"Pediatric-type" Gastrointestinal Stromal Tumors in Adults: Distinctive Histology Predicts Genotype and Clinical Behavior

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Abstract: Gastrointestinal stromal tumors (GISTs) rarely affect children, mainly girls. Pediatric GISTs typically arise in the stomach as multifocal tumors with a multinodular growth pattern, epithelioid morphology, lymph node metastases, an absence of *KIT* and *PDGFRA* gene mutations, and indolent behavior. Occasional GISTs in adults show similar features. Such tumors are not widely recognized. GISTs with a multinodular growth pattern in patients over the age of 18 years were retrieved from surgical and consultation files. Hematoxylin and eosin-stained slides were reviewed, immunohistochemistry was performed, and *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12, 14, and 18) genes were screened for mutations. Clinical follow-up was obtained. Sixteen cases were identified, affecting 13 women and 3 men (median age, 31.5 y; range, 19 to 56 y), all in the stomach. The mean tumor size was 5.4 cm (range, 1.8 to 11 cm); 4 were multifocal. All tumors showed a multinodular or plexiform architecture and epithelioid (N = 3) or mixed epithelioid and spindle cell (N = 13) morphology. Five tumors had vascular invasion; 6 had focal necrosis. Mitotic activity ranged from 3 to 156/50 high-power fields (8 tumors had ≤5/50 high-power fields). Using Armed Forces Institute of Pathology risk stratification, categories for primary tumors were: none (N = 2), very low risk (N = 3), low risk (N = 3), moderate risk (N = 3), and high risk (N = 5). By immunohistochemistry, all tumors were positive for KIT, 82% DOG1, 72% CD34, 18% caldesmon, 9% S-100, 8% smooth muscle actin, and 0% desmin. All tumors were wild type for *KIT* and *PDGFRA* in the exons that were screened. At primary resection, 9 patients (56%) had lymph node metastases and 3 patients had liver metastases. Follow-up ranged from 16 months to 16 years (median, 5 y). Two tumors recurred locally in the stomach and 7 patients developed subsequent metastases to the lymph nodes (N = 5), liver (N = 3), and peritoneum/omentum (N = 3). Primary tumors from 7 patients with metastases were Armed Forces Institute of Pathology low risk, very low risk, or no risk of recurrence. None of the metastatic tumors responded to treatment with imatinib mesylate. One patient died of disseminated liver and intra-abdominal metastases and the remaining patients were alive at last follow-up. Gastric GISTs in adults with a multinodular or plexiform growth pattern and epithelioid or mixed morphology are similar to pediatric GISTs. Unlike conventional adult GISTs, this distinctive subset predominantly affects women, often metastasizes to lymph nodes, and lacks mutations in *KIT* and *PDGFRA*. Current risk assessment criteria do not reliably predict behavior for this group. Although metastases are common and most tumors are imatinib resistant, they pursue a relatively indolent clinical course. Recognition of "pediatric-type" GISTs in adults is critical for prognosis, appropriate therapy, and follow-up.

Key Words: gastrointestinal stromal tumor, KIT, PDGFRA, tyrosine kinase inhibitor, sarcoma, soft tissue tumor

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Gastrointestinal stromal tumors (GISTs) most often arise in the wall of the stomach or small intestine of middle-aged and elderly adults.[5,16,22] Histologically, the majority of GISTs (70%) show spindle cell morphology, whereas approximately 20% show epithelioid and 10% show mixed morphology.[12,16] GISTs range from incidental, small indolent tumors to large aggressive sarcomas that typically metastasize to the liver and peritoneum. Lymph node metastases are very rare in GISTs.[22] Risk of metastasis can be estimated based on tumor location, size, and mitotic rate.[15] Activating mutations in *KIT* or *PDGFRA* tyrosine kinase receptor genes are found in approximately 85% of GISTs.[8,13] Most GISTs respond to targeted tyrosine kinase inhibitor therapy with imatinib mesylate[6,23] or sunitinib malate.[7]

However, when they do, pediatric GISTs typically arise in the stomach (often antrum) of female patients.[1,17,21] In contrast to adult GISTs, these tumors are characterized by multifocality, multinodular architecture, epithelioid morphology, lymph node metastases, an absence of *KIT* and *PDGFRA* mutations, and indolent

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behavior in the face of metastatic disease.[1,17,19] Therefore, these tumors differ from adult GISTs in their histologic findings, genotype, and clinical behavior.

Occasional GISTs in adults show features similar to pediatric GISTs. These "pediatric-type" GISTs are not widely recognized. In this study, we describe 16 pediatric-type GISTs diagnosed in patients over the age of 18 years. These tumors are important to recognize, given their distinctive clinical behavior and lack of response to conventional therapy.

MATERIALS AND METHODS

GISTs with a multinodular growth pattern diagnosed in patients over the age of 18 were included. Sixteen cases in total were identified. Eleven cases were selected based on the histologic findings without knowledge of mutational status, including 9 cases received between 2006 and 2010. These cases were identified prospectively by one of the authors (J.L.H.) from the surgical and consultation files of the Department of Pathology of the Brigham and Women's Hospital, Boston, MA (of 355 GISTs reviewed by the author during this time period, including 127 primary gastric tumors). Two additional cases were identified retrospectively through a search of the pathology database at Brigham and Women's Hospital using the terms "multinodular" and "infiltrative." In addition, 5 cases with a multinodular architecture, which were already known to lack mutations in *KIT* and *PDGFRA*, were identified retrospectively through a search of the referral files of the Department of Pathology of the Oregon Health and Science University, Portland, OR. The primary tumors were originally excised between 1994 and 2009.

Four micrometer-thick hematoxylin and eosin-stained sections were reviewed to assess the architectural and cytologic features, mitotic rate [expressed as mitotic figures per 50 high-power fields (HPF); total area, 12.5 mm^2], and the presence of lymphovascular invasion and necrosis. Immunohistochemistry was performed using the following antibodies and conditions and the Envision Plus detection system (Dako, Carpinteria, CA): KIT (polyclonal; 1:250; Dako); DOG1 (clone K9; 1:50; Leica Biosystems, Newcastle Upon Tyne, UK); CD34 (clone QBEnd-10; 1:400; Dako); desmin (clone D33; 1:500; Dako); smooth muscle actin (clone 1A4; 1:20000; Sigma, St. Louis, MO); caldesmon (h-CD; 1:300; Dako); and S-100 protein (polyclonal; 1:4000; Dako). Antigen retrieval (pressure cooker; citrate buffer pH 6.0) was used for DOG1 and caldesmon. Appropriate positive and negative controls were used. Screening for mutations in each of the exons tested (*KIT* exons 9, 11, 13, and 17; *PDGFRA* exons 12, 14, and 18) was carried out using a combination of PCR and high-resolution melting curve analysis on a Roche LightCycler 480 (details available on request). Clinical follow-up data (when available) were obtained from the electronic medical records and/or the referring pathologists. This study was approved by the institutional review boards of the participating institutions.

TABLE 1. Clinical Features of 16 Adult Patients With Pediatric-type Gastrointestinal Stromal Tumors

Case	Age (y)/ Sex	Site	Size (cm)	Risk Stratification	Metastasis at Primary Surgery	Local Recurrence	Subsequent Metastasis	Follow-up (Status)
1	49/F	Corpus (greater curvature)	11	High	LN		Liver and omentum, 3.5 y	63 mo (DOD)
2	29/F	Antrum	4	Very low	LN	Yes, 2 y	LN, 2 y	5 y (AWD)
3	19/F	Antrum	3.5	Moderate	LN		LN, 1 y; liver, 8 y	9 y (AWD)
4	23/M	Antrum	6	High	LN		LN and peritoneum, 45 mo	88 mo (AWD)
5	31/M	Corpus (greater curvature)	4.6	Moderate	No			NA
6	38/F	Corpus (fundus)	6.8	Low	LN, liver			27 mo (AWD)
7	39/F	Corpus (fundus)	2	None	No		LN and liver, 14 y	16 y (AWD)
8	56/F	Antrum	Multifocal; up to 2.2	Very low	LN			16 mo (ANED)
9	31/F	Antrum	6	High	No		Liver, 8 mo	27 mo (AWD)
10	22/M	Corpus	Multifocal; up to 7.2	High	Liver			59 mo (AWD)
11	46/F	Corpus	Multifocal; up to 5.2	High	LN			67 mo (ANED)
12	30/F	Stomach, unspecified	8	Low	No			25 mo (ANED)
13	32/F	Corpus and antrum	Multifocal; up to 1.8	None	LN			5 y (ANED)
14	41/F	Corpus	3.4	Very low	LN			16 mo (AUNK)
15	32/F	Antrum	NA	At most moderate	No	Yes, 10 y		15 y (ANED)
16	25/F	Antrum	9	Low	Liver		LN and peritoneum, 9 mo	7 y (AWD)

ANED indicates alive, no evidence of disease; AUNK, alive, disease status unknown; AWD, alive with disease; DOD, dead of disease; F, female; LN, lymph node; M, male; NA, data not available.

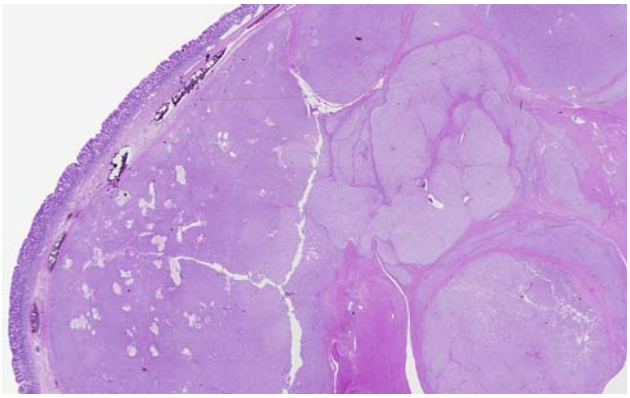

FIGURE 1. Scanning image of a pediatric-type GIST showing a multinodular growth pattern through the wall of the stomach (case 16; 25-year-old female patient).

RESULTS

Clinical Findings

The clinical features are summarized in Table 1. Sixteen cases were identified, affecting 13 women (81%) and 3 men (19%). The age at diagnosis ranged from 19 to 56 years, with a median age of 31.5 years. All primary tumors were located in the stomach (7 corpus, including 2 greater curvature and 2 fundus; 7 antrum; 1 both corpus and antrum; and 1 unspecified portion) and were treated by surgical excision.

Macroscopic Features

The tumor size ranged from 1.8 to 11 cm, with a mean size of 5.4 cm. Four of the tumors were grossly multifocal: 1 case with 2 tumors up to 2.2 cm; 2 cases with a dominant mass (5.2 and 7.2 cm), along with several additional smaller nodules; and 1 case with numerous small nodules up to 1.8 cm. One of the tumors showed ulceration of the mucosal surface.

Microscopic Features

All the tumors showed a multinodular architecture (per inclusion criteria), generally with well-circumscribed small nodules or broad bands of tumor dissecting through the muscularis propria, often imparting a plexiform appearance (Figs. 1–4). One tumor showed areas of strikingly infiltrative growth with a trabecular pattern (Fig. 5). Two tumors infiltrated the mucosa. Three (19%) tumors showed purely epithelioid and 13 tumors (81%) showed mixed epithelioid and spindle cell morphology (Fig. 6). None of the tumors were composed of only spindle cells. In the epithelioid areas, most tumors showed high cellularity and lacked significant intercellular stroma (corresponding to the "hypercellular" epithelioid subtype of Miettinen et al[18]). Three tumors contained foci of marked nuclear pleomorphism (Fig. 7). Lymphovascular invasion was identified in 5 (31%) tumors (Fig. 8A). Although not grossly appreciated, 6 (38%) tumors showed focal necrosis. Mitotic activity ranged from 3 to 156/50 HPF (8 tumors had ≤ 5 mitoses/50 HPF). Using Armed Forces Institute of Pathology risk stratification criteria (Table 1),[15] 2 tumors would be classified as no risk, 3 tumors as very low risk, 3 tumors as low risk, 3 tumors as moderate risk, and 5 tumors as high risk for metastasis.

Immunohistochemical Findings

By immunohistochemistry, all tumors were diffusely positive for KIT (Fig. 2B, Fig. 9A), whereas 9 of 11 (82%) tumors showed immunoreactivity for DOG1 (Fig. 3B,

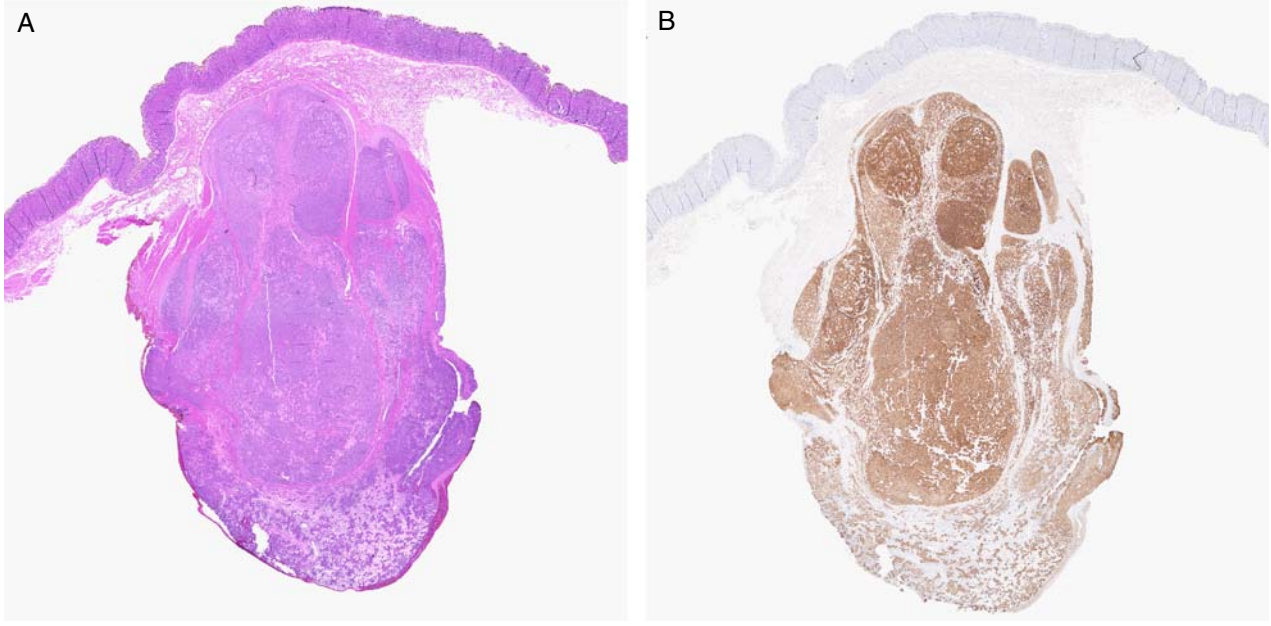

FIGURE 2. A, Pediatric-type GIST in the stomach of a 39-year-old female patient (case 7). B, Immunohistochemistry for KIT highlights the multinodular architecture.

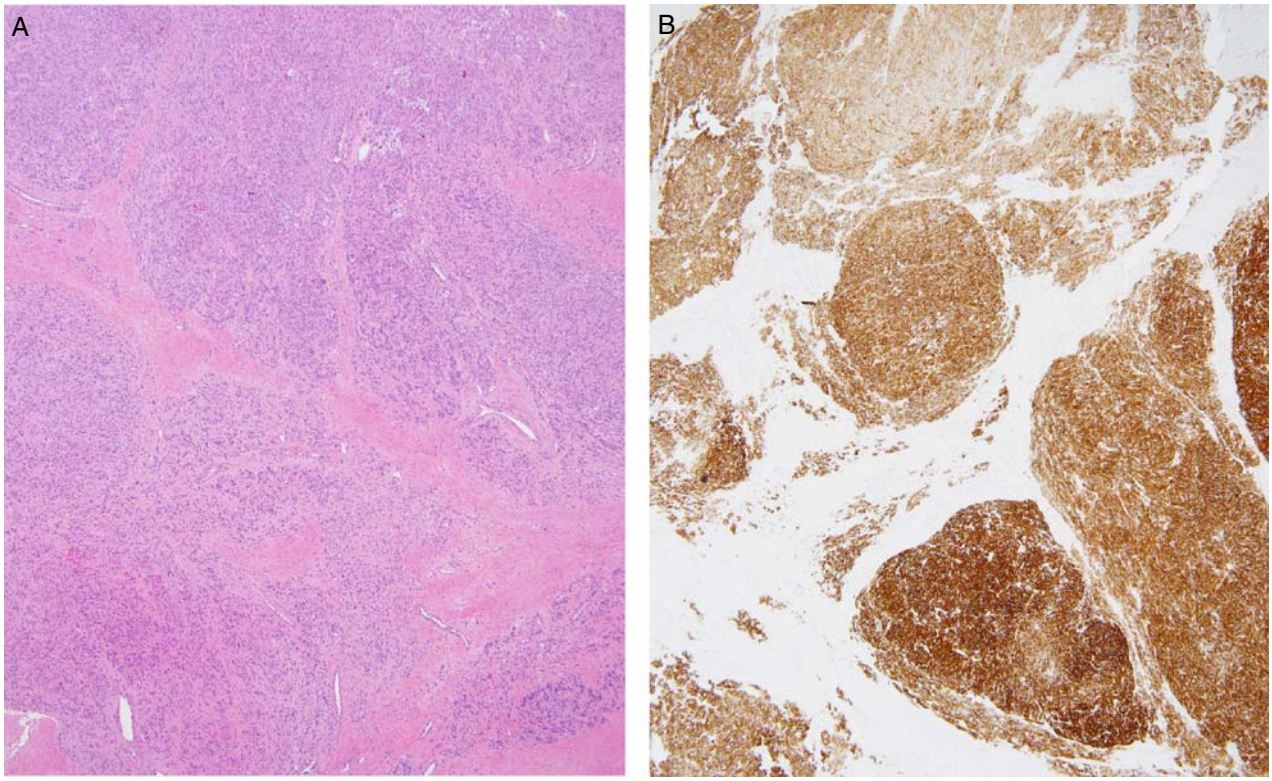

FIGURE 3. A, Nodules of epithelioid GIST infiltrating the gastric muscularis propria (case 8; 56-year-old female patient). B, Immunohistochemistry for DOG1 accentuates the plexiform growth pattern.

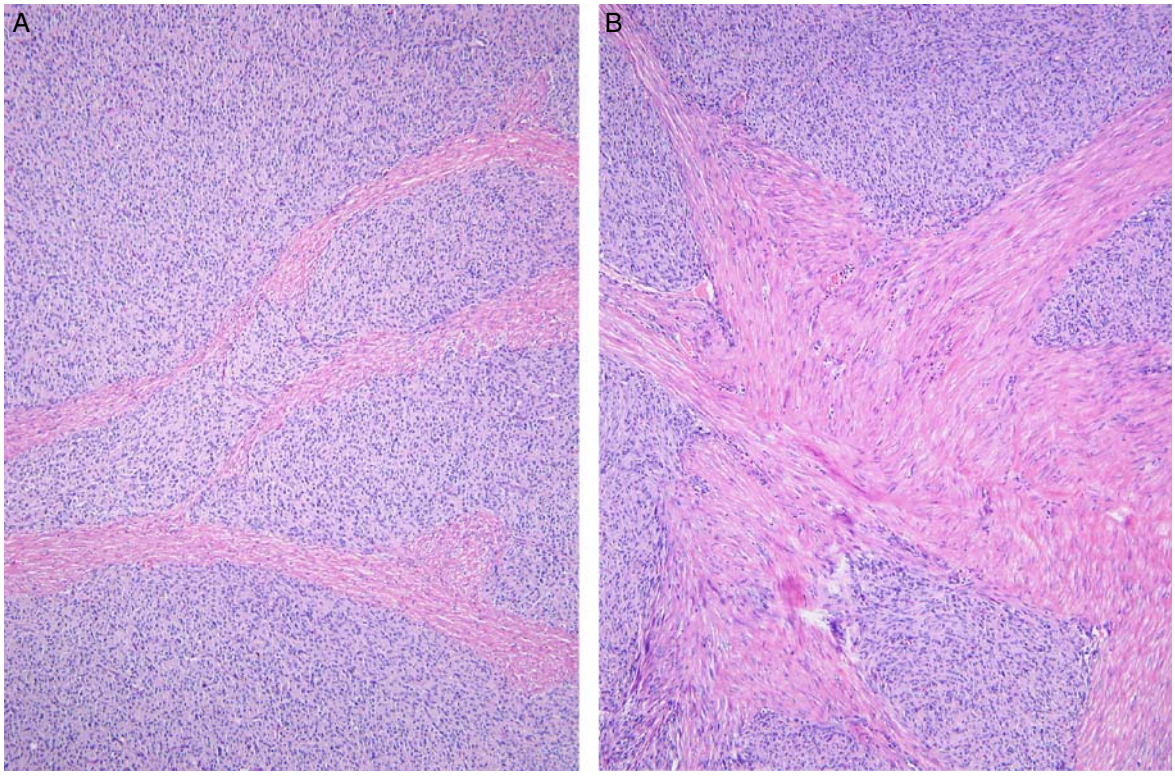

FIGURE 4. Well-circumscribed lobules of epithelioid GIST from the stomach of a 31-year-old male patient (A; case 5), in areas showing seemingly discontiguous tumor nodules separated by smooth muscle (B).

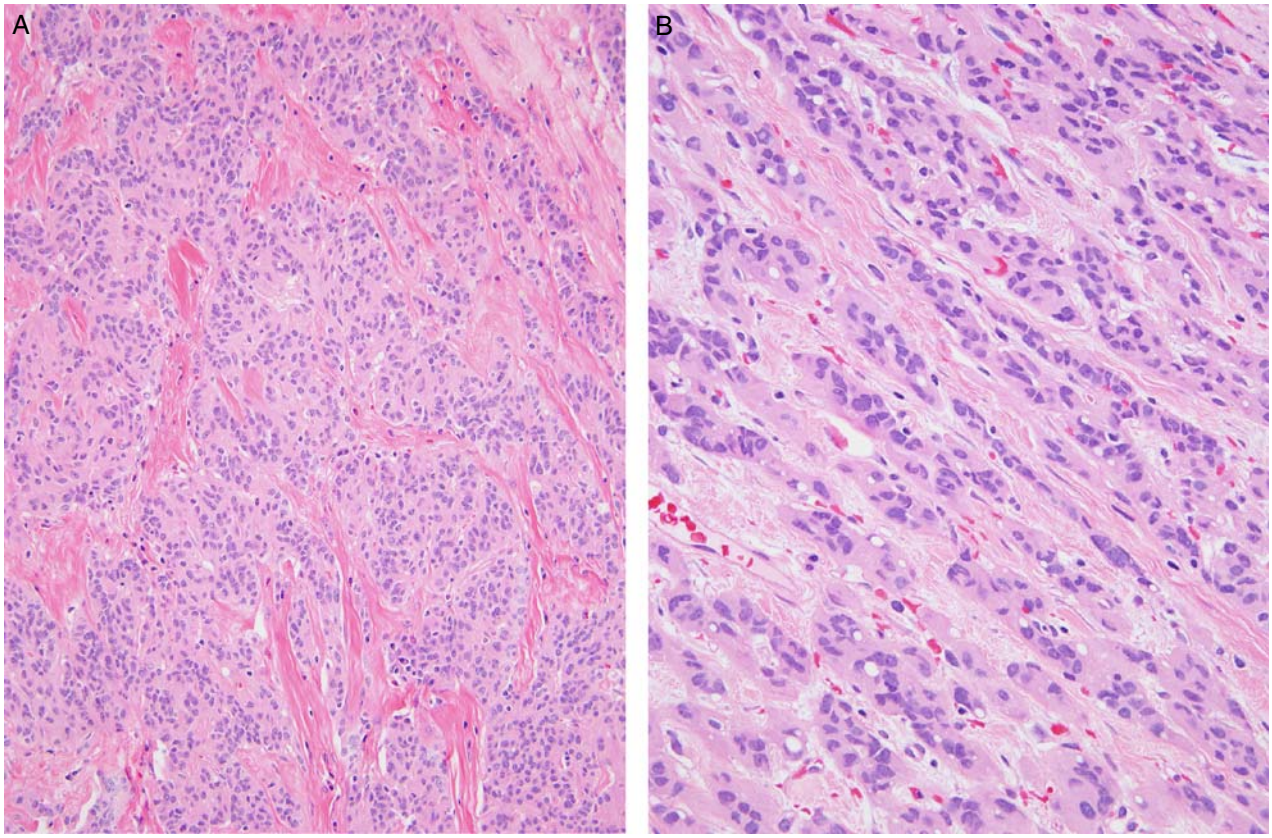

FIGURE 5. Pediatric-type GIST from a 41-year-old female patient showing a complex, infiltrative architecture (A; case 14), with a focally trabecular growth pattern (B).

Fig. 9B) and 9 of 13 (72%) for CD34. Only 2 of 11 (18%) tumors were positive for caldesmon, 1 of 11 (9%) for S-100, 1 of 12 (8%) for smooth muscle actin, and none for desmin.

Molecular Findings

Exons 9, 11, 13, and 17 of *KIT* and 12, 14, and 18 of *PDGFRA* were screened for mutations. All 16 tumors were wild type for both *KIT* and *PDGFRA* in the exons that were examined. It should be noted that the genotype was already known for 5 of the tumors at the time of case selection.

Treatment and Follow-up

At primary resection, 9 patients (56%) had lymph node metastases (Fig. 8B), and 3 patients had liver metastases. Clinical follow-up ranging from 16 months to 16 years (median, 5 y; mean, 6 y) was available for 15 patients (Table 1). Two tumors recurred locally in the stomach and 7 patients thus far have developed subsequent metastases to the lymph nodes (5 patients), liver (3 patients), and peritoneum/omentum (3 patients). In total, 10 patients (62.5%) either presented with or subsequently developed lymph node metastases. Resected primary tumors from 7 patients with metastases (5 to lymph nodes and 4 to liver) were Armed Forces Institute of Pathology low risk, very low risk, or no risk of recurrence. Eleven patients were treated with imatinib mesylate, 2 in the adjuvant setting and 9 with metastatic disease; none of the patients showed radiologic evidence of a response to therapy. Eight patients with progressive disease were subsequently treated with sunitinib malate, 2 of whom experienced severe side effects requiring discontinuation of therapy; 2 of 5 patients with follow-up showed a response to treatment. No additional follow-up was available for other patients treated with sunitinib. At the last follow-up, thus far 1 patient has died of disseminated liver and intra-abdominal metastases (63 mo after primary tumor excision), 8 patients are alive with metastatic disease, 5 patients are alive without disease, and 1 patient is alive with unknown disease status. On follow-up imaging, 1 patient (case 2) had radiographic evidence of a lung lesion with features suggestive of a pulmonary chondroma and another patient (case 16) had an adrenal mass suspicious for a pheochromocytoma. These findings raise the possibility of Carney triad and Carney-Stratakis syndrome, respectively. Neither lesion has been biopsied or surgically excised as of yet.

DISCUSSION

In this study, we have shown that gastric GISTs in adults with a multinodular or plexiform growth pattern are biologically and clinically similar to pediatric GISTs.

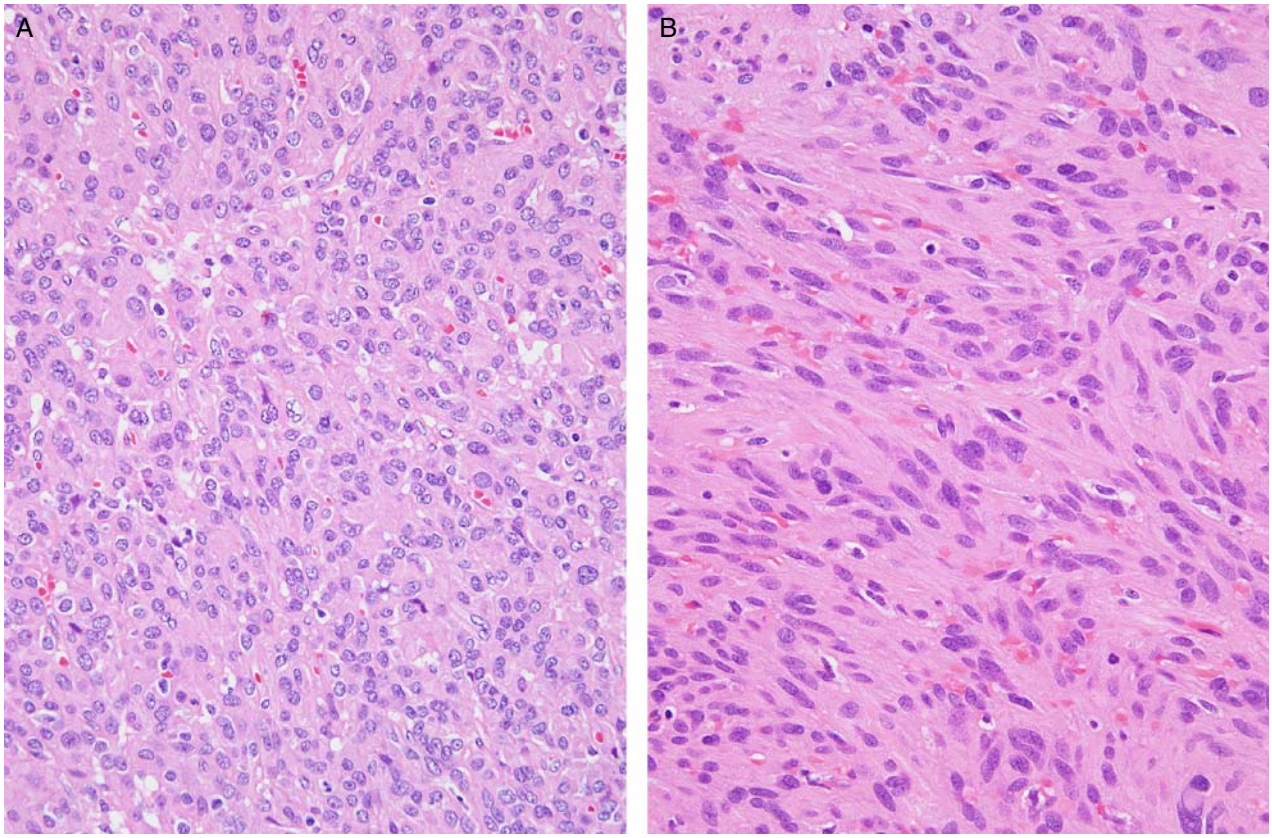

FIGURE 6. Most pediatric-type GISTs showed mixed epithelioid (A) and spindle cell (B) morphology. Note the high cellularity with no intercellular stroma.

Unlike conventional adult GISTs, pediatric-type GISTs have a striking predilection for women (approximately 80%), occur equally in the gastric body and antrum, consist of purely epithelioid or mixed epithelioid and spindle cells with uniform hypercellularity (without significant stroma), often metastasize to lymph nodes, and lack mutations in *KIT* and *PDGFRA*. Irrespective of tumor size and mitotic rate, many of these tumors metastasize to the liver and peritoneum. Not surprisingly (given the "wild-type" genotype),[8] imatinib mesylate is an ineffective therapy for patients with advanced pediatric-type GISTs. Despite the development of metastases, these tumors pursue a relatively indolent clinical course; only 1 patient in our study has died of disease after a median follow-up of 5 years.

Pediatric GISTs have distinctive pathologic features and clinical behavior, quite different from conventional adult GISTs (see below). The tumors arising in adults in our study are essentially indistinguishable from their counterparts in children. For example, in a study of 44 gastric GISTs in children and young adults (21 y of age or younger) by Miettinen et al,[17] 73% of patients were female, 72% of tumors arose in the gastric antrum, and 76% were purely or predominantly epithelioid, most of which showed the hypercellular histologic pattern similar to the cases in our study. In addition, also similar to the tumors in our series, most of the pediatric GISTs showed a plexiform growth pattern. None of the 13 genotyped pediatric tumors in that study had mutations in *KIT* or *PDGFRA*.[17] Although liver and peritoneal metastases were observed in around one third of patients, there was no mention of lymph node metastases. It should be noted that, similar to our study, 2 patients experienced local recurrences in the stomach (which alternatively may represent additional foci in the setting of multifocal disease). Some of the patients survived for many years (up to 22 y) with liver metastases, showing the relatively indolent behavior of pediatric GISTs. In a study of 5 pediatric and 10 young adult GISTs by Prakash et al,[21] all 5 pediatric tumors affected female patients and arose in the stomach as multifocal, multinodular tumors with a wild-type genotype, all but 1 with epithelioid or mixed morphology. Three pediatric tumors metastasized to the lymph nodes, 4 recurred locally in the stomach, and all 5 spread to the liver and/or peritoneum. Of the 10 GISTs in young adults, 3 were wild-type gastric tumors in female patients, 1 of which was multifocal, and 1 of which spread to regional lymph nodes. Two of these latter patients experienced long-term survival despite liver and peritoneal metastases. In another study of 17 pediatric GISTs by Agaram et al,[1] 80% of 15 patients with wild-type tumors were female, and again multifocality, nodular

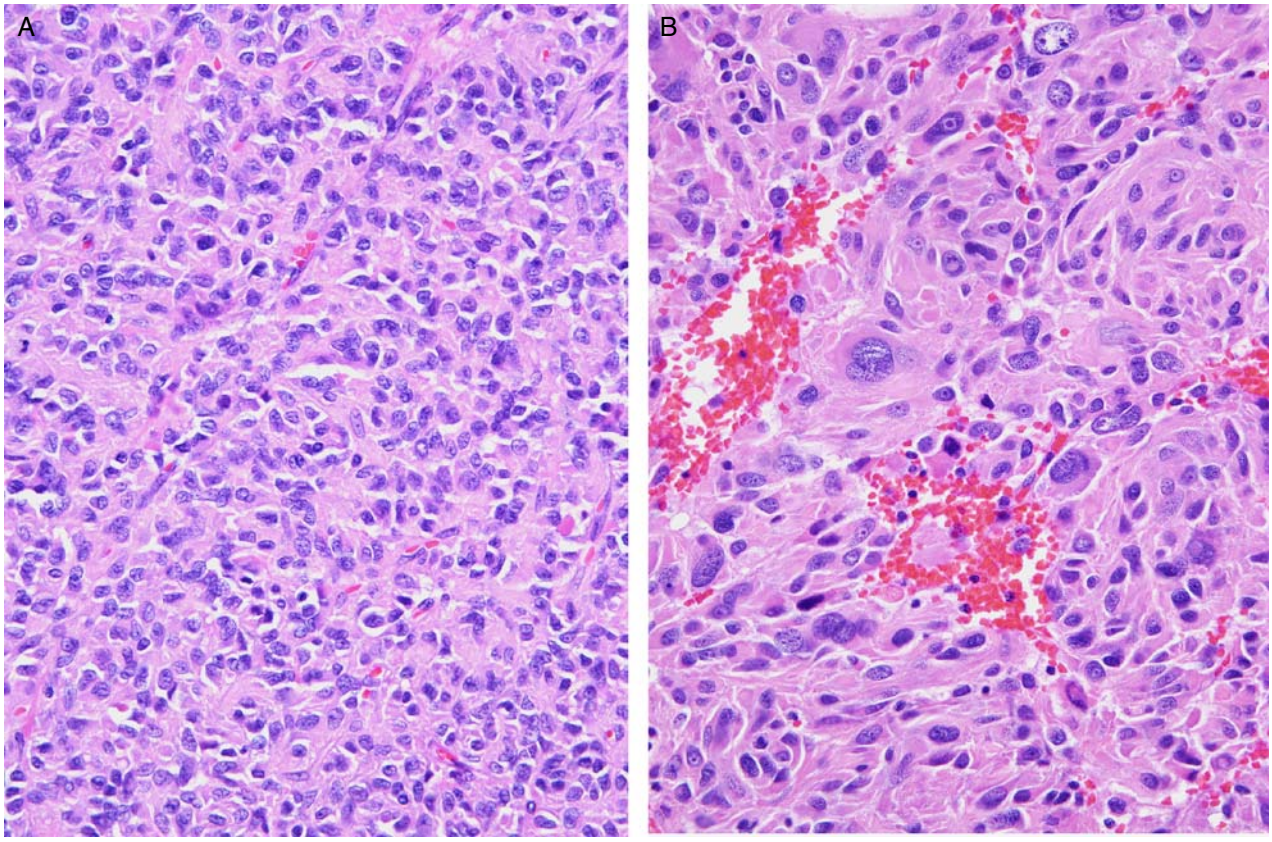

FIGURE 7. A hypercellular epithelioid GIST from a 38-year-old female patient (A; case 6) showing focal areas with striking nuclear pleomorphism (B). Three tumors in this study showed pleomorphism.

growth, and epithelioid or mixed morphology were typical features. Ten of 12 patients (83%) with over 6 months of follow-up developed metastases to perigastric lymph nodes (36%), peritoneum (72%), and liver (45%).[1] Similar to the adult patients in our study, responses to imatinib seem to be uncommon in pediatric patients with metastatic GIST,[1] although sunitinib may show some antitumor activity in a subset of pediatric patients with imatinib-resistant tumors.[1,9]

As mentioned above, the clinical and pathologic features of pediatric-type GISTs differ significantly from conventional adult gastric GISTs. In a large study of 1765 gastric GISTs by Miettinen et al,[18] male and female patients were equally affected (in contrast to the striking female predominance in pediatric-type GISTs), and most patients were between 50 and 80 years of age, with a median age of 63 years; only 2.7% of tumors arose in patients younger than 21 years. Most gastric GISTs arose in the corpus; only 29% of tumors involved the antrum. Although epithelioid and mixed epithelioid and spindle cell patterns are relatively common in gastric GISTs (50% overall in the study by Miettinen et al[18]), most epithelioid gastric GISTs show a prominent collagenous stroma (the so-called "sclerosing epithelioid" subtype); only 6% of gastric GISTs in this study were of the "hypercellular" epithelioid subtype, whereas all pediatric-type GISTs in our current study showed high cellularity without significant stroma. Similar to pediatric-type GISTs, liver and intra-abdominal dissemination was the typical pattern of tumor progression. However, none of the patients in the gastric GIST study by Miettinen et al[18] developed lymph node metastases, whereas lymph nodes were involved in just more than 60% of the patients in our study. The finding of lymph node metastases in a gastric GIST should therefore be a clue to the possibility of a pediatric-type wild-type tumor. It should be noted that local recurrences in the wall of the stomach are exceedingly rare in conventional gastric GISTs; as such, limited gastric resection (even enucleation) can be sufficient for local control.[18]

GISTs that harbor mutations in *PDGFRA* also exhibit differences from the majority of adult GISTs with activating *KIT* mutations.[4,10] For instance, nearly all *PDGFRA*-mutant GISTs arise in the stomach and show purely or predominantly epithelioid morphology, but lack the multifocality and multinodular architecture of pediatric-type GISTs.[10] By immunohistochemistry, nearly one quarter of *PDGFRA*-mutant GISTs are either KIT negative or show only limited immunoreactivity in scattered cells.[10] Of 11 gastric GISTs with a *PDGFRA* exon 14 mutation in a study by Lasota et al,[11] all but 1 showed epithelioid morphology, around half of which showed sclerosing features. Unlike pediatric-type GISTs, however, these *PDGFRA* exon 14-mutant tumors affected

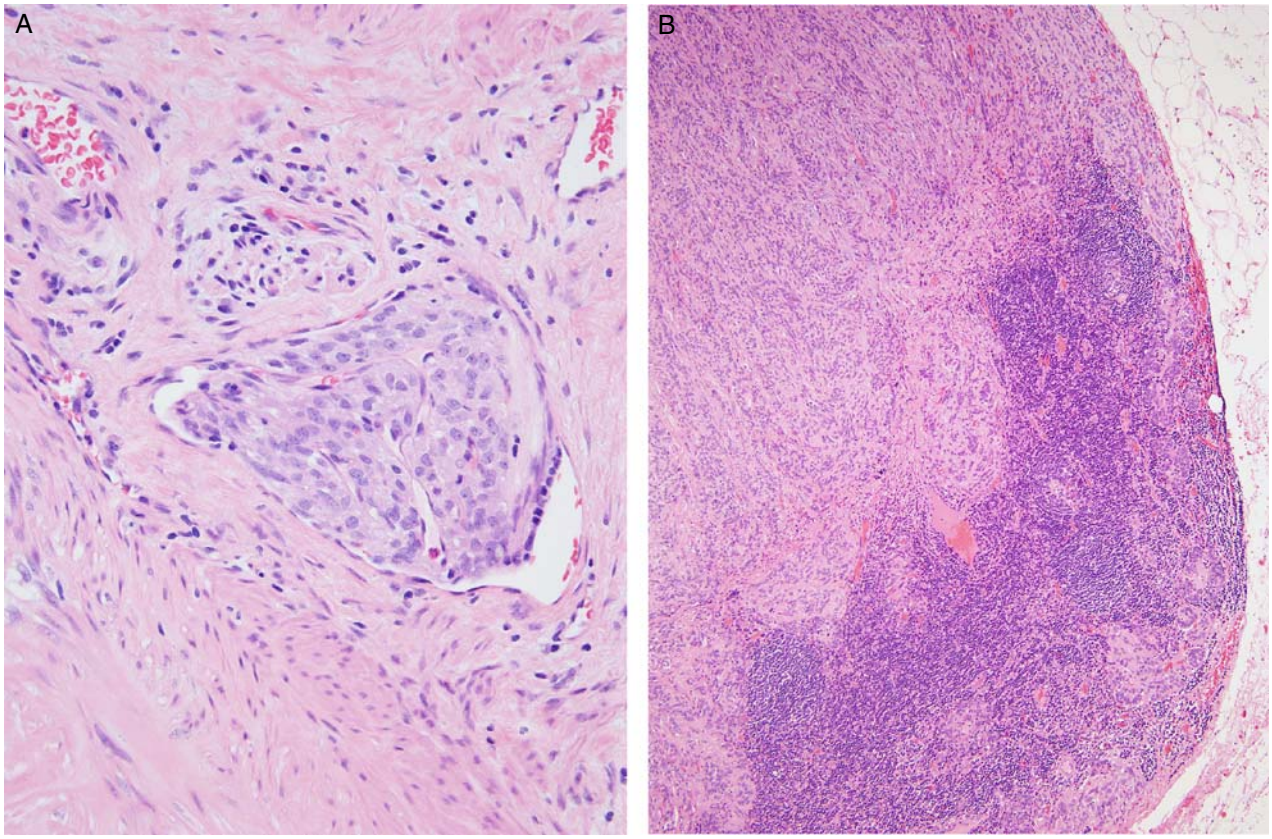

FIGURE 8. A, Lymphovascular invasion was identified in approximately one third of tumors. B, GIST metastatic to a perigastric lymph node. This was a common occurrence irrespective of primary tumor size or mitotic activity.

male and female patients equally, and the majority of tumors (64%) was negative for KIT or at most showed only focal staining. Most *PDGFRA*-mutant gastric GISTs pursue a benign clinical course and lymph node metastases are not seen.[10,11]

GISTs may also occur as part of the Carney triad (gastric GIST, paraganglioma, and pulmonary chondroma)[2] and Carney-Stratakis syndrome (the "dyad" of gastric GIST and paraganglioma).[3] In a study by Zhang et al[24] of 104 gastric GISTs in patients with the Carney triad, the pathologic and clinical features were similar (if not identical) to pediatric-type GISTs: female predominance (88%); multifocality and a multinodular growth pattern; epithelioid or mixed morphology (86%), usually with the hypercellular histologic pattern; lymph node metastases (29%); local recurrence; and indolent behavior even with metastatic disease. No mutations in *KIT* or *PDGFRA* have been identified in patients with the Carney triad.[14] GISTs in the Carney-Stratakis syndrome also seem to be multinodular with both spindle cell and epithelioid morphology,[3] although the pathologic features of only small numbers of such tumors have been described. In a study of 5 families with the Carney-Stratakis syndrome, 5 patients had a gastric GIST, diagnosed at a mean age of 24 years. Three of these patients had lymph node metastases at resection.[3] Unlike the Carney triad, there does not seem to be a female patient predominance. Patients with the Carney-Stratakis syndrome harbor germline mutations in one of the succinate dehydrogenase complex subunit genes.[20] It should be noted that on follow-up, 2 of the patients in our study have radiographic findings suggesting that they may have one of these syndromes: 1 patient with a lung lesion suggestive of a pulmonary chondroma and 1 patient with an adrenal mass suspicious for a pheochromocytoma. Neither of these patients have had these tumors sampled as of yet for histologic confirmation. These findings suggest that patients with gastric GISTs showing pediatric-type histology should be evaluated for the possibility of Carney triad or Carney-Stratakis syndrome and potentially should be screened for paragangliomas.

It is not possible to determine the incidence of pediatric-type GISTs in adults based on our study, even if only the prospectively identified cases are considered, in large part owing to consult bias: the majority of patients whose GISTs we review in consultation have already developed metastases and many have already failed standard imatinib therapy. Aggressive tumors are therefore overrepresented in our practice. However, to provide a sense of their rarity, the 9 pediatric-type GISTs identified prospectively by one of the authors (J.L.H.) represent 2.5% of GISTs reviewed by this author during a 5-year period, including 7% of primary gastric tumors.

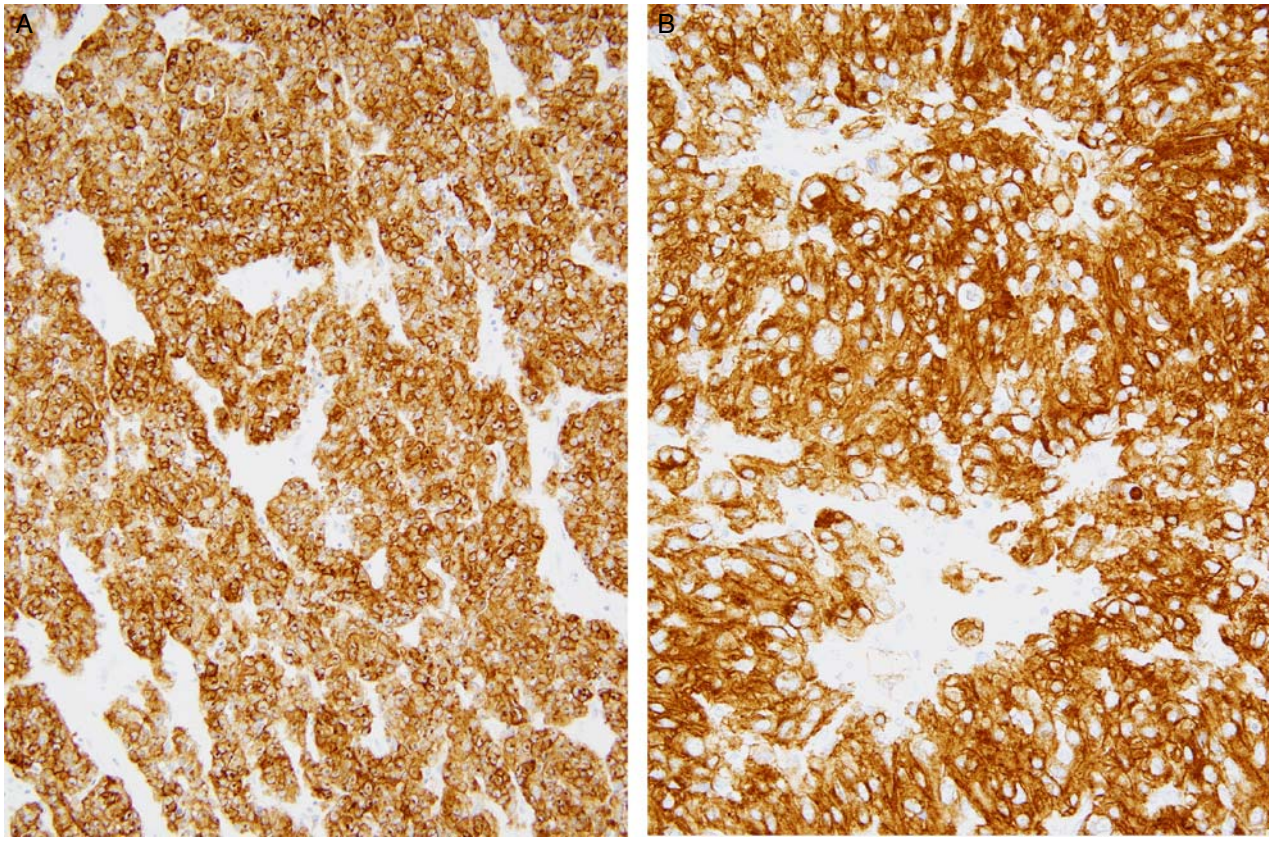

FIGURE 9. All pediatric-type GISTs showed strong diffuse immunoreactivity for KIT (A). Most tumors were also positive for DOG1 (B).

As indicated, this is likely an overestimate of their true incidence in an unselected group of GISTs.

In summary, gastric GISTs in adults with a multinodular or plexiform growth pattern and epithelioid or mixed morphology are similar to pediatric GISTs. Unlike conventional adult GISTs, this distinctive subset predominantly affects women, often metastasizes to lymph nodes, and lacks mutations in *KIT* and *PDGFRA*. Current risk assessment criteria applied to adult GISTs do not reliably predict behavior for this group. Although metastases are common and the tumors are imatinib resistant, they pursue a relatively indolent clinical course. Some patients with advanced disease may benefit from sunitinib through undefined mechanisms. However, it is likely that other tyrosine kinase inhibitors or other therapeutic approaches will be required to treat patients with metastatic tumors of this type. Recognition of pediatric-type GISTs in adults is critical for prognosis, appropriate therapy, and follow-up.

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