RESEARCH ARTICLE / *Araştırma Makalesi*

Demographic, Histopathological and Immunohistochemical Characteristic Findings of Gastrointestinal Stromal Tumors: A Single-Centered Study

Gastrointestinal Stromal Tümörlerin Demografik, Histopatolojik, ve İmmünohistokimyasal Karakteristik Bulguları: Tek Merkez Çalışması

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Abstract

Objective	Gastrointestinal stromal tumor (GIST) is the most frequent mesenchymal tumor of the gastrointestinal tract, arises from or is differentiated towards interstitial cell of Cajal. The aim of this study is to review the demographic, histopathological and immunohistochemical characteristics of cases diagnosed with GIST in the light of the literature.
Materials and Methods	Forty-five GIST cases diagnosed between 2010 and 2018 in Kayseri City Hospital's pathology clinic were included in the study. The cases were reevaluated retrospectively by hematoxylin-eosin sections and immunohistochemical staining.
Results	Twenty-one of the cases (46.66%) were female, and 24 (53.33%) were male. The average age was 64.9 years. 4/45 (8.88%) of the cases included in the study were in the very low risk, 20/45 (44.44%) were in the low risk, 8/45 (17.77%) were in the intermediate risk, and 13/45 cases (28.88%) were in the high-risk group.
Conclusion	Histopathology and immunohistochemical studies are important for the accurate diagnosis, classification, prognosis, and treatment in GISTs. The centers should prepare their report formats according to internationally accepted report samples and consensus criteria, and significant macroscopic and microscopic findings and immunohistochemical examination results should be given as a list at the end of the report.
Keywords	gastrointestinal stromal tumors; histopathology; immunohistochemistry staining

Öz

Amaç	*Gastrointestinal stromal tümör (GİST), gastrointestinal sistemin en sık görülen mezenkimal tümörüdür, interstisyel Cajal hücresinden kaynaklanır veya farklılaşır. Bu çalışmanın amacı GIST tanılı olguların demografik, histopatolojik ve immünohistokimyasal özelliklerini literatür ışığında gözden geçirmektir.*
Gereç ve Yöntemler	*Çalışmaya Kayseri Şehir hastanesi patoloji kliniğinde, 2010-2018 yılları arasında tanı konulan 45 GİST olgusu dahil edildi. Olgular retrospektif olarak hematoksilen-eozin kesitleri ve immünohistokimyasal boyamaları ile yeniden değerlendirildi.*
Bulgular	*Olguların 21'i (%46,66) kadın, 24'ü (%53,33) erkekti. Yaş ortalaması 64.9 idi. Çalışmaya dahil edilen olguların 4/45'i(%8,88) çok düşük, 20/45'i (%44,44) düşük, 8/45'i (%17,77) orta derecedeydi ve 13 / 45 olgu (%28.88) yüksek risk grubundaydı.*
Sonuç	*GİST'lerde doğru tanı, sınıflandırma, prognoz ve tedavi için histopatoloji ve immünhistokimyasal çalışmalar önemlidir. Merkezler, rapor formatlarını uluslararası kabul görmüş rapor örneklerine ve fikir birliği kriterlerine göre hazırlamalı ve özel makroskobik ve mikroskobik bulgular ile immünohistokimyasal inceleme sonuçları raporun sonunda liste halinde verilmelidir.*
Anahtar Kelimeler	*gastrointestinal stromal tümörler; histopatoloji; immünohistokimyasal boyama*

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal system (GIS)[1-5] It is known that GISTs, of which immunohistochemical and ultrastructural characteristics are heterogeneous, originate from the interstitial cells of Cajal (ICC) or their stem cell-like precursors. The cells of Cajal are specialized connective tissue cell precursors that are found in the GIS and act as an intestinal pacemaker.[1,6-8] While the cells of Cajal immunohistochemically positively react with CD117, CD34, Dog1 and vimentin, they negatively react with desmin and S100.

GISTs are a rare tumor group, and they constitute 0,1-3% of all GIST tumors.[9] These tumors can be located anywhere in the GIS, from the esophagus to anus. While the most common localization is in the stomach with 60-70%, the localization in the small intestine ranks the second with 25-35%. Other localizations include the colon, rectum, appendix (5%), and esophagus (2-3%), respectively. Lesions that cannot be distinguished histopathologically and immunohistochemically from GISTs can also be observed in the mesenterium, omentum, and retroperitoneum.[1,10-12] The localization outside the gastrointestinal canal is rarer (1%). The primary and metastatic different neoplasms should be evaluated by the clinical and pathological correlation.

GISTs are observed at an average age of 55-60 years in adults. They are extremely rare in children.

Although their clinical behavior and prognostic symptoms are not distinct, they are tried to be estimated by the localization, diameter, cellularity, infiltrative development, and mitotic index of the tumor.[6]

Most of GISTs indicate Protooncogenic tyrosine kinase KIT receptor and less commonly Platelet-derived growth factor receptor alpha (PDGFRA) mutation.[1-3,13] In GISTs, C-KIT(CD117), CD34, DOG1, positivity is helpful in the immunohistochemical diagnosis.

The aim of this study is to review the demographic, histopathological and immunohistochemical characteristics of cases diagnosed with GIST in the light of the literature.

MATERIAL and METHODS

Forty-five GIST cases diagnosed in the Kayseri City hospital pathology clinic between 2010-2018 were included in this descriptive study. The identity clinical information of these cases was obtained from archival records and material-related block and pathology slide archive. The cases were reevaluated retrospectively by hematoxylin-eosin(HE) sections and immunohistochemical staining. CD117, CD34, desmin, smooth muscle actin(SMA), vimentin, S100, Ki-67 staining were used in the immunohistochemical panel. Incomplete immunohistochemical staining was completed. The cases were grouped according to the localizations, gender, age, tumor diameters and histopathological features.

To determine the biological behavior of the tumor, the cases were divided into four groups, being very low, low, intermediate and high risk, based on the 2002-National Institutes of Health (NIH)consensus risk categorization according to the tumor diameter and mitotic index (Table 1).[5] While evaluating immunohistochemical staining, internal staining in the tissue was considered for positive control. Cytoplasm and cytoplasmic membrane staining for CD 117, CD34, S100, SMA, desmin and vimentin were considered positive. When Ki-67 staining pattern was evaluated, positively stained nuclei was calculated as % by thousand cells were counted in the area of intense staining. Histological typing discussed in three groups, as spindle, epithelioid and mixed (spindle + epithelioid). The rate of cellularity and pleomorphism was evaluated in three groups by a semiquantitative method, being low (+), intermediate (++), and high (+++). Necrosis and hemorrhage were evaluated as present (+), not present (-).

Table 1 National Institute of Health (NIH, United States) consensus criteria for GIST rısk assesment		
Risk	Size	Mitotic count (per 50 HPF)
very low	<2cm	<5/50
low	2-5cm	<5/50
intermediate	<5cm 5-10cm	6-10/50 <5/50
high	>5cm >10cm any	>5/50 Any >10/50
HPF: high power field GIST: Gastrointestinal Stromal Tumors		

Tumor diameters were specified in centimeters (cm). For the mitotic index in the cases, mitosis was counted at 50 sites in a 40- high magnification field (HPFs).

This study is a descriptive research.

The study was approved by the Ethical Committee of the institution (Kayseri Şehir Hastanesi, TUEK, tarih:15.11.2018, sayı:76397871, karar no:20).

RESULTS

Forty-five GIST cases, selected in the pathology clinic between 2008 and 2018 were included in this study.

Twenty-one of the cases (46.66%) were female, and 24 (53.33%) were male. The youngest patient included in the study was a male patient aged 43 years, and the oldest patient was a female patient aged 88 years. While the oldest patient had a low-risk group jejunal GIST, the youngest patient had a low-risk group stomach GIST. The average age was 64.9 years. 4/45 (8.88%) of the cases included in the study were in the very low risk, 20/45 (44.4%) were in the low risk, 8/45 (17.7%) were in the intermediate risk, and 13/45 cases (28.88%) were in the high-risk group (Table 2).

Table 2. Tumor risk stratification in GIST		
	Number of cases (n:45)	Percentage (%)
Very low	4	8.88%
Low	20	44.44%
İntermediate	8	17.77%
High	13	28.88%
GIST: Gastrointestinal Stromal Tumors		

25/45 (55.5%) of the GISTs cases were located in the stomach, of 11/45(24.4%) cases in the duodenum, of 5 /45 (11.1%) cases in the jejunum, of 2/45 (4.4%) cases in the ileum, and 2/45(4.4%) cases were located in the rectum (Table 3).

Table 3. Localizations of GIST cases		
Localization	Number of cases (n:45)	Percentage (%)
Gastric	25	55.55%
Duodenum	11	24.44%
jejenum	5	11.11%
ileum	2	4.44%
rectum	2	4.44%
GIST: Gastrointestinal Stromal Tumors		

The largest tumor diameter was 20 cm in a female patient with stomach localization,and the smallest tumor diameter was 1 cm.

The most common histological patern were spindle, other patterns were spindle+epithelioid (mixed), and epithelioid cell type of the GIST cases (Table4).

Table 4. Histological patern of GIST		
Histological patern	Number of cases (n:45)	Percentage (%)
Spindle	35	77.77%
Spindle+epitheloid	8	17.77%
Epitheloid	2	4.44%
GIST: Gastrointestinal Stromal Tumors		

While the number of cases exhibiting the infiltrative growth pattern was 20/45 (44.4%), the number of cases exhibiting the expansive growth pattern was 25/45(55.5%). Cellularity was low (+) in 13 of the cases (28.8%), intermediate (++) in 22 of the cases (48.8%), and high (+++) in 10 of the cases (22.2%). Pleomorphism was evaluated in three groups: low (+), intermediate (++), and high (+++). (Table5).

Table 5. Degree of GIST pleomorphism

Pleomorfizm	Number of cases (n:45)	Percentage (%)
Mild(+)	27	60%
Moderate(++)	10	10%
Severe(+++)	8	7.77%

GIST: Gastrointestinal Stromal Tumors

Liver metastases were present in 2 cases in the high-risk group with severepleomorphism with stomach localization.

The highest mitosis ratio was 25/50 HPF,and it belonged to a 46-year-old female case with a 7x4-cm GIST with spindle morphology located in the small intestine. The lowest mitosis ratio was 1, and it belonged to a female case with a 1-cm GIST with spindle morphology located in the jejunum.

The case with the highest Ki-67 index with 50% was a 56-year-old female patient in the high-risk group of the spindle cell type with stomach localization. While immunohistochemical CD117 reacted positively in all of the cases examined, CD34 positivity could not be found in only 4 cases (8.8%) with CD34.

While there was positive staining with SMA in 14 cases (31.1%), no case was stained with desmin.

Focal positive staining with S100, among immunohistochemical staining, was observed only in 1 case (2.2%), and it was a 74-year-old case with a stomach GIST who had liver metastasis. In the examination of all GIST cases in the pathology archive, a 20-cm diameter tumor located in the stomach was found to be pancreas-invasive in a 56-year-old female patient in a high-risk group who exhibitednecrosis and hemorrhage. Accompanying synchronous adenocarcinoma with the same localization as GIST is present in 3 of the cases.

While 2 of the cases were cases with high-risk GIST located in the colon and had adenocarcinoma with the same localization, synchronous, and intermediate differentiation, the case with a low-risk GIST located in the stomach was accompanied by adenocarcinoma of intestinal type, with intermediate differentiation and stomach localization.

DISCUSSION

Gastrointestinal stromal tumors are the most frequent mesenchymal tumors that can develop in the gastrointestinal tract, from the esophagus to anus throughout the GIS.[14] GISTs were first described in 1940. Studies on KIT expression were conducted between 1998-1999[15,16].GISTs containing KIT tyrosine kinase receptors are a specific tumor group separated from other gastrointestinal tumors with these features.[17] The activation of this receptor causes the development of resistance to apoptosis and uncontrolled cell proliferation. Most patients do not have any symptoms due to the tumor size and localization in the early stage of GISTs. Patients with symptoms may experience abdominal discomfort, pain, vomiting, hematemesis, melena, dysphagia, anemia, and fatigue. While the most common symptom in some publications is hemorrhage, it is abdominal mass followed by gastrointestinal bleeding and pain due to mucosal ulceration in other publications.[18,19] In general, mucosal ulceration is the sign of mucosal ulceration.[20] Small GISTs are often incidentally found duringendoscopy, radiological studies, or surgery performed for another reason.[1,7] There are incidental GIST cases in the literature found after Sleeve gastrectomy performed for obesity surgery[14]. A major part of incidentally found GISTs smaller

than one cm is associated with low grade-benign behavior.[21] The smallest tumor diameter in this study was 0.5 cm, which was found incidentally in the rectum during endoscopy and it was in a very low-risk group.

GISTs are observed at an average age of 55-60 years.[7,11] The average age of the cases in this study was found to be 64.9 years.

In the literature, the male and female genders have equal incidence ratio.[18,19,22] and the male/female ratio in this study is 24/21 (53.33%/46.66%) withmild male dominance. In the literature, there are series in which the dominance of male patients is reported to be mildly dominant.[23] The findings of the present are consistent with the literature. GISTs are most commonly located in the stomach and in the small intestine in the second place.[10,11] In this study, GISTs in 55% of the cases were located in the stomach and in 40% of the cases in the small intestine (duodenum, jejunum, ileum). The esophagus localization is reported to be below 5% in the literature.[1,11] In this series, there are no GIST cases with esophageal localization, and this is consistent with the literature. There are no cases located outside the gastrointestinal system, and there are tumor nodules in the omentum in the GIST case with small intestine localization.

GISTs can range in dimensions from a few millimeters to 40 cm. The average tumor size is 5-8 cm. In this study, the largest tumor diameter is 20 cm and the smallest tumor diameter is 0.5 cm, which is consistent with the literature. With variable macroscopic images, nodules may be cystic, hemorrhagic, and necrotic. Cystic degeneration, hemorrhage, and central necrosis can be observed in large-sized GISTs (Figure1).[6,10]

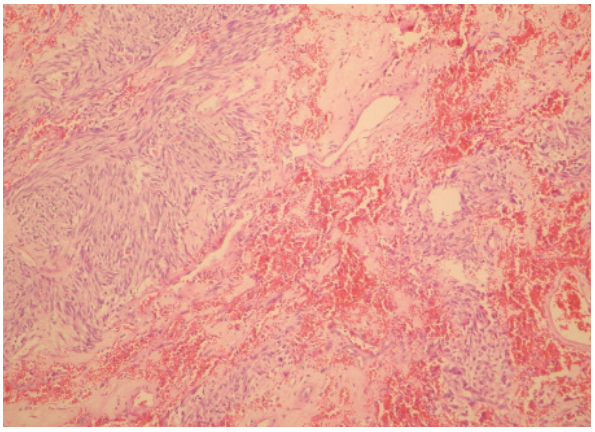

Figure1: Hemorrhage and necrosis in large-sized, hematoxylin eosinx10

Hemorrhage was found in 17 (37.77%) of our cases and necrosis in 12 (26.66%) cases. Many types of cells and growth patterns can be found in necrosis GISTs.

There are two main types of cells, spindleand epithelioid, in the majority. Microscopically, 70% are of spindle cell, 20% are of epithelioid and 10% are of mixed type. In the present series, 35 cases (77.77%) were found to be of spindle type, 8 cases (17.77%) of mixed type, and 2 cases (4.4%) of epithelioid type.

In spindle cell GISTs, growth patterns in the form of short bundles and fascicules are observed (Figure2a, Figure2b). Epithelioid cell GISTs consist of circular-polygonal shaped cells with a round-oval nucleus, eosinophilic or clear cytoplasm (Figure3). A distinctive myxoid stroma can be observed at varying rates in GISTs. A myxoid stroma was observed in one of our cases. If a distinctive cytoplasmic vacuole is formed in the GIST cell, the nucleus is pushed to the periphery, and a signet-ring appearance may occur. There are cases with this feature in the literature. In the present series, 1 case was the epithelioid type and contained signet-ring-like cells.

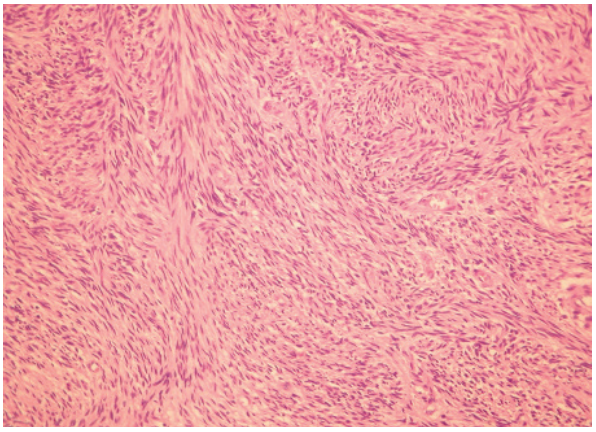

Figure2a: Spindle cell type, hematoxylin eosinx10

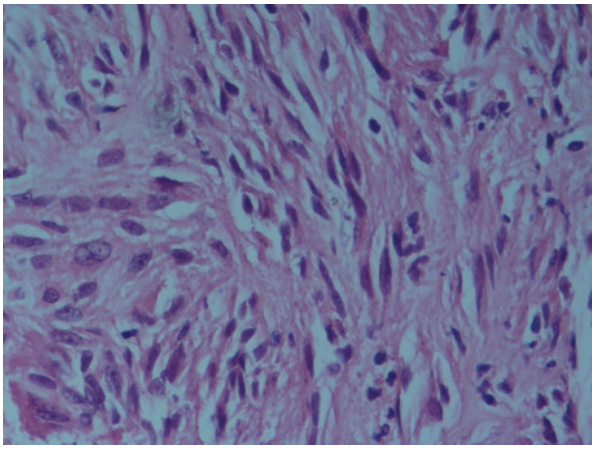

Figure2b: Pleomorphic,spindle cells in gastrointestinal stromal tumor, hematoxylin eosinx20

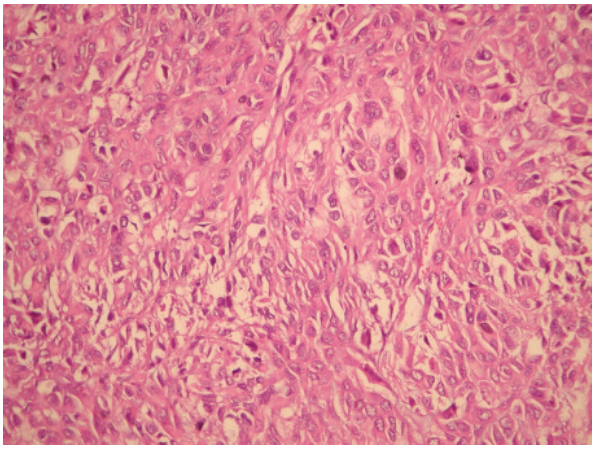

Figure3: Epithelioid cell type , hematoxylin eosinx20

Clinical and histopathological findings and the immunohistochemical staining panel are used in the diagnosis, classification, and prognosis determination of GISTs. In the immunohistochemical panel, vimentin, SMA,desmin, S100, CD34, CD117, and Ki 67 are used[24-26]. In the present study, the same antibodies were evaluated on the immunohistochemical panel. In new studies in the literature, the DOG-1 protein is one of the new proteins with high sensitivity and specificity ratios[13, 27]. In this study, the DOG-1 protein was found to be positive in 5 GIST cases in the pathology records. DOG1 exhibits cytoplasmic and/or membranous staining. KIT is positive in 30% of negative cases. It is expressed independently of the mutation type. However, it should not be used alone instead of CD117. Cases that have the typical GIST morphology but are CD117 and DOG1-negative should consult reference centers.

In GISTs, CD117 is observed to be 95-100% positive, CD34 70-80% positive, SMA 20-40% positive, desmin1-2% positive, and S100 5% positive.[4,7,17] CD117 is usually cytoplasmic (most common), membranous, and perinuclear point-like (Golgi zone staining), or as the combination of these. Although the CD117 expression is significant for diagnosis, it is not the only determinant.

Ki-67, which is added to the immunopanel, is a proliferation determinant used in many tumors and it has been revealed in the studies of Zhao et al. that Ki-67 is an independent prognostic factor and high Ki-67 percentages are accompanied by high-risk GISTs and poor prognosis.[28,29] Values above 10% are accepted as the high proliferation index.

A positive reaction was determined in all cases (45/45) with CD117(Figure4) and in 91.1% of cases (41/45) with CD34, and it is consistent with the literature. In this study, while 14 GIST cases (31.11%) exhibited SMA-positivity and 1 case (2.2%) exhibited S100-positivity, there was no case exhibiting desmin-positivity. In this study, the highest Ki-67 proliferation was found to be 50%, and the lowest

proliferation was below 1%. The Ki-67 proliferation index of all high-risk group GIST cases was found to be above 10% (Figure5). The Ki-67 proliferation index of 2 GIST cases with liver metastasis was found to be above 30%.

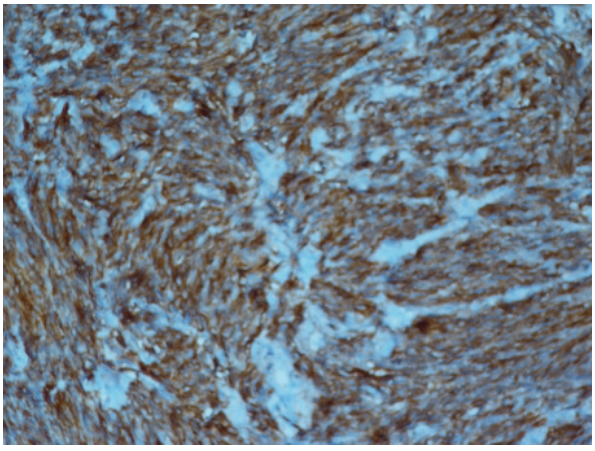

Figure4: CD117 immünohistochemical positive stain in GIST

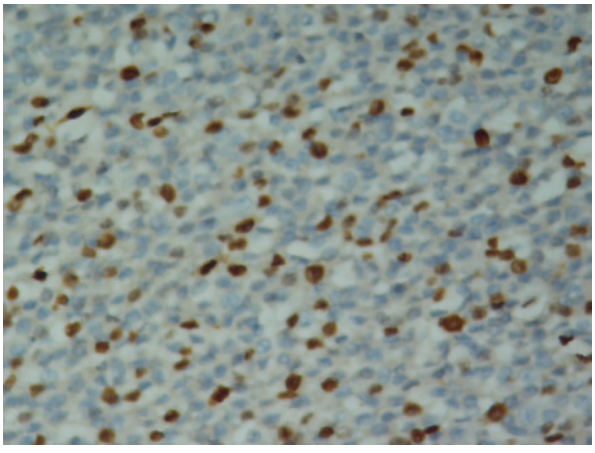

Figure5: Ki67 Immunoreactivity in gastrointestinal stromal tumor

GISTs are a heterogeneous group of tumors of which biological behavior is difficult to estimate in advance. The prognosis is attempted to be determined by parameters such as the tumor diameter, localization, growth pattern, cell type, cellularity, pleomorphism, mitotic index, necrosis, and immunophenotyping studies.[7, 10, 27-30]

The diagnostic criteria for the malign behavior in GISTs according to the tumor size and mitotic activity of the NIH GIST study group in 2002 are presented in Table 1. In this table, the tumor diameter and mitosis count, among the most important findings for the prognosis, were used. GISTs are divided into 4 groups, being very low-risk, low-risk, intermediate-risk, and high-risk. In the present study, 13 cases (28.8%) are in the high-risk group, 8 cases (17.7%) are in the intermediate-risk group, 20 cases (44.4%) are in the low-risk group, and 4 cases (8.88%) are in the very low-risk group.

The malign potential of most GISTs is uncertain. The advanced age, male gender, presence of metastasis at the time of diagnosis, incomplete resection of the tumor,high mitotic index are independent risk factors.[31] The cell type and atypia have also been used as prognostic criteria in some publications.[20,32] The standard surgical treatment in GISTs is the complete surgical resection in the absence of metastases. The most important aim of surgery is the complete excision of the tumor without causing tumor rupture. Following the complete resection, patients are followed-up closely. Imatinib mesylate and multiple tyrosine kinase inhibitors are used in the treatment of GISTs.[33] The standard treatment of metastatic GISTs is conventional treatments. A partial response is received in approximately 65-70% of patients.

GISTs frequently intra-abdominally metastasize to the omentum, peritoneum, mesenteric tissues, and liver. There was liver metastasis in 50% of GISTs at the time of diagnosis.[34] While liver metastasis occurs probably through hematogenous ways, other intra-abdominal metastases occur with the tumor cell culture to the abdominal cavity. In this study, tumor nodules were found in the omentum in one case, and liver metastasis was found in two cases at the time of diagnosis.

CONCLUSION

Immunohistochemical studies are important for the accurate diagnosis, classification, prognosis, and treatment in GISTs. The centers should prepare their report formats according to internationally accepted report samples and consensus criteria, and significant macroscopic and microscopic findings and immunohistochemical examination results should be given as a list at the end of the report. Cases that exhibit the GIST morphology but are CD117/DOG1-negative should be consulted in reference centers. The mutation analysis studies should be performed if necessary.

The study was approved by the Ethical Committee of the institution (Kayseri Şehir Hastanesi, TUEK, tarih:15.11.2018, sayı:76397871, karar no:20).

Written informed consent was obtained from patients who participated in this study.

There are no conflict interest.

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