal Pathology Service of the Massachusetts General Hospital, Boston, USA.

The histological examination confirmed the presence of a dense, diffuse mucosal lymphoplasmacytic infiltrate with only scattered residual glandular elements with intraluminal abscesses. An ill-defined granulomatous process was also noted. Some inflammation spilled over into the superficial submucosa where an ill-defined perivascular distribution of the lymphohistocytic and plasma cell rich infiltrate raised the possibility of involvement by gastric syphilis.

Based on this information, the patient was subsequently investigated and found to be HIV-negative but serologic testing revealed a reactive polyclonal hypergammaglobulinemia, a positive Venereal Disease Research Laboratory (VDRL) blood test of 1:16, and *T. pallidum* agglutination assay (TPHA) of 1:1,028. Despite a non-contributory Warthin-Starry stain, gastric syphilis was then strongly considered, and the paraffin-embedded thin sections of resected tissue were forwarded to the Laboratory Reference and Research Branch, Division of STD Prevention, Centers for Disease Control and Prevention in Atlanta, Georgia to perform direct fluorescent antibody staining specific for *T. pallidum* and polymerase chain reaction (PCR) for treponemal DNA detection (Two specific DNA targets: 47 kDa lipoprotein gene and DNA polymerase I gene (*pol A*) for *T. pallidum* were used in the real-time simplex PCR test).

Direct immunofluorescent-antibody test results revealed the presence of numerous spirochetes that were immunologically specific for pathogenic treponemes. *Real-time PCR* probes detected positive signals from duplicated DNA samples extracted from two separate paraffin-embedded thin sections as well as from the positive DNA control.

Diagnosis: Gastric syphilis

Discussion:

Reported cases of gastric involvement by *T. pallidum* have been rare in the medical literature. Ikebe et al. (1) reviewed 59 cases of gastric syphilis reported between 1971 and 1990. Since 1990, only 34 cases with 2 from HIV-infected patients have been documented (2). The accurate mode of the syphilitic infection was not known in the present case. The patient was found to be HIV-negative on two occasions.

Documented symptoms of gastric syphilis are usually non-specific and include nausea, vomiting, abdominal pain and weight loss. Complications including gastric hemorrhage, perforation, and gastric outlet obstruction have also been reported, but are less common (3). Gastric syphilis may exhibit a variety of endoscopic and radiographic appearances including mucosal erosions, shallow ulcers, rugal hypertrophy, and nodularity that are indistinguishable from gastric lymphoma or linitis plastica.

Routine staining with hematoxylin and eosin of the gastric biopsy typically shows marked, diffuse, chronic inflammation composed of a dense lympho-plasmacytic cell infiltrate with or without granulomas, often in a perivascular distribution. Endarteritis obliterans may also be present. The findings are etiologically non-specific and a high index of clinical suspicion is needed to prompt further evaluation and definitive diagnosis.

Gastric syphilis remains a rare manifestation of the secondary and tertiary forms of the disease, which may affect young adults. It is exceedingly difficult to make a definitive diagnosis on the basis of biopsy findings, since spirochetes are seen infrequently and histopathologic findings are often nonspecific. Unless gastric syphilis is suspected and appropriate staining or molecular testing performed, the diagnosis cannot be made with certainty. The diagnosis has often been inferred in retrospect when examination of gastric lesion is negative for cancer, serologic tests are positive for syphilis, and the gastric lesion resolve after therapy with penicillin. Gastric syphilis should be considered in patients at risks for STD who complain of nausea, vomiting, weight loss, and abdominal pain and in whom unusual gastric lesions or presumed peptic ulcers unresponsive to standard therapy are encountered.

Warthin-Starry silver stain is capable of demonstrating spirochetes and confirming the diagnosis. However, this method cannot differentiate *T. Pallidum* from contaminating oral or skin spirochetes. In the present case, we have employed the FITC-labeled anti-*T. pallidum* monoclonal antibody stain combined with the most recent molecular diagnostic testing, real-time PCR, to

confirm the diagnosis of gastric syphilis. Both methods are specific for *T. pallidum* detection with higher sensitivity and a faster diagnosis achieved by the real-time PCR (4,5).

After the diagnosis of gastric syphilis, the patient was treated by antibiotic therapy and has improved. No post-therapy specimens have been taken so far.

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Case 7

This biopsy was obtained from an area of “esophagitis” in a patient with scleroderma.
“Iron Pill Esophagitis”

In our patient population, mucosal iron (ferrous sulfate) is found in about 1% of patients undergoing upper tract endoscopic biopsies. Iron is well-recognized for its capacity to cause corrosive injury in the esophagus but in a hospital population, it is not uncommon to find iron associated with an esophageal ulcer or erosion. While it can be argued that such a phenomenon is a result of a prior injury in which an iron tablet becomes embedded, the corrosive and toxic nature of iron itself suggests that the iron pill has caused the injury. Regardless, it is still worth learning to recognize “iron pill esophagitis” as the patient can then be encouraged to ingest the medication in a crushed form with a soft food (such as applesauce or yogurt). Using Johns Hopkins material, Abraham et al (1) have studied the clinical and histologic features of 36 upper gastrointestinal tract biopsies from 33 patients (24 gastric, 9 esophageal, 1 gastroesophageal junction, and 2 duodenal) containing characteristic brown crystalline iron material, and evaluated the amount and tissue distribution of the iron. They also investigated the prevalence of iron-associated mucosal injury on the endoscopic examinations. The biopsies typically displayed luminal crystalline iron adjacent to the surface epithelium or admixed with luminal fibrinoinflammatory exudates. Most biopsies (83%) showed crystalline iron deposition in the lamina propria, either covered by an intact epithelium, subjacent to small superficial erosions, or admixed with granulation tissue. Three biopsies (8%) demonstrated iron-containing thrombi in mucosal blood vessels. Erosive or ulcerative mucosal injury was present in the majority of biopsies (83%). The amount of iron accumulation in cases with mucosal injury was greater than in cases without mucosal injury. Iron medication (usually ferrous sulfate) was confirmed in 25 of 33 patients (76%). However, as an argument for iron causing injury as a secondary event, half of the patients (17 of 33, 51%) also had underlying infectious, mechanical, toxic, or systemic medical conditions that could have initiated or exacerbated tissue injury.

In any biopsy in which there has been injury to the mucosa, reactive fibroblasts can be a component. At times, these can proliferate exuberantly and have atypical (probably hypoxic) features. Pseudoepitheliomatous epithelium may appear in the area of the repairing mucosa.

Other Drugs/Agents Known To Cause Mucosal Injury

Kayexalate

The use of Kayexalate (sodium polystyrene sulfonate) for the management of hyperkalemia was approved for use in the United States in 1975. Kayexalate is a cation-exchange resin that can be instilled into the lower gastrointestinal tract as an enema preparation or into the upper gastrointestinal tract either orally or by nasogastric tube. When administered orally or by nasogastric tube, sodium cations are first released from the resin and exchanged for hydrogen ions in the acidic milieu of the stomach. As the resin passes through the intestines, hydrogen is exchanged for potassium, which is then eliminated in the feces along with the remainder of the altered resin, thereby lowering the serum potassium concentration.

In the early use of Kayexalate, the resin was typically administered as a suspension in water. Although generally well tolerated, some patients were reported to develop gastric and bowel opacifications as a result of concretions of crystalline resin. It therefore became increasingly popular to administer Kayexalate in a suspension with hypertonic sorbitol, which reduces the frequency of Kayexalate bezoar formation and colonic impaction by promoting an osmotic diarrhea. In 1987, Lillemoe et al. (2) reported five uremic patients who developed colonic necrosis temporally associated with the use of Kayexalate in sorbitol and contributed to death in four of

the five patients. That study also provided experimental evidence implicating sorbitol as the agent responsible for colonic necrosis in a rat model.

More recently, it has become apparent that kayexalate can be associated with severe mucosal injury in the upper GI tract as well, and a series of such cases has been reported by Abraham et al(3). In most instances, kayexalate is easy to recognize in endoscopic biopsies and the clinician can be alerted if there is associated ischemic GI tract disease or erosive lesions.

Kayexalate crystals are lightly basophilic on hematoxylin and eosin stain, red on PAS/Alcian blue and acid-fast stains, and blue on Diff-Quik staining. The crystals display a characteristic crystalline mosaic pattern that resembles fish scales and is faintly present in many cases on routine hematoxylin and eosin stain, but is better demonstrated on acid-fast, PAS/Alcian blue, and Diff-Quik stains. It is this mosaic pattern that allows the distinction from between kayalexate crystals and histologically similar cholestyramine crystals. Kayexalate crystals are refractile but not polarizable.

Taxol, Colchicine

Taxol, an antineoplastic agent with a novel mechanism of action, can be associated with striking mitotic arrest associated with epithelial necrosis and ulceration the esophagus(4) . The mitotic arrest is associated with bundling of intermediate filaments secondary to accumulation of polymerized microtubules. Thus the histologic correlate is the presence of arrested mitoses with ring forms. With taxol, the findings tend to be striking in the esophagus, whereas, in colchicine toxicity, the small bowel is more likely to be severely altered.

Fosamax

The bisphosphonates (BPs) are a relatively new class of drugs which prevent osteoclast mediated bone reabsorption and have therefore been found effective in the treatment of osteoporosis, Paget's disease and the hypercalcemia of malignancy(5).

Ingestion of alendronate sodium (Fosamax) and related medications by osteoporotic patients has been associated with esophagitis and esophageal ulcer(6-18). Alendronate can damage the esophagus both by toxicity from the medication itself and by nonspecific irritation secondary to contact between the pill and the esophageal mucosa ("pill esophagitis"). Abraham and colleagues reported 10 patients who experienced erosive/ulcerative esophagitis while ingesting alendronate(9). Biopsies from all patients showed inflammatory exudate and inflamed granulation tissue as characteristic of any ulcer site. Polarizable crystalline foreign material was present in six of 10 biopsies (60%). Multinucleated giant cells within the inflammatory exudate were near the crystalline foreign material in three of 10 biopsies (30%). Adjacent squamous epithelium typically showed active inflammation and a reactive appearance with enlarged, hyperchromatic nuclei. Multinucleated squamous epithelial giant cells were present in two of 10 cases (20%). Microorganisms were unusual; scattered fungi and/or viral inclusions were present in only two of 10 biopsies (20%). The key is that there is no specific histologic finding, but it is worthwhile to be aware of this complication of such medicines so concern can be relayed appropriately to the clinician. However, it is now known that modifications in dosing schedules of this medication (19) can reduce mucosal injury and it is less likely to be encountered in practice.

These agents should be avoided in patients with achalasia and other motility disorders of the esophagus, esophageal stricture or preexisting severe reflux esophagitis. However, patients with reflux disease can probably be treated with a proton pump inhibitor (PPI) and then safely have biphosphonate therapy with continued concomitant use of the PPI.

“Thermal Injury”

We have occasionally observed a pattern of injury in our biopsy material which we believe may be a reflection of thermal injury (?taking hot beverages after heating them microwave ovens?). Biopsies showing a “thermal injury” pattern display an unaltered

basal layer and “mummification” of the superficial squamous epithelium such that there are “ghost” nuclei and the mucosa sloughs.

Corrosive Ingestion (e.g. Lye, Bleach)

Like the esophageal injury associated with fosamax, corrosive injury does not result in a specific pattern of injury (although saponification may accompany lye ingestion) and cannot be identified directly (like iron or kayexalate). However, it can usually be correlated with an ingestion history in a pediatric patient or a psychiatric setting. Endoscopically, severe ulceration is seen and endoscopists have described a strong bleach-like odor even when the patient has ingested lye. Microscopically, extensive necrosis is found. Those who survive are likely to have severe stricturing disease with all its complications. The key with such patients is that they require lifetime follow-up as they are prone to develop squamous cell carcinoma(20).

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Case 8

This slide was prepared from a 7 cm mass excised from the stomach of a 61 year old woman.

Gastric Stromal Tumors

The stomach is the most common site for gastrointestinal stromal tumors (GIST, efig 325) and they are occasionally diagnosed on mucosal biopsies. Typically those diagnosed on biopsies are aggressive lesions that have invaded the mucosa. GISTs are mesenchymal tumors arising in the GI tract and occasionally within the abdomen with no GI connection. The earlier literature attempted to classify them as smooth muscle or nerve sheath tumors, but even in the benign tumors evidence for such differentiation was difficult to find. Mazur and Clark coined the term stromal tumor in 1983(1). GISTs show differentiation towards (and supposedly arise from a precursor of) interstitial cells of Cajal which are normally concerned with motility of the gut(2, 3). This category is considered to subsume the ultrastructurally defined rare lesions previously known as gastrointestinal autonomic nerve tumors (GANT). The availability of specific antibodies and clarification of their immunohistochemical profile has facilitated diagnosis. However, careful morphologic examination and clinicopathological correlation remain essential for excluding mimics and for assessment of likely behavior in this heterogeneous group of neoplasms.

GISTs comprise 5-10% of all sarcomas (for comparison, retroperitoneal = 15% and extremity 42%), and around 25% of GISTs are malignant, representing about 1% of all GI malignancies. They are most common in adults aged 50-60. These tumors vary in differentiation and prognosis according to their location within the GI tract. Esophageal GISTs are rare, but 50-70% involve the stomach, 25-40% the small intestine (of which 10-20% arise in duodenum, 27-37% in jejunum, 27-53% in ileum) and < 10% are colorectal (50% colonic, 50% rectal). They are least frequent in the esophagus (where smooth muscle tumors are more usually found), colon and rectum. GIST-type tumors arising in omentum, peritoneum and retroperitoneum have been identified, comprising 6.7% of the large AFIP series of 1008 GISTs (4).

Tumors present with primary mass, pain or bleeding (46%) or metastasis (47%) and two thirds exceed 5cm at presentation. Malignant GIST are rare with about 5 per

million of population (compared with 25 per million for soft tissue sarcomas). There is an increased incidence of GIST including multiple tumors in small intestine in patients with NF-1, possibly associated with interaction between the NF-1 gene product and c-kit) and GIST is occasionally familial (associated with a germline c-kit mutation, see below). Some patients have second cancers, and some epithelioid gastric stromal tumors are associated with paraganglioma and pulmonary chondroma in Carney's triad.

About 20% are malignant. The consensus is that 5 mitoses per 50 hpf and >5cm are adverse prognostic factors(5). The five-year survival of gastric GISTs is about 40%, with improvement in completely resected cases. There is no evidence that radical surgery improves survival, so that the least extensive surgical procedure compatible with complete excision is advisable. Gastric GISTs are more frequent in males, but young patients, especially female, have an improved outcome; Persson et al (1992) reported 4 patients less than 26 years old who had metastasizing gastric epithelioid leiomyosarcomas, involving liver, nodes, peritoneum, and who all survived for 17-48 years.

Epithelioid GISTs are the old leiomyoblastomas of Stout (the term epithelioid leiomyoma was introduced in the 1969 WHO). They comprise about 11% of gastric GISTs, of which 73-81% are benign. Large tumors in the fundus or cardiac area and posterior wall are more likely to be malignant. 47-60% of tumors metastasize, usually within 2 years and survival after metastasis is about 8 months. Lee et al found tumors larger than 6 cm had a worse outcome, and in the series of Appelman et al, no tumor <5.5 cm metastasized, and only one < 6cm. In the latter series, 1 case with no mitoses metastasized, 12% with 1-5 mitoses per 50 hpf metastasized and all cases with >10 mitoses per 50 hpf. (None had 6-10). Benign tumors had 0-5 mitoses per 50 hpf. Metastasis occurred from 55% of well differentiated and 75% of poorly differentiated epithelioid leiomyosarcomas. Ma et al also found that tumors with >5 mitoses per 50 hpf had malignant potential. In our series, necrosis had significant negative impact(6).

Most GISTs are spindle cell tumors with variable palisading, peculiar paranuclear vacuoles, and collagen fibrils. On a practical note, it is epithelioid GISTs that are most likely to cause diagnostic problems on mucosal biopsies as they are readily mistaken for a host of epithelioid and epithelial neoplasms. It is advisable to perform an immunohistochemical panel in assessing them to include CD117/c-kit, S100 protein (to address melanoma) and a cytokeratin stain to address signet cell carcinoma. The majority of GIST have kit mutations and are CD117/c-kit stain positive, but 5-10% lack kit mutations and some in the c-kit negative subset have alternate mutations of platelet derived growth factor alpha instead(7-9). Since about 70% of GISTs express CD34, this can also be included in a diagnostic panel. On mucosal biopsies, it is difficult to assess tumor size and mitotic counts to prognosticate but it is possible to make a diagnosis in many cases and allow the patient to be scheduled for an operation to remove the tumor. On resection specimens a "recipe" for this has been published(10), Table 1. Some observers took issue with this as it assumes that all GISTs are potentially malignant and does not take site into account but is still a useful construct for attempting a prognostic "forecast". Trupiano et al have published criteria that they believe allow separation of benign gastric stromal tumors from those they regard as not benign(11)(efig 333). We have attempted to apply these to a series of gastric GISTs and had one "outlier" case(6)

so we continue to add a note of caution to reports on large gastric stromal tumors that appear otherwise benign.

The AFIP group has the largest accumulated series of gastric stromal tumors, and has reported a large series of 1,765 GISTs confined to the stomach with good follow-up information(12). There was a slight male predominance (55%) and a median age of 63 years. Only 2.7% of tumors occurred before the age of 21 years and 9.1% before the age of 40 years. The tumors varied from 0.5 to 44 cm (median, 6.0 cm) and most commonly presented with GI bleeding; 12% were incidentally detected. Histologic variants recognized among the spindle cell tumors included sclerosing, palisaded-vacuolated, hypercellular, and sarcomatous and among the epithelioid tumors, sclerosing, dyscohesive, hypercellular, and sarcomatous. Outcome was strongly dependent on tumor size and mitotic activity. Only 2% to 3% of tumors <10 cm and <5 mitoses/50 HPFs metastasized, whereas 86% of tumors >10 cm and >5 mitoses/50 HPFs metastasized. However, tumors >10 cm with mitotic activity <5/50 HPFs and those <5 cm with mitoses >5/50 HPFs had a relatively low metastatic rate (11% and 15%). A small number of patients survived intra-abdominal metastasis up to over 20 years. Tumor location in fundus or gastroesophageal junction, coagulative necrosis, ulceration, and mucosal invasion were all unfavorable factors (P < 0.001), whereas tumor location in antrum was favorable (P < 0.001). Probably the key feature of this very large series is that it allowed separating out a “benign” category of gastric GISTs based on large numbers of cases(12). This group has proposed malignancy criteria specific to the stomach which are shown in Table 2. Another important feature of the AFIP study is that mucosal extension by gastric GISTs was evidence that the tumor would behave badly. This feature remained equivocal based on several earlier smaller studies (including our own!(6)). However, based on these data from Miettinen et al (12), if we encounter a gastric GIST on a mucosal biopsy, it is likely malignant and we should suggest this in our reports. Based on the large AFIP series of gastric GISTs, KIT/CD117 is found in 91% of gastric GISTs, CD34 in 82%, SMA in 18%, and desmin in 5%; the latter 2 tend to be focal.

As a last diagnostic “tip”, pathologists should be aware that a number of lesions other than GIST display CD117. Perhaps fibromatoses are most likely to result in diagnostic errors(13, 14). We have had some success with using beta catenin for this separation [only fibromatoses show nuclear staining](14, 15).

Table 1. Suggested Prognostic Criteria for Resected GISTs FROM ALL ANATOMIC SITES (10)

Risk Category	Size (cm)	Mitotic counts/50 high power fields
Very low risk	<2	<5
Low risk	2-5	<5
Intermediate risk	<5	6-10
	5-10	<5
High risk	>5	>5
	>10	Any

	Any size	>10
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Table 2. Suggested Prognostic Criteria for Resected GISTs SPECIFIC TO STOMACH (12)

Risk Category	Size	Mitotic Counts (per 50 high power fields)
Benign	No larger than 2 cm	No more than 5/50
Probably Benign	>2, ≤ 5 cm >5, ≤ 10 cm	No more than 5/50 No more than 5/50
Uncertain	No larger than 2 cm	>5/ 50
Low to Moderate Malignant Potential	>10 cm >2, ≤ 5 cm	Not more than 5/ 50 >5/ 50
High Malignant potential	>5, ≤ 10 cm > 10 cm	> 5/ 50 > 5/ 50

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