RESEARCH ARTICLE

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Clinicopathological Features of Gastrointestinal Stromal Tumors and Review of the Literature: A Single Institution Experience

ABSTRACT

Objective: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasias of the gastrointestinal system (GIS). The malignancy potential of GISTs may vary ranging from indolent tumors to progressive malignant tumors. This study aims to define clinicopathological and immunohistochemical features of GISTs diagnosed in our institute with a review of the literature.

Methods: A total of 28 GIST cases were included in the study. The Hematoxylin&Eosin stained slides of surgical resection materials and cell blocks and immunohistochemistry performed slides were reviewed by a pathologist. The immunohistochemical expression with CD117, DOG-1, CD34, SMA, and S100 was scored between 0 and 3 points according to staining intensity. Descriptive statistics were used in the study. The demographic data, prognostic histopathological, and immunohistochemical findings are evaluated with the literature indications.

Results: Eleven of the cases were male and seventeen were female. The age range was 18-88. The most common site of GISTs was the stomach, followed by the small intestine, colorectal region, and, esophagus. Twenty of the tumors were resected surgically, four were endoscopic biopsy material and four were fine-needle aspiration biopsies. The tumor size in measurable materials ranged from 0,2 to 22 cm. The mitotic count in 50 HPF ranges from 0 to 10. Seven of the GISTs were high grade and the remaining 21 were low grade. The majority of the cases were composed of spindle cells, 3 were epithelioid and 3 were the mixed type with spindle and epitheloid cells.

Conclusions: A variety of criteria has been proposed to estimate the malignancy potential of GISTs and predict prognosis but definite prognostic criteria remain uncertain. Further studies with larger series of GISTs consisting of different types of biopsy materials may help define criteria to predict prognosis precisely.

Keywords: Gastrointestinal Stromal Tumors, CD117, DOG-1, CD34, Prognosis.

Gastrointestinal Stromal Tümörlerin Klinikopatolojik Özellikleri ve Literatürün Gözden Geçirilmesi: Tek Merkez Deneyimi

ÖZET

Amaç: Gastrointestinal stromal tümörler (GİST) gastrointestinal sistemin en sık görülen mezenşimal neoplazileridir. GİST'lerin malignite potansiyeli indolen tümörlerden progresif malign tümörlere kadar değişken olabilir. Bu çalışmada merkezimizde tanı almış GİST'lerin klinikopatolojik ve immünohistokimyasal özelliklerini literatür eşliğinde gözden geçirmek amaçlanmıştır.

Gereç ve Yöntem: Toplam 28 GİST olgusu çalışmaya dahil edilmiştir. Cerrahi rezeksiyon materyalleri ile hücre bloklarından hazırlanan Hematoksilen&Eozin boyalı preparatlar ile immünohistokimya uygulanmış preparatlar patoloji uzmanı tarafından değerlendirilmiştir. CD117, DOG-1, CD34, SMA ve S100 immünohistokimyasal ekspresyonları boyanma yoğunluğuna göre 0-3 puan arasında skorlanmıştır. Çalışmada deskriptif istatistikler kullanılmıştır. Demografik bulgular, prognostik histopatolojik ve immünohistokimyasal sonuçlar literatür eşliğinde değerlendirilmiştir.

Bulgular: Olguların 11'i erkek, 7'si kadındı. Yaş aralığı 18-88 arasındaydı. GİST'ler için en sık görülen lokasyon mide olup bunu ince barsak, kolorektal bölge ve özofagus takip etmekteydi. Tümörlerin 20'si cerrahi olarak çıkarılmış olup, 4'ü endoskopik biyopsi, kalan 4'ü ince iğne aspirasyon biyopsi materyaliydi. Tümör çapı ölçülebilen materyallerde tümör çapı 0,2 ile 22 cm arasındaydı. 50 büyük büyütme alanında mitoz sayısı 0 ile 10 arasındaydı. GİST'lerin 7'si yüksek dereceli, 21'i düşük dereceliydi. Olguların çoğunluğu iğsi hücrelerden oluşmakta olup, 3'ü epiteloid, 3'ü mikst tipteydi.

Sonuç: GİST'lerin malignite potansiyelini tahmin etmek için çeşitli kriterler öne sürülmüş olsa da kesin prognostik kriterler belirlenmemiştir. Çeşitli biyopsi materyallerinden oluşan daha büyük vaka serilerinde yapılacak çalışmalar prognozu daha kesin öngörebilecek kriterlerin belirlenmesine yardımcı olacaktır.

Anahtar Kelimeler: Gastrointestinal Stromal Tümör, CD117, DOG-1, CD34, Prognoz

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasias of the gastrointestinal system (GIS), derived by differentiation to the interstitial cells of Cajal (1). GISTs are rare tumors that indicate an incidence of 10-15 per million (2). They consist of less than 1% of all GIS tumors (3).

The majority of GISTs develop through activating mutations in KIT and/or platelet-derived growth factor receptor (PDGFR) (1). The oncogenic mutations in these genes result in activation of the tyrosine kinase receptor, which regulates proliferation and growth (4). The mutations in c-kit or platelet-derived growth factor receptor alpha (PDGFRA) exist in almost 85-90% of GIST cases (3). The remaining 10% cases are succinate dehydrogenase-deficient GISTs, NF1-associated GISTs, translocation-associated GISTs, and, BRAF V600E–mutated GISTs (3,5,6,7). Hirota et al. reported expression of CD117 (c-KIT) immunohistochemically is a key diagnostic marker for GISTs in the year 1998 (8). Positivity of CD117 helps in differential diagnosis to distinguish GISTs from other mesenchymal tumors such as leiomyomas and leiomyosarcomas (1). Immunohistochemically, almost up to 95% of GISTs are stained with CD117 (9,10). DOG-1 gene encodes a calcium-activated chloride and bicarbonate channel (11). DOG-1 is also an immunohistochemical marker that is frequently expressed in GISTs (up to 98%) and interstitial Cajal cells (12). Almost 70% of GISTs show positive staining with CD34 (13). GISTs may be stained with Smooth muscle actin (SMA), S100, and Desmin with less frequency (14). This study aims to define clinicopathological and immunohistochemical features of GISTs diagnosed in our institute with a review of the literature.

MATERIAL AND METHODS

The study was performed according to the tenets of the Helsinki Declaration and according to approval by the local Ethics Committee of the Duzce University Medical School (prot. No 2022/56 of April 2022).

A total of 29 GIST cases diagnosed in 2012–2022 were included in the study. The inclusion criteria were (i) histopathologic diagnosis of GIST; (ii) sufficient clinical history; and (iii) sufficient pathology material for immunohistochemical analysis. The exclusion criteria were (i) insufficient tumor tissue for immunohistochemistry and (ii) insufficient histological and immunohistochemical features for the diagnosis of GIST. All cases were recruited from the archives of the Pathology Department of Duzce University School of Medicine. Demographic data such as age, gender, tumor size, the type of biopsy material, and localization of tumor were obtained from pathology reports and patient files. Descriptive statistics (mean, standard deviation, number, and percentage) were used in the study.

The Hematoxylin&Eosin (H&E) stained slides of surgical resection materials and cell blocks and immunohistochemistry performed slides with CD117, DOG-1, CD34, SMA, S100, and ki67 were reviewed by a pathologist. The assay was performed using the Ventana Benchmark XT (Ventana-Roche Diagnostics, Meylan, France). The localization of the tumor, growth pattern, mucosal ulceration, necrosis, tumor grade, cell type (spindle, epithelioid or mixed), and surgical margins were evaluated from the H&E slides. Tumor grade, cell types, and pathological stage were defined due to criteria of the World Health Organisation (WHO) classification of tumors of the digestive system, 2019 (2). Cellularity and pleomorphism are determined as low, mild, or high. Categorization of tumors was made based on United States (US) Armed Forces Institute of Pathology (AFIP) data to define the relationship between mitotic rate and tumor size to the prognosis of GISTs. The immunohistochemical expression with CD117, DOG-1, CD34, SMA, and S100 was scored between 0 and 3 points according to staining intensity. No staining was considered 0, light staining 1, moderate staining 2, and strong staining 3 points. Staining percentage points were determined using a manual count of stained cells and the total number of tumor cells. The staining percentage has been evaluated in 5 categories: Negative, less than 25%, between 25%-50%, between 50%-75%, and more than 75%. The mitotic count from the fifty fields (/50 HPF) with the highest number of mitotic figures was determined. After the hotspot was identified under low magnification, the ki-67 labeling index was determined as a percentage by a manual count.

RESULTS

Eleven of the cases were male and seven were female. The age range was 18-88, with a mean age of 62.21. The median age was calculated as 65.5. The most common site of GISTs was the stomach (n=14), followed by the small intestine (n=10), colorectal region (n=3), and, esophagus (n=1). Twenty of the tumors were resected surgically, four were endoscopic biopsy material and four were fine needle aspiration (FNA) biopsies. The symptoms at presentation vary. Seven of the patients had abdominal masses. Five patients had abdominal pain and 3 had dyspepsia, 1 patient had fatigue, 1 patient had difficulty with swallowing and, 2 patients had reflux. Three patients applied to the hospital with gastrointestinal bleeding and 1 patient with ileus. Four cases were

detected incidentally during obesity surgery and 1 during hydatid cyst operation. The tumor size in measurable materials ranged from 0,2 to 22 cm and the mean tumor size was 5.27 cm. In tissue biopsy materials 17 of the tumors have expansive borders, and 7 show infiltrative borders. Except for the slides prepared from cell blocks of FNA materials, 6 of the cases have shown mucosal ulceration. Necrosis was present in 6 cases, 4 of them are high grade. The mitotic count (MC) in 50 HPF ranges from 0 to 10. Seven of the GISTs were high grade and the remaining 21 were low grade. The majority of the cases were composed of spindle cells (22), 3 were epithelioid and 3 were the mixed type with spindle and epitheloid cells. The cellularity of the GISTs was low in 11 cases, mild in 12, and high in 5. Two of the tumors with mild cellularity were high grade. Pleomorphism was low in 19 cases, mild in 7, and high in the remaining 2. Due to TNM classification, in tumor size measurable cases, 6 of GISTs were pT1, 7 were pT2, 7 were pT3 and 2 were pT4. For the tumors with measurable tumor size, 6 of the GISTs located in the stomach were category 1, 2 were category 2 and 1 was category 5. Only one case was category 1 in small bowel GISTs; 3 were category 2, 2 were category 3a, 3 were category 6a and 1 was category 6b. The colorectal localized GISTs were categories 3a,6a, and 6b. All GIST cases showed positive staining with CD117. The majority of the cases showed a staining percentage of more than 75% (n=23). The staining percentage between 50-75% was observed in remained 5 cases. In 15 cases CD117 staining was strong enough to take 3 points, 11 cases showed moderate staining and 2 cases had light staining with 1 point (Fig.1). DOG-1 immunoreactivity was seen in more than 75% of 18 patients, between 50-75% in 5, between 25-50% in 3, and less than 25% in one case. The intensity of staining points with DOG-1 were 3 in 12, 2 in 10, and 1 in 5 cases. CD34 was stained more than 75% in 17 cases, between 50-75% in 4 and less than 25% in one case. Six cases were negative with CD34. The satining intensity of CD34 was strong in 16 cases (3 points), moderate in 5 (2 points) and, light in 1 (1 point). Most cases were negative with SMA, but 3 cases showed focal positive staining (<25%). No immunoreactivity with s100 was observed in the majority of the cases, only in 2 cases showed focal positivity (<25%) with s100. The ki67 labeling index is between 1 to 50% in hot spots, but in the majority of the cases (24/28), the proliferation index was under 10% (Fig.2). Three cases had metastases. Two high-grade tumors had metastases to the liver and lymph nodes, and one low-grade tumor had a metastatic tumor in the liver.

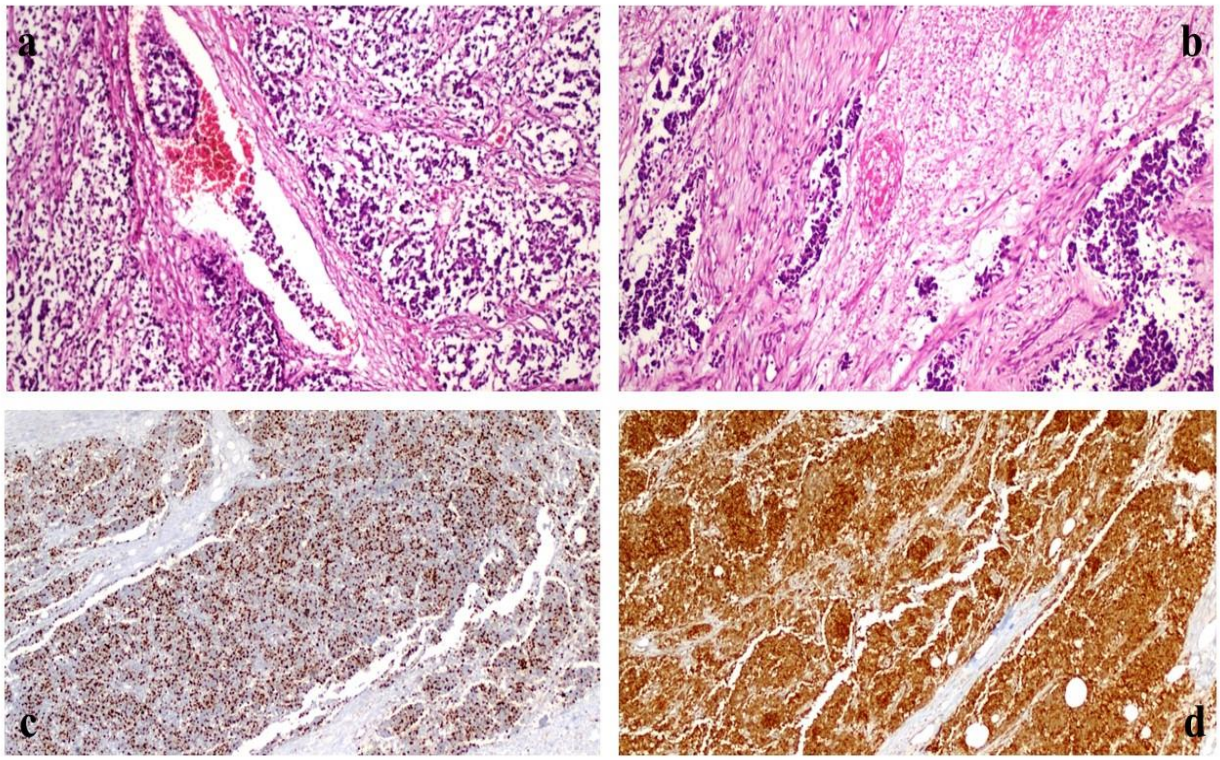

Figure 1. The tumor composed of small epithelioid morphology showed vascular and perineural invasion (H&E, x10, a and b), with a high ki67 labeling index (c) and diffuse CD117 immunoreactivity (d).

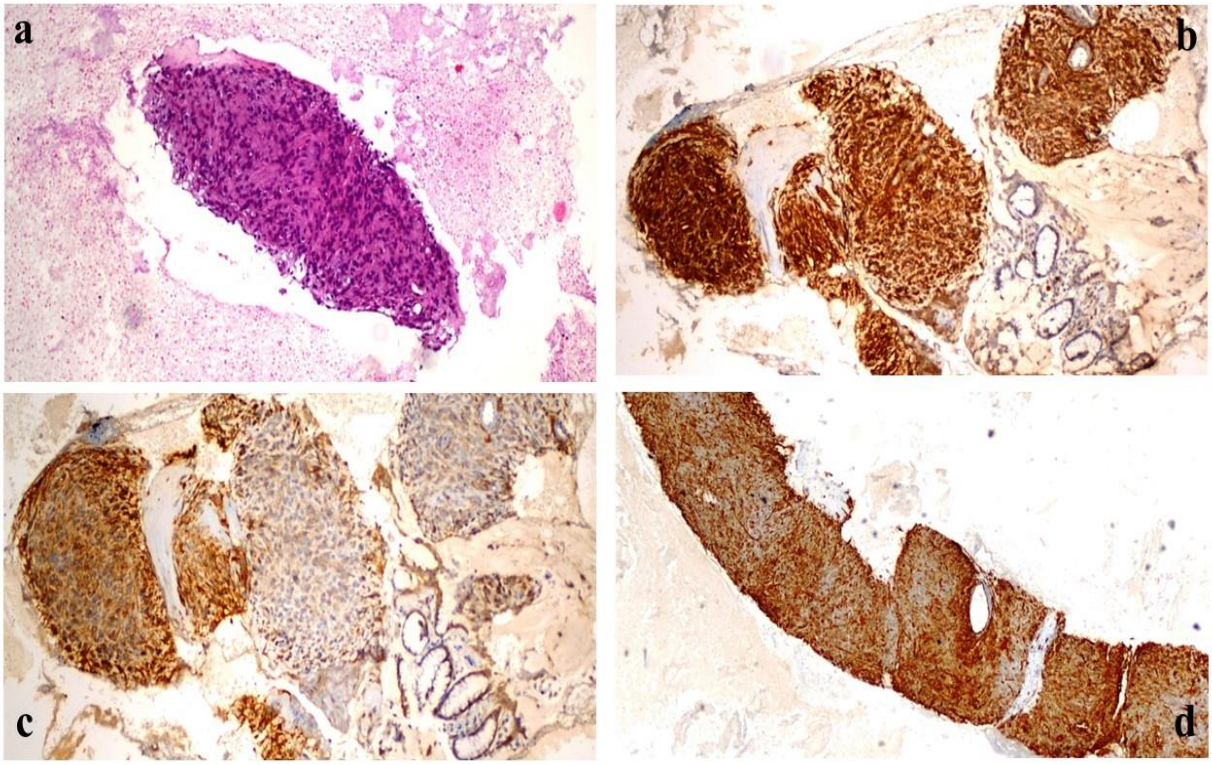

Figure 2. The cell block prepared from ultrasound-guided fine-needle aspiration (EUS-FNA) (a, H&E, x10) showed positive immunstaining with CD117 (b, x10), DOG-1 (c, x10) and CD34 (d, x4).

DISCUSSION

The number of cases may vary due to geographic locations (15). GISTs may occur at any age but there is a tendency to later decades of life (median age 60-65) with a slight predominance of males consistent with our series (2). The most common location for GISTs is the stomach, small bowel, colon, rectum, and esophagus (16). Appendix and extragastrointestinal sites such as omentum, mesentery, and retroperitoneum are rare locations, that consist of less than 5% of all GISTs (2,16). A very small proportion of GISTs may arise within the abdominal cavity and show no apparent connection to any part of the gastrointestinal tract. In such cases entitled extra-gastrointestinal GISTs (10). All of our cases were located in GIS. The symptoms may be vague, mostly bleeding and anemia related to mucosal ulceration. Abdominal pain, discomfort, and new mass may lead to the discovery of the tumor (1,2,3). A variety of symptoms were encountered in our series such as bleeding, abdominal pain, and dyspepsia but interestingly, some tumors were incidentally found during obesity surgery. A careful macroscopic examination of sleeve gastrectomy materials may be helpful in the early detection of GISTs and other tumors.

Since the new immunohistochemical markers are being added to the diagnostic panel of GISTs, CD117 still seems to be the best diagnostic marker. But 5-10% of cases are negative. The staining rates of DOG-1 are very similar to CD117 (17). Unallied of CD117 expression, DOG-1 is a specific and sensitive marker for GISTs. Recently, several studies claimed DOG1 is a more sensitive marker in the diagnosis of GISTs compared to CD117 in both surgical resection materials and cytologic cell blocks (11). CD34 was commonly used in the diagnosis of GISTs before the identification of CD117. But the sensitivity and the specificity of CD34 are low compared to other markers (18). All GIST cases showed positive staining with CD117 in our series. Except for one case, all GISTs were stained with DOG-1. CD34 was negative in six cases. These findings are compatible with the literature and CD34 seems to be less sensitive than CD117 and DOG-1.

Approximately up to 20% of GISTs have metastatic disease at diagnosis (19). The most characteristic sites for GIST metastasis are the abdominal cavity, liver, and lymph nodes. Metastases to lymph nodes are more frequent in pediatric and young adult patients. The lungs, bones, and brain are rare locations for GIST metastasis (10). Three patients had metastatic disease in our series, all three of them were adults with age ranges 38-69. Two cases had liver metastasis and one had metastasis to the regional lymph nodes.

With a variety of classifications from the National Institutes of Health (NIH), AFIP has proposed several criteria to predict prognosis and estimate the potential of malignancy of GISTs, but uncertainty in potential prognostic factors remains (2,19). The most important prognostic factors are tumor size, localization of the tumor, mitotic count, and, tumor rupture (4,19). To count the mitotic figures in 50 hpf, rather than 10 is recommended because GISTs mostly have a low mitotic index (4). Positive surgical margins, tumor necrosis, the genotype of the tumor, and the immune response may also play important role in prognosis. All these parameters were evaluated in this study.

Tumor necrosis is accepted as a significant histopathologic parameter to predict prognosis and recurrence in soft tissue tumors for a long time (20,21). Yi et al. suggested that tumor necrosis may be associated with a poorer prognosis for GISTs in a meta-analysis (19). Recently, many studies reported a variety of possible prognostic factors for GISTs including tumor necrosis, still, the outcomes are controversial (16, 22, 23, 24). The discordance among studies may be associated with small sample sizes such as our study. Liu et al. reported that tumor necrosis has a statistically significant relation with aggressive biological parameters such as nuclear atypia, higher mitotic count, tumor rupture, and larger tumor size (16). In our study, 4 of 6 cases with tumor necrosis were high grade and category 6a and 6b due to AFIP risk criteria.

Yokoi et al. defined new histopathological criteria for assessing the malignant potential of GISTs. The criteria are based on the presence of hemorrhage/ necrosis, tumor size (<5 vs ≥5cm), and ki67 labeling index (<3% vs ≥3%) (24). Based on these criteria, 5 of 6 tumors are malignant with tumor necrosis in our study. When Yokoi's criteria are applied among the GISTs with measurable tumor size, 9 of 23 cases were malignant and, 3 of 9 malignant tumors were low grade with risk category 3a due to AFIP. But there is a consistency among benign cases, 13 of 14 benign GISTs are low grade in our series. Amin et al. categorized GISTs in three groups by combining mitotic count (MC) and tumor size as prognostic parameters: (1) benign: MC less than 5, tumor smaller than 5 cm; (2) borderline: MC less than 5, tumor larger than 5 cm; and (3) malignant: MC greater than 5, tumor any size (25). Due to Amin's category, 13 were benign, 3 were borderline and 7 were malignant in our series. When compared to grade, all benign and borderline GISTs were low grade and all malignant cases were high grade. There is a strong compatibility between grade and Amin's criteria for malignancy in our series.

Miettinen et al. proposed three categories for GISTs as probably benign, probably malignant, and uncertain or low malignant potential based on tumor localization (intestinal or gastric), tumor size, and mitotic count (26). Due to this categorization, 12 were probably benign, 8 were probably malignant and 3 were in the uncertain or low malignant potential category in our series. All of the cases in the probably benign and uncertain or low malignant potential category were low grade, and 7 of 8 cases categorized as probably malign were high grade. These findings favor the common tendency to predict prognosis by tumor size, and mitotic count in GISTs.

The ki67 labeling index is a useful indicator for cell proliferation but yet, but a definite cut-off point for predicting prognosis in GISTs remains unclear. Zhou et al. suggested two cut-off points for ki67. When the ki67 index is higher than 8%, it may predict an unfavorable prognosis (27). Four cases had a higher than 8% ki67 labeling index in our series, They were all high-grade tumors with stages T3 and T4. Two of them had metastases to the liver and lymph nodes. Three of the patients with a high ki67 labeling index passed in 1 to 7 months after diagnosis. These findings support the suggestions about a high ki67 labeling index correlates with an unfavorable prognosis.

Nevertheless, measuring tumor size may not be possible at the time of diagnosis in small endoscopic and fine-needle aspiration biopsies. For submucosal gastric tumors, new safe, and effective biopsy techniques are available. Physicians can provide efficient tumoral tissue for histopathological diagnosis from the submucosal layer with FNA (28). In recent years, new methods such as liquid biopsies started to be used (29). Trindade et al. found endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) is superior to ultrasound-guided fine-needle aspiration (EUS-FNA) for diagnostic efficiency in cases with suspicion of GISTs (30). In our series, 8 of 28 cases were obtained with EUS. Four patients underwent EUS-FNB and 4 patients underwent EUS-FNA. All 8 cases are diagnosed with GIST and samples were efficient to perform immunohistochemistry and diagnostic evaluation.

CONCLUSIONS

In the past years, besides new molecular studies helping us understand the genetic pathway of GISTs, it is also easier to diagnose GISTs with immunohistochemical markers even from minimal tumor tissue obtained with EUS-FNA and EUS-FNBs. Although various studies shared data to define definite prognostic parameters to predict the behavior of GISTs, it remains controversial. In this study, we compared the prognostic and immunohistochemical features of GISTs with the findings of the literature, yet it seems to require more studies in larger series to reveal criteria for understanding the behavior of GISTs.

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