

Gastrointestinal stromal tumors: A multicenter study of 1160 Turkish cases

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Background/aims: The aim of this multicenter study was to determine the histopathological features and immunohistochemical profiles of gastrointestinal stromal tumors diagnosed in Turkish patients. **Material and Methods:** Twenty-eight participating centers registered their gastrointestinal stromal tumor cases on a nationwide database. The diagnosis of gastrointestinal stromal tumor relied upon hematoxylin & eosin features and the results of antibody panel including CD117, CD34, desmin, smooth muscle actin, S-100 protein, and Ki67. The database consisted of parameters including age, gender, location, and all other histopathological and immunohistochemical findings. Statistical analysis was performed using Pearson, Kruskal-Wallis, Mann-Whitney U, and Spearman tests. **Results:** From all of the gastrointestinal stromal tumors in the database, 1160 cases with a male to female ratio of 1.22 and a mean age of 56.75 years were included in the study. The most common location was the stomach (45.0%), followed by the small intestine, omentum-peritoneum, large intestine, and esophagus (32.0%, 12.6%, 9.3%, 1.1%, respectively). The risk groups were distributed as: 6.1% very low, 21.7% low, 19.3% intermediate, and 53% high-risk cases. Many histopathologic findings were correlated with risk groups. CD117 was positive in 95.3% of gastrointestinal stromal tumors, whereas CD34 was positive in 74.9%, smooth muscle actin in 45.9%, desmin in 9.2%, and S-100 in 19.1%. Though no significant relation was found between CD117 expression and tumor location, CD34, smooth muscle actin and Ki67 expressions significantly varied in different locations ($p=0.001$) and risk groups. **Conclusions:** The results of this multicenter study demonstrated that features other than tumor size and mitosis and immune markers other than CD117 and Ki67 included in the antibody panel seem to be useful as predictive risk factors.

Key words: GIST, gastrointestinal stromal tumor, histopathologic features, immunohistochemistry

Gastrointestinal stromal tümörler: 1160 vakayı içeren Türkiye’de çok merkezli çalışma

Amaç: Bu çok merkezli çalışmada Türkiye’den toplanan gastrointestinal stromal tümör vakalarında histopatolojik ve immunohistokimyasal özellikleri belirlemek amaçlanmıştır. **Yöntem ve Gereç:** Oluşturulan ulusal bir veritabanına 28 merkezden gastrointestinal stromal tümör vakaları kaydedildi. Gastrointestinal stromal tümör tanısı hematoxilin-eosin bulgularına ve CD117, CD34, desmin, SM Actin, S-100 protein, ve Ki67’yi içeren antikor paneli sonuçlarına dayandırıldı. Veritabanı yaş, cinsiyet, tümör yeri, diğer histopatolojik ve immunohistokimyasal bulguları içermekteydi. Pearson, Kruskal Wallis, Mann Whitney U ve Spearman testleri kullanılarak istatistik araştırma yapıldı. **Bulgular:** Veritabanındaki 1160 gastrointestinal stromal tümör vakasında erkek/kadın oranı 1.22 ve ortalama yaş 56.75 idi. En sık görülen yer mide (%45.0) olup, bunu ince barsak, omentum-periton, kalın barsak ve ösofagus izlemekteydi (Sırasıyla %32.0, %12.6, %9.3, %1.1). Vakaların %6.1’ü çok düşük, %21.7’si düşük, %19.3’ü orta ve %53’ü yüksek riskliydi. Pek çok histopatolojik bulgu risk gruplarıyla ilişkiliydi. CD117 %95.3 vakada pozitifken, %74.9 vakada CD34, %45.9 SMA, %9.2 desmin, %19.1 S-100 pozitifdi. CD117 ile tümör yeri arasında anlamlı ilişki saptanmadı, ancak CD34, SMA ve Ki67 ekspresyonları tümör yerine ve risk gruplarına göre anlamlı fark gösterdi ($p=0.001$). **Sonuç:** Bu çok merkezli çalışma sonuçları, tümör çapı ve mitoz dışında patolojik ve CD117 ve Ki67 dışında immun önemli risk faktörleri olduğunu göstermektedir.

Anahtar kelimeler: GIST, gastrointestinal stromal tümör, histopatolojik bulgular, immunohistokimya

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract (1,2). Traditionally, these tumors were classified as smooth muscle, nerve sheath or autonomic nerve tumors (1,3-10) until the term GIST was introduced in order to define these tumors as a histogenetically neutral group, which could neither be verified as neurogenic or of smooth muscle origin. With the aid of immunohistochemistry, GISTs are now considered to originate from interstitial Cajal cells (7-11) which, like GISTs, express c-kit protooncogene product (CD117), a transmembrane tyrosine kinase receptor molecule. Immunohistochemical studies have made it clear that more than 94% of these tumors are c-kit-positive and frequently express a myeloid progenitor cell antigen, CD34 (1,7-9,12). A significant subset has immunophenotypic characteristics of smooth muscle, neural differentiation or both (1,2,7-9,11,13).

GISTs are also known for their wide variability in biologic behavior and for the difficulty in determining their malignant phenotype (1,7,10,14). Several studies addressing the problem of predicting prognosis in GISTs have concentrated on tumor size, mitotic rate, and other histologic features like cellularity, anaplasia and location (1,7,8,15,16). Though some degree of correlation was found for several features, their reproducibility was poor due to considerable inter-observer variation (15). The presence of a high mitotic count is generally accepted as the best indicator of malignancy (1,7,8,17-19).

There are only a few large series in which the histopathological features of GISTs were studied and correlated with risk groups (13,17,20,21). In a multicenter study, we analyzed 1161 patients with GIST and aimed to determine the histopathological features and immunohistochemical profiles of GISTs in Turkish patients.

MATERIALS AND METHODS

In 2004, the Working Group of GIST was founded in Turkey with the participation of 10 centers, and a nationwide database (www.tpd.org.tr/gist) was developed. The criteria for the diagnosis of GIST relied upon hematoxylin and eosin (H&E) analysis and an immunohistochemistry panel including CD117, CD34, desmin, smooth muscle actin (SMA), S-100 protein, and Ki67, and was standar-

dized by the Working Group. The gross and microscopic features included in the report and also in the database of GIST are shown in Table 1. The database consisted of parameters including patient age, gender, tumor location, size, number of mitoses/50 high power fields (HPF), and other histopathological and immunohistochemical findings. The risk of aggressive behavior of the tumors was calculated according to the National Institutes of Health (NIH) consensus statement of 2001 (7). During the last five years, 28 centers registered 1161 GIST cases, which were retrospectively collected or recently diagnosed on the database.

The results of histopathologic features and immunohistochemical findings of all cases in the database were reviewed by two expert pathologists. The cases without complete outcome data were excluded before the statistical analyses. Pearson correlation analysis was used for describing the linear association between location, size, mitosis, invasion depth, lymph node and distant metastasis, and risk categories with gender, histopathologic features like cell type, cellularity, atypia, growth pattern, necrosis, and immunohistochemical expressions. Kruskal-Wallis and Mann-Whitney U tests were performed for nonparametric variables.

RESULTS

In 1161 registered GIST cases with complete data on the database, the male to female ratio was 1.22 and the mean age was 56.75 years (median: 58, range: 7-98 years). The most common location was the stomach (45.0%), followed by the small intestine (32.0%), omentum and peritoneum (9.3%), large intestine (12.6%), and esophagus (1.1%).

The mean tumor size was 7 cm (median: 8.89 cm, range: 0.1 cm – 60 cm). The mean number of mitoses was 12.5/50 HPF (median: 4/50 HPF, range: 0-300/50 HPF (Figure 1A) The spindle cell type (Figure 1B) was observed in 66%, epithelioid cell type (Figure 1C) in 10.1% and mixed type in 23.9% of GISTs. Cellularity of the tumors was high (Figure 1D) in 77.3% of tumors and low in 22.7%. High cytologic atypia (Figure 1E) was found in 41.2%, and mild atypia was observed in 58.8% of the cases. Frequencies of other macroscopic and microscopic features are given in Table 1.

When correlation between the location and histopathologic features was analyzed, significant differences between the mean sizes and number of

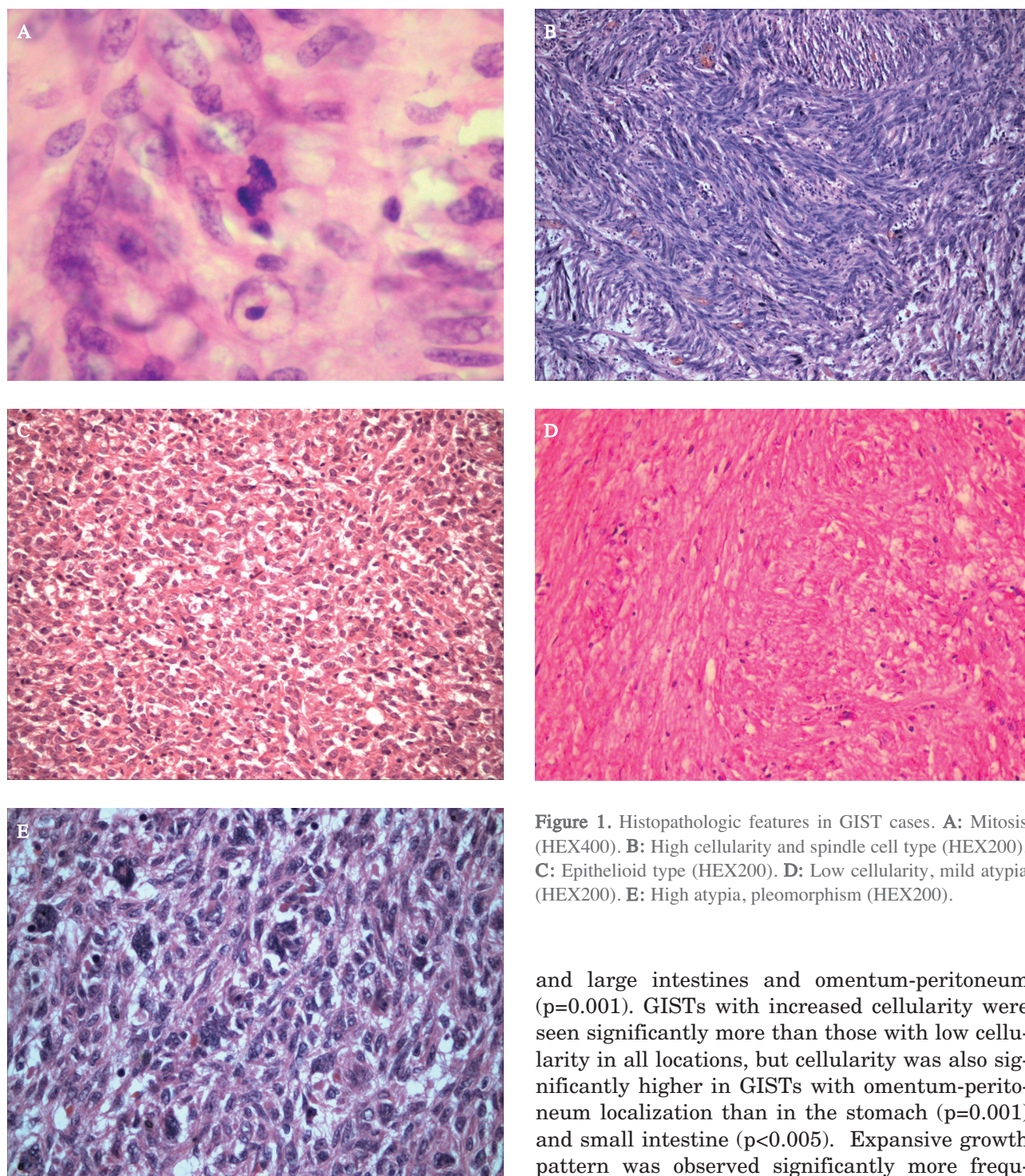


Figure 1. Histopathologic features in GIST cases. **A:** Mitosis (HEX400). **B:** High cellularity and spindle cell type (HEX200). **C:** Epithelioid type (HEX200). **D:** Low cellularity, mild atypia (HEX200). **E:** High atypia, pleomorphism (HEX200).

mitoses in relation to tumor location were observed ($p=0.001$). The mean size of omental-peritoneal tumors was larger than of gastric, large and small intestinal tumors ($p=0.001$), which were larger than gastric ones ($p<0.005$). The lowest mitotic rate was found in gastric GISTs, while it significantly increased in the order of small ($p<0.005$)

and large intestines and omentum-peritoneum ($p=0.001$). GISTs with increased cellularity were seen significantly more than those with low cellularity in all locations, but cellularity was also significantly higher in GISTs with omentum-peritoneum localization than in the stomach ($p=0.001$) and small intestine ($p<0.005$). Expansive growth pattern was observed significantly more frequently in stomach tumors in comparison to small and large intestine ($p<0.05$) and omentum-peritoneum GISTs ($p=0.001$), where mostly an infiltrative pattern was observed.

Distribution of risk groups was as follows: 6.1% very low, 21.7% low, 19.3% intermediate, and 53% high risk. Significant differences were observed between the risk groups in relation to tumor location. High-risk cases were more common in all lo-

Table 1. Distribution of gender and major pathologic features

	Case Number	%
Gender		
Male	638	55
Female	522	45
Location		
Stomach	505	45.3
Small intestines	359	32.2
Large intestines	107	9.6
Omentum, peritoneum	144	12.9
Esophagus	5	0.7
Tumor size		
<2 cm	103	8.9
2-5 cm	247	21.3
5.1-10 cm	447	28.5
>10 cm	363	31.3
Mitosis		
<5/50 HPF	629	54.7
5-10/50 HPF	218	19
10/50 HPF	302	26.3
Risk Groups		
Very low	69	6.1
Low	246	21.7
Moderate	219	19.3
High	601	53
Cell type		
Epithelioid	116	10.1
Spindle	759	66
Mixed	275	23.9
Cellularity		
Low	261	22.7
High	890	77.3
Cytologic atypia		
Low	474	41.2
High	676	58.8
Growth Pattern		
Expansive	758	67.4
Infiltrative	334	29.7
Mixed	33	2.9
Necrosis		
Present	520	45.2
Absent	630	54.8
Hemorrhage		
Present	623	54.6
Absent	517	45.4
Ulceration		
Present	316	27.9
Absent	818	72.1

cations (40% in stomach, 54% in small intestine, 65% in large intestine and 80% in omentum-peritoneum). High-risk tumors showed significantly more frequent distant organ metastasis ($p=0.001$). Among the histopathologic features, epithelioid and mixed cell types ($p=0.001$), increased cellularity ($p=0.001$), cytologic atypia ($p=0.001$), microscopic necrosis ($p=0.001$), ulceration ($p=0.001$), and hemorrhage ($p=0.001$) were positively while spindle cell type was inversely correlated with increasing risk ($p=0.001$). Serosa and adjacent organ in-

vasion correlated significantly with increased risk ($p=0.001$).

Immunohistochemical Features

CD117 was positive (Figure 2A) in 95.3% of GISTs, whereas 74.9% CD34 (Figure 2B), 9.2% desmin (Figure 2C), 45.9% SMA (Figure 2D), 19.1% S-100 (Figure 2E) positive cases were observed. Cut off between low and high proliferation index of Ki67 (Figure 2F) was accepted as 10%, and the number of cases with low Ki67 index was more than high index cases (70.9% vs 29.1%, respectively); the proliferative indices were significantly correlated with mitosis, size, location, risk groups, depth of invasion ($p=0.001$), and lymph node metastasis ($p=0.014$).

No significant relation was found between CD117 expression and tumor location, while CD34, SMA and Ki67 expressions varied significantly in different locations. CD34 positivity was more common in stomach GISTs (88%) than in small and large intestine and omentum-peritoneum tumors ($p=0.001$), while SMA was more commonly observed in omentum-peritoneum (57%) and small intestinal GISTs (54%) in comparison to gastric tumors (41%) ($p=0.001$). High Ki67 index (>10%) was observed significantly more commonly in omentum-peritoneum (43.8%) and large intestine GISTs (44.6%) than in stomach (26.3%) and small intestine (29.2%) GISTs ($p=0.001$).

Significant differences were observed in CD34, SMA and desmin expressions and Ki67 indices in relation to risk groups; index of Ki67 ($p=0.001$) increased in parallel with the risk, while CD34 ($p=0.002$), SMA ($p=0.05$) and desmin positivity ($p=0.001$) decreased as the risk increased.

DISCUSSION

GISTs are uncommon mesenchymal tumors of the gastrointestinal tract that occur equally in both sexes and predominantly in middle-aged and older persons, with a median age between 50 and 60 years, and they are rare before the age of 40 years (1,20-22). The age and sex of the patients included in our study appear similar to the literature.

GISTs may arise anywhere in the gastrointestinal tract (GIT) and in extra-GI locations, particularly in the mesentery, omentum and retroperitoneum. Fifty to 70% of lesions arise in the stomach, 20% to 30% in the small bowel, 10% in the large bowel, 5% in the esophagus, and 5% elsewhere in the abdominal cavity (1,7,12,16,17,20,23-25). Occasio-

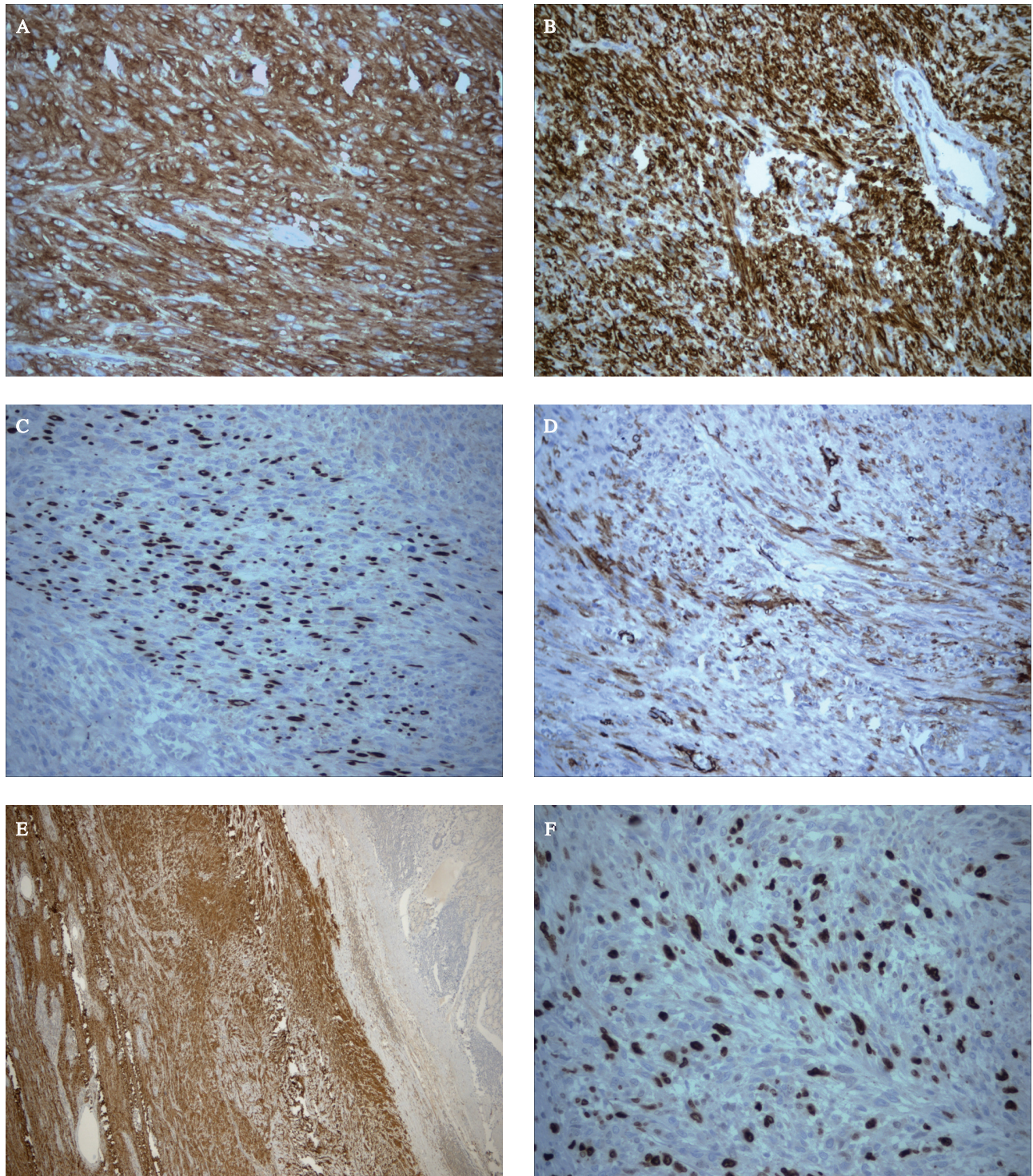


Figure 2. Immunohistochemical findings: **A.** CD117 positivity (CD117X200). **B.** CD34 positivity (CD34X200). **C.** Desmin positivity (DesminX200). **D.** SMA positivity (SMA X200). **E.** S100 positivity (S100X100). **F.** Ki67 high index (Ki67X400).

nally, the tumors may be multicentric (1,2,7,21). In our study, the stomach and small intestine were the most common locations, while the frequency of large intestine location (10.0%) was similar to that in other series. Interestingly, omentum-peri-

toneum localization (14%) was higher and that of the esophagus was lower (0.5%) than in other reports. GISTs outside the GIT in the abdomen, especially in the omentum, mesenteries, and retroperitoneum, are usually accepted as metastatic or

possibly detached from their GIT origin. However, a small number of apparent primary tumors have been reported in these sites (20). Either sufficient diagnostic procedures were not done or more clinical and operational information was not given, and the real location of these cases could not be determined.

The size of GISTs ranges from 0.3 cm to over 30 cm in diameter. The tumor size of our cases ranged from 0.1 cm to 60 cm, with a median of 7 cm. The histopathologic features other than tumor size and mitosis are cell type, cellularity, nuclear atypia, tumor necrosis, ulceration, and hemorrhage (1,2,7,14,16). Up to 50% of cases may show ulceration of the overlying epithelium (2,27). The lesions are generally well circumscribed although not encapsulated (2). Small GISTs often form solid subserosal, intramural, or less commonly, polypoid intraluminal masses. A majority of larger GISTs form external, sometimes pedunculated masses attached to the outer aspect of the gut involving the muscular layers. Most of our cases (67.4%) had expansive tumor borders.

There are some site-specific variations in morphology. A significant proportion of gastric and small intestinal GISTs are small (1). Similarly, gastric GISTs in our study was the smallest. Epithelioid lesions occur far more often in the stomach than elsewhere (70% to 80%), whereas spindle cell lesions have a particular tendency to the small and large bowel (1,7,21). In our study, epithelioid type was more common in the stomach; however, no significant difference was observed.

We used the consensus approach of Fletcher *et al.* (7) for predicting the risk groups in this study (Table 1). According to this approach, the most important favorable prognostic variables are small tumor size (<5 cm) and low mitotic count (<5/50 HPF) (1,10,13,17,27,28). There is a well-established relationship between these parameters and tumor behavior based on several large clinicopathologic studies (20). In these studies, the number of high-grade or malignant cases are more than other groups (21,26,27). There were 6.1% very low, 21.7% low, 19.3% intermediate, and 53% high-risk cases in our study.

Several studies suggest that malignant GISTs may occur in younger age groups (1,24,27). However, others observed a much less aggressive behavior in children and young adults (2). In our cases, there was a significant relation between age and

risk groups, supporting the first suggestion that high-risk tumors are found in young patients.

The prognosis in GISTs also depends to some extent on anatomic site. There is a trend for small bowel tumors to have the worst prognosis and esophageal tumors the best, where most gastric tumors have low risk (1,2,12,18,25). Small intestinal GISTs have a more aggressive behavior than gastric GISTs, with similar size and mitosis parameters, especially including tumors of more than 5 cm with low mitotic rates. In addition, small intestinal GISTs tend to be larger and more advanced when diagnosed (20). Some authors believe that the majority of esophageal and colonic lesions are malignant (1). Our study supported the previous investigation, as the ratio of small intestinal cases with high risk was more than of those tumors in other locations.

The degree of cellularity differs in low-risk versus high-risk cases with an adverse outcome. Prominent nuclear pleomorphism is an uncommon feature (1,2,30) and correlates with poor prognosis (2,7,12,19,28). In our cases, cellularity and atypia were significantly increasing in parallel to the risk, and the ratio of cases with mild atypia was higher although not significant. Ulceration, necrosis and hemorrhage all correlate with risk, although such features are not usually predictive of clinical behavior. However, foci of unequivocal tumor necrosis are generally associated with malignancy (2,12,18,19,22,30-32). The status of microscopic margin of resection does not affect survival (13). Although some authors suggest epithelioid and spindle cell tumors have different clinical behavior- in which epithelioid has poorer (7,19,21) survival- some do not agree (27,30). In our cases, cell pattern seemed to be predictive of outcome, as spindle pattern was inversely while epithelioid type was positively correlated with increasing risk.

The controversy over the histogenesis of the GIST has been based largely on immunohistochemical studies using a panel of antibodies. It is now appreciated that c-kit immunoreactivity defines this group of tumors showing differentiation toward or being derived from interstitial cells of Cajal, which are known as GI pacemaker cells. In contrast, the less common true smooth muscle and Schwann cell neoplasms of the GIT do not over-express c-kit protein immunohistochemically. c-kit positivity is seen in 95% of GISTs and should be required for either diagnosis of GIST or determination of eligi-

bility for treatment. (7,12,20). In our study, CD117 was positive in most of our GIST cases. It became evident that approximately 80% to 85% of gastric GISTs and 50% of small intestinal GISTs are CD34-positive, the hematopoietic progenitor cell antigen (20). However, Schwann cell neoplasms and a proportion of smooth-muscle tumors also show CD34 positivity (7). In our study, CD34 positivity was the same. Approximately 30% to 40% of GISTs, more often small intestinal than gastric tumors, are positive for SMA, the expression of which is sometimes reciprocal with that of CD34 (1,7,15,20), and around 5% show immunopositivity for S-100; desmin positivity is extremely uncommon (1-2% of cases) and invariably focal (7,15). In our cases, the ratios were close to this report except for S-100 positivity. The higher frequency of S-100 positivity may be the result of less-specific antibodies or differences in interpretation (1).

CD117 positivity is seen in all histological variants and risk groups of different sites (1). In our cases, no significant relation was found between CD117 expression and tumor location. The immunophenotype of true c-kit-positive GIST varies to some degree by location, with CD34 positivity seen most consistently in colorectal, esophageal and malignant lesions, while it has not been found to be a significant prognostic factor in gastric and small intestinal GISTs (20), and SMA positivity is seen most often in small bowel (1,7,12,16,18,20, 23,34) and omental-mesenteric tumors (33). In our study, SMA was significantly more common in small intestinal and omental-peritoneal cases, similar to other studies; however, CD34 positivity was observed significantly more in the stomach and decreases in conjunction with increasing risk.

Desmin is observed in esophageal, gastric and omental-mesenteric tumors with the highest frequency and never in malignant gastric and small intestinal GISTs. (20,31,35). In a few studies, besides desmin, SMA in gastric tumors appears to correlate with good prognosis (14,15,20,31). Similarly, in our study, SMA and desmin positivity decreased with increasing risk. Miettinen (20,31) reported that S-100 is expressed in malignant tumors and seems to be more common in small intestinal than in gastric GISTs. Based on a small number of cases, S100 protein positivity seemed to

be an adverse prognostic factor in gastric but not in small intestinal GISTs (20). In our cases, there was no significant difference between S-100 positivity, location and risk.

Attempts to correlate cellular morphology with immunophenotype have not been successful. Epithelioid GISTs tend to show less intense positivity of CD34 (30) and CD117 as compared with the spindle cell tumors (35). Two-thirds of spindle cell tumors express desmin and SMA but usually in less than 10% of the tumor cells. Of the round cell tumors, only less than 10% express desmin and SMA (16). However, Miettinen et al. (20,31) observed more desmin and S-100 positivity in epithelioid tumors. In our cases, there was no significant relationship between cell type and muscle antibodies.

Many authors have attempted to define more objective indices of likely behavior, including immunohistochemical markers of cell proliferation like Ki-67 and proliferating cell nuclear antigen (PCNA) (7,35). Different studies report that Ki-67 proliferative index of greater than 10% is an indicator of poor prognosis together with tumor size and mitotic activity (9,18,19,34,37-41), except in small intestinal tumors (27). In our cases, low Ki67 index was significantly more common in the stomach and small intestine and increased significantly in parallel with the risk overall. Also, Ki67 was correlated significantly with mitosis and size, which were the powerful prognostic parameters.

In conclusion, our nationwide multicentric study is one of the few reports of large series of GISTs. The demographic, clinical and histopathological features of GISTs in Turkey seem to be in accordance with the previously published large series. The results of this multicenter study demonstrated that features other than tumor size and mitosis and immune markers other than CD117 and Ki67 included in the antibody panel also seem to be useful in risk stratification. Studies with long follow-up and response to therapy of GIST cases will form the basis of our future projects in order to determine the biological behavior of these tumors in our country.

Conflict of interest: We declare that we have no conflict of interest.

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