

Characteristics of gastrointestinal stromal tumors in a Middle Eastern population

Fareed H. Barakat, MD, FASCP, Hussam A. Haddad, MD, EBP, Ismail I. Matalka, MD, FRCPath, Mohammed S. Al-Orjani, MD, EBP, Mahmoud M. Al-Masri, MD, FRCS, Maher A. Sughayer, MD, FCAP

ABSTRACT

الأهداف: توضيح الصفات النسيجية الكيميائية المناعية، والصفات الوبائية للأورام السدوية المعوية المعدية (GIST) في سكان الشرق الأوسط.

الطريقة: تعد هذه الدراسة الإسترجاعية لجميع أورام النسيج الضام داخل البطن (باستثناء الأورام العضلية المخططة المضغية لدى الأطفال، وأورام الخلايا الدائرية الزرقاء الصغيرة) تم جمع الحالات بين عامي 2001م و 2008م من أرشيف دائرة علم الأمراض، مركز الحسين للسرطان، عمان، ومستشفى الملك عبد الله الجامعي، إربد، الأردن. تمت دراسة الصفات النسيجية الكيميائية المناعية لجميع الحالات. أجريت الدراسة في مركز الحسين للسرطان في عمان - الأردن، خلال الفترة ما بين يناير وأغسطس 2009م.

النتائج: أظهرت الدراسة أن الأورام السدوية المعوية المعدية تشكل 45% من أورام النسيج الضام داخل البطن (42 من 93 حالة) مع كون المعدة المكان الرئيسي لها (17 حالة، 40.5%). تم تصنيف 27 حالة من حالات الورم السدوي المعوي المعدي (64.3%) كأورام عالية الخطورة، و 4 حالات (9.5%) كأورام متوسطة الخطورة، و 6 حالات (14.3%) كأورام متدنية الخطورة، و 2 حالة (4.8%) كأورام متدنية الخطورة جداً. أظهرت الفحوصات النسيجية الكيميائية المناعية إيجابية قوية ومنتشرة (+3) ل CD117 في 85.7% من حالات الأورام السدوية المعوية المعدية ول CD34 في 65% من الحالات. كما تبين أن الأورام عالية الخطورة أكثر شيوعاً في المرضى الذكور (نسبة الذكور إلى الإناث = 1.7:1) بينما الأورام غير عالية الخطورة هي أكثر شيوعاً في المرضى الإناث.

خاتمة: تظهر نتائج الدراسة أن الصفات النسيجية الكيميائية المناعية للأورام السدوية المعوية المعدية في المرضى الأردنيين مشابهة لصفاتها الموصوفة سابقاً في الجماعات السكانية الأخرى. كما تظهر الدراسة أن الأورام عالية الخطورة هي أكثر شيوعاً بشكل قليل في المرضى الذكور.

Objectives: To demonstrate the immunohistochemical and epidemiological characteristics of gastrointestinal stromal tumors (GIST) in a Middle Eastern population.

Methods: This is a retrospective analysis of all intra-abdominal mesenchymal tumors (excluding childhood embryonal rhabdomyosarcoma and small round blue

cell tumors) collected from the archives of the Pathology Departments of King Hussein Cancer Center, Amman, and King Abdullah University Hospital, Irbid, Jordan between 2001 and 2008. The immunohistochemical profile of all cases was studied at King Hussein Cancer Center, Amman, Jordan, between January and August 2009.

Results: Gastrointestinal stromal tumors comprised 45% of the intra-abdominal mesenchymal tumors (42 out of 93 cases), with the most common site being the stomach (n=17, 40.5%). Twenty-seven GIST cases (64.3%) were classified as high risk, 4 (9.5%) as intermediate risk, 6 (14.3%) as low risk, and 2 (4.8%) as very low risk. Immunohistochemistry showed diffuse and strong positivity (+3) for CD117 in 85.7% of GIST cases, and for CD34 in 65% of cases. The high-risk tumors were more common in male patients (M:F=1.7:1), while the non-high risk tumors were more common in female patients.

Conclusion: The immunohistochemical profile of GIST in Jordanian patients is similar to previously published data from other populations, with a slight male preponderance for high-risk GISTs.

Saudi Med J 2010; Vol. 31 (7): 797-802

From the Departments of Pathology (Barakat, Haddad, Sughayer), and Surgery (Al-Masri), King Hussein Cancer Center, Amman, and the Department of Pathology (Matalka, Al-Orjani), King Abdullah University Hospital, Irbid, Jordan.

Received 24th March 2010. Accepted 25th May 2010.

Address correspondence and reprint request to: Dr. Maher Sughayer, Chairman, Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Queen Rania Al-Abdullah Street, PO Box 1269, Amman 11941, Jordan. Tel. +962 777491216. Fax. +962 (6) 5300 460 Ext. 1552. E-mail: msughayer@khcc.jo

Disclosure. This study was partially supported by a grant from Novartis Pharmaceuticals, Amman, Jordan.

Gastrointestinal stromal tumor (GIST) is a phenotypically and genotypically distinct entity representing the most common primary mesenchymal neoplasm of the digestive tract.^{1,2} Although a GIST may be identified by light microscopy, a definite diagnosis usually requires a panel of immunohistochemical markers to confirm the morphological impression, thus distinguishing GISTs from other potential soft-tissue mimics occurring in the intestine, such as smooth muscle, and neurogenic tumors, desmoids, solitary fibrous tumors, inflammatory pseudotumors, and fibroid polyps.³ The diagnosis of GIST is often suspected histologically. Most cases have remarkably uniform appearances falling into one of 3 categories: GIST of spindle cell type (70%) that are composed typically of relatively uniform eosinophilic cells arranged in short fascicles or whorls, GIST of epithelioid type that are composed of rounded cells with variably eosinophilic or clear cytoplasm, and a subset of cases (approximately 10-20%) of either spindle cell or epithelioid type, most notable when located in the small intestine, are associated with stromal skeinoid fibers.⁴ Although GISTs may arise anywhere in the GI tract, in recent years identical lesions have been also described to occur in extra-GI locations including the mesentery, omentum, and retroperitoneum. The immunohistochemical demonstration of KIT expression in these lesions has helped to validate their existence, particularly in exceptional sites such as the gallbladder, or urinary bladder.⁴ In 2001, the National Institutes of Health (NIH) workshop defined CD117 (KIT) as the most specific marker for GIST. Aside from consistent positivity for CD117 (KIT), approximately 60-70% of GISTs show immunopositivity for CD34, 30-40% show immunopositivity for smooth-muscle actin (SMA), and around 5% show immunopositivity for S-100 protein. None of the latter antigens are specific for GIST. Desmin positivity in true KIT-positive GISTs is extremely uncommon (1-2% of cases).⁴ The standard and the mainstay of therapy of GIST was and is still surgical resection. Immunohistochemistry should be carried out in all cases suspected of being GIST, because an accurate diagnosis would make a subset of these tumors (advanced and metastatic) eligible for treatment with tyrosine kinase inhibitors. These are small molecules that show high efficacy in advanced and metastatic GISTs that usually do not respond to conventional chemotherapy or radiotherapy.³ Historically and before the era of KIT testing, these tumors were uniformly fatal when advanced, and were treated by other modalities, however, nowadays tyrosine kinase inhibitors are considered cornerstones in the treatment of GISTs especially when metastatic, hence, the importance of recognizing this immunophenotype.⁵ Published

information on GISTs in the Middle East is limited. This study was conducted to evaluate intra-abdominal mesenchymal tumors looking for misdiagnosed GIST, and to study the demographical and epidemiological characteristics of GIST in Jordan.

Methods. The study is a retrospective analysis of intra-abdominal mesenchymal tumors from the archives of the Pathology Departments of King Hussein Cancer Center, Amman, and King Abdullah University Hospital, Irbid, Jordan between 2001 and 2008. Ninety-three intra-abdominal mesenchymal tumors were collected. The cases were retrieved by searching for all mesenchymal tumors that occurred in the abdomen, pelvis, retroperitoneum, mesentery, and abdominal wall. Certain cases were excluded from the study; these included childhood embryonal rhabdomyosarcoma and small round blue cell tumors, such as desmoplastic small round cell tumor, neuroblastoma, Wilms' tumors, and lymphomas. Variables including age, gender, tumor site, tumor size, mitotic activity, and differentiation were evaluated. The tumors were graded as high, intermediate, low risk, and very low risk based on NIH criteria (Table 1).⁴ Similarly they were also assigned to risk categories according to the Miettinen and Lasota criteria (Table 2).⁶ The immunohistochemical profile of all cases was studied. This included CD117, CD34,

Table 1 - National Institutes of Health risk of aggressive behavior in gastrointestinal stromal cancers.⁴

Risks	Size, cm (largest dimension)	Mitotic count/High power field
Very low risk	<2	<5/50
Low risk	2-5	<5/50
Intermediate risk	<5	6-10/50
Intermediate risk	5-10	<5/50
High risk	>5	>5/50
High risk	>10	any mitotic rate

Table 2 - Risk categories according to Miettinen and Lasota.⁶

Group	Size (cm)	Mitosis/50 HPFs	Gastric GISTs	Small intestine GISTs
1	≤2	≤5	Very low if any	Very low
2	>2 - ≤5	≤5	Low	Low
3a	>5 - ≤10	≤5	Low	Intermediate
3b	>10	≤5	Intermediate	High
4	≤2	>5	Low*	High*
5	>2 - ≤5	>5	Intermediate	High
6a	>5 - ≤10	>5	High	High
6b	>10	>5	High	High

HPF - high power fields, GIST - gastrointestinal stromal tumors,
*Denotes tumor categories with very small numbers of cases

S100, desmin, and smooth muscle actin. The study was carried out at King Hussein Cancer Center, Amman, Jordan, between January and August, 2009 and was approved by the Institutional Review Board at King Hussein Cancer Center.

All specimens studied were fixed in 10% buffered formalin and embedded in paraffin. The cases were evaluated by routine hematoxylin and eosin (H&E)-stained sections. Immunostains were performed using the labeled Streptavidin-Biotin method. These included CD34 (QBEND-10, monoclonal, ready to use; Ventana Medical Systems, Strasbourg, France), CD117 (KIT, rabbit monoclonal, Ventana Medical Systems, Strasbourg, France), smooth muscle actin (H4CL-1, mouse monoclonal, ready to use, Ventana Medical Systems, Strasbourg, France), desmin (DE-R-11, mouse monoclonal, ready to use, Ventana Medical Systems, Strasbourg, France), and S-100 protein (Rabbit polyclonal, ready to use; Ventana Medical Systems, Strasbourg, France). Two pathologists chose representative blocks from each case. All stains were interpreted with external positive and negative controls, and with positive internal control whenever possible. A 4-tier system was used to score the immunostaining results: +3 (diffuse and strong positivity): if more than 25% of the tumor cells showed intense staining; +2 (diffuse weak or focal strong positivity): if more than 25% of the cells showed weak to moderate staining, or if less than 25% of the cells showed intense staining; +1 (weak and focal): if less than 25% of the cells showed a weak to moderate staining; and negative (-) if no staining at all was seen. Two pathologists evaluated the cases separately, and a consensus was reached in each case. Stains were unavailable for SMA in 7 cases, desmin in 4 cases, S100 in 3 cases, and CD34 in 2 cases. Missing stains were due to unavailability of the corresponding paraffin blocks. A mesenchymal tumor was defined as a GIST if it was CD117 positive or CD34 positive and negative for the other markers, provided that the morphology was compatible with the common GIST phenotype.

Statistical analysis was carried out by the Research Office at King Hussein Cancer Center using the Fisher Exact Test to look for association between risk category on one hand and gender, location or age on the other hand. All analysis was performed using Statistical Analysis System version 9.1 (SAS Institute Inc, Cary, NC).

Results. Ninety-three intra-abdominal mesenchymal tumors were retrieved. None of these cases proved to be a misdiagnosed GIST; however 2 malignant fibrous histiocytoma cases were reclassified into a more specific entity (de-differentiated liposarcoma). Gastrointestinal stromal tumors comprised 45% of the intra-abdominal

mesenchymal tumors (42 out of 93 cases). Twenty-two out of the 42 cases were observed in men, with a male to female ratio of 1.1:1. The mean age was 53 years, slightly higher in males (55 years) than in females (51 years) (Figure 1). The most common sites of GIST are

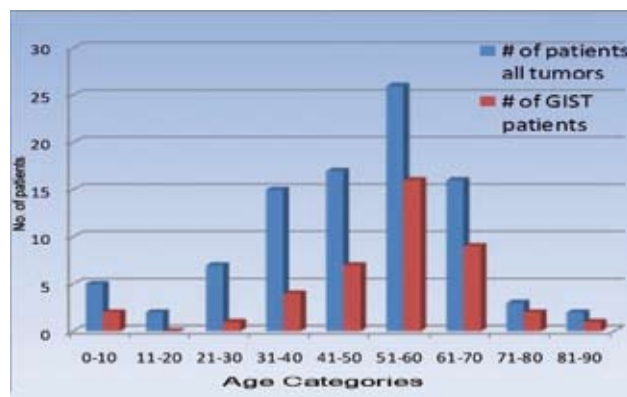


Figure 1 - Age distribution of gastrointestinal stromal tumors and all mesenchymal tumors.

Table 3 - Site distribution of all tumors.

Site of tumors	Percentage
Abdomen	25
Stomach	20
Retroperitoneum	20
Small bowel	13
Pelvis	10
Colon	8
Gallbladder	2
Liver metastasis	2

Table 4 - Risk, age, distribution and location of gastrointestinal stromal tumors.⁴

Risk	Number	Age range	Median (year)	Male to female ratio	Site
Very low	2	49-60	54.5	1:1	Rectum: 1, small intestine 1
Low	6	22-80	56.3	1:2	Stomach: 4, Small intestine: 2
Intermediate	4	2-66	56.1	1:3	Small intestine: 2 stomach: 1 colon: 1
High	27	38-77	55.5	1.7:1	Stomach: 10 Small intestine: 7 Abdomen: 4 Colon: 2 Pelvis: 2 Gallbladder: 1 Mesentery: 1
Not applicable	3				Stomach: 1 Liver: 2*

*Two cases were excluded from risk categorization due to presentation in a metastatic site (liver).

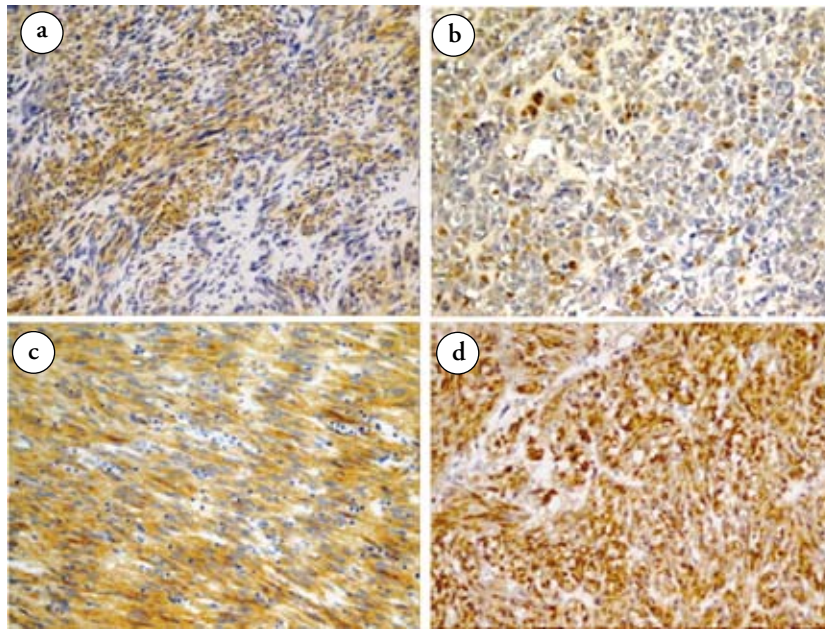


Figure 2 - CD117 immunostain showing a) focal weak positivity, b) focal strong positivity, c) diffuse weak positivity, and d) diffuse strong positivity.

summarized in Table 3. The location could not be further specified in 6 cases; 4 were from the abdomen, and 2 were from the pelvis with no further specification. The risk categorization (using Fletcher criteria), age distribution, and location of GISTs are summarized in Table 4. One case was not graded due to the small size of the biopsy, and 2 others due to presentation in a metastatic site (liver) with no identifiable primary tumor. By applying Miettinen and Lasota criteria (Table 2),⁶ there were no very low risk gastric cases, while 5 of the gastric cases were categorized as low risk, 2 cases as intermediate, and 8 cases as high risk. The non-gastric cases risk assignment remained unchanged. Immunohistochemistry showed diffuse and strong positivity (+3) for CD117 in 85.7% of GIST cases, and at least +1 positivity in 95% of cases (Figures 2a-2d). Diffuse and strong positivity (+3) for CD34 was noted in 65% of GIST cases, and at least +1 positivity in 72.5% (26 and 29 out of 40 cases available for evaluation). Diffuse and strong positivity (+3) for smooth muscle actin was detected in 23% of GIST cases, and at least +1 positivity in 48.5% (8 and 17 out of 35 cases available for evaluation). Diffuse and strong positivity (+3) for S-100 protein was detected in 13% of GIST cases, and at least +1 in 28% (5 and 11 out of 39 cases available for evaluation). Desmin was negative in all cases.

Discussion. Gastrointestinal stromal tumors (GISTs), previously uniformly classified as smooth muscle tumors, constitute the most common mesenchymal

tumors of the stomach and small intestine.^{1,2} The total number of GIST cases reviewed in this study was 42 cases. It constituted 45% of intra-abdominal mesenchymal tumors. The GISTs are positive for CD117 (KIT) in most cases, which is the best defining feature for this tumor. Many of these tumors and mostly the malignant tumors exhibit mutations in the exon 11 of the c-kit gene.⁷ While CD117 negative GIST do exist; we made that diagnosis based on morphological criteria in addition to immunohistochemical staining, excluding all other possible differential diagnoses.

In this study, 40 out of 42 cases (95.2%) classified as GISTs were positive for CD117, and none were positive for desmin. Inclusion of the 2 CD117-negative cases was based on the fact that they were negative for actin, desmin, and S-100 protein, and positive for CD34. They are included because of their histological similarity to GIST.⁸ The CD117-negative cases were considered by Miettinen et al⁷ to represent undifferentiated variants of GIST, but recent studies have shown that these tumors may contain similar genetic mutations to those which are CD117-positive. In this study, the most common site of GISTs was the stomach (n=17, 42.5%), followed by the small intestine (n=12, 28.6%), and the large intestine (n=3, 7%, one from the rectum and 2 from the colon). Gastrointestinal stromal tumors of the colon, excluding the rectum, are rare as compared with other gastrointestinal locations, apart from the esophagus where GISTs are even less common.⁷ There were only 3 cases in the large intestine; one of them was

rectal, hence comprising all together 7%. These findings are similar to other published studies.⁹⁻¹¹ In 6 cases, the site of the tumor was not specified, and if these were excluded from the distribution it will become as follows: gastric (n=17, 47.2%), small intestine (n=12, 33.3%), and large intestine (n=3, 8.3%). These figures are closer to the published data and to the review by Miettinen and Lasota in which the stomach comprises around 60% of GISTs, followed by small intestine (35%), and large intestine (<5%).¹¹ Another study on 37 cases of GISTs found that the most common site of involvement was also the stomach (29.7%), followed by the small intestine (24.3%), while colorectal GISTs comprised (2.7%).⁹ In another study by Lee et al¹⁰ that included 62 GISTs, the primary tumor sites were stomach (44%) and small intestine (47%). In this study there was no gender predilection in the overall group. In their review Miettinen and Lasota also document no clear gender predilection.¹¹

Age distribution of GISTs ranged from 2-81 years with an average of 53 years, including all risk groups. This is almost a decade earlier than other studies, in which the mean age ranged from 59.2-63 years.^{4,11-13} This can be explained by the fact that most of the Jordanian population is young, and the age distribution already leans more towards the young. As for all other mesenchymal tumor group, the median age was 42 years, which is a decade earlier than GISTs.

Twelve cases were classified as non-high risk and 29 cases were classified as high risk. There was no significant relationship between the age and the risk group, or between the site and the risk group, however, a statistically significant association was found between gender and the high risk histology group versus non-high risk groups ($p=0.01$; Fisher exact test). The male to female ratio is 1.7:1 in the high risk group, and 1:2.25 in the other (non-high risk) groups. This means that males are more prone to have high risk GIST as compared to females. This observation that malignant GISTs may be slightly more common in men was previously described.¹¹

The CD117 is a rather specific marker reducing the possibility of false-positive results. When we consider "+1 and above" staining as positive the positivity rate is similar to most published data, and was found to be 95%.^{4,11} CD34 scored +3 in most cases, and in this study the percentage of all positive cases was 72.5%, which is also similar to published data.¹ As for desmin it was consistently negative, which is compatible with the published data as well.⁴ In our hands, S100 protein and SMA are non-specific markers, and should be read and interpreted carefully. We believe that only diffuse and strong positivity should be taken into account when assessing S100 and SMA positivity. Nevertheless, in this study the percentage was 13% for S100 protein, which is

a bit higher than published data (approximately 5%).⁴ This study showed that SMA staining was +3 in 23% of cases, and +2 or more in 48% of cases. This is close to the results found by Fletcher and Rauf (30-40%).^{4,9} The c-kit mutations are considered nowadays to be a molecular marker for GIST.^{8,14} The presence of c-kit mutations confirms the diagnosis of GIST tumors when KIT immunostaining is negative.⁸ These mutations are important because they are detected more often in malignant GIST cases.^{8,14}

One limitation to this study most obviously is the absence of molecular analysis, since it was not available at the time we conducted this study. Another limitation is the fact that most cases were referral from other institutions to confirm the diagnosis for treatment purposes. That made it difficult for us to follow up the patients' outcome.

In summary, our findings show that GIST is becoming a better recognized entity, and is being dealt with as a specific category of tumors that warrants a good index of suspicion and a specific immunohistochemical work up. Our results also show that the demographic and epidemiological findings are more or less similar to the data published in the literature, albeit with a difference in age predilection. In this study, we suggest that males are more prone to have high risk GISTs as compared to females. This has been also previously described,¹² however, further studies will be needed to determine the relation between risk group and gender.

References

- Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; 30: 1213-1220.
- Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol* 2000; 24: 211-222.
- Rossi G, Valli R, Bertolini F, Marchioni A, Cavazza A, Mucciariini C, et al. PDGFR expression in differential diagnosis between KIT-negative gastrointestinal stromal tumours and other primary soft-tissue tumours of the gastrointestinal tract. *Histopathology* 2005; 46: 522-531.
- Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002; 33: 459-465.
- DeMatteo RP. The GIST of targeted cancer therapy: a tumor (gastrointestinal stromal tumor), a mutated gene (c-kit), and a molecular inhibitor (STI571). *Ann Surg Oncol* 2002; 9: 831-839.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006; 23: 70-83.
- Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Gastrointestinal stromal tumors and leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases. *Am J Surg Pathol* 2000; 24: 1339-1352.

8. Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M. Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. *Am J Pathol* 1999; 154: 53-60.
9. Rauf F, Bhurgri Y, Pervez S. Gastrointestinal stromal tumors: a demographic, morphologic and immunohistochemical study. *Indian J Gastroenterol* 2007; 26: 214-216.
10. Lee JL, Ryu MH, Chang HM, Kim TW, Kang HJ, Sohn HJ, et al. Clinical outcome in gastrointestinal stromal tumor patients who interrupted imatinib after achieving stable disease or better response. *Jpn J Clin Oncol* 2006; 36: 704-711.
11. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; 130: 1466-1478.
12. Orosz Z, Tornóczy T, Sági Z. Gastrointestinal stromal tumors: a clinicopathologic and immunohistochemical study of 136 cases. *Pathol Oncol Res* 2005; 11: 11-21.
13. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004; 22: 3813-3825.
14. Taniguchi M, Nishida T, Hirota S, Isozaki K, Ito T, Nomura T, et al. Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. *Cancer Res* 1999; 59: 4297-4300.

Related topics

Bokhary RY, Al-Maghrabi JA. Gastrointestinal stromal tumors in western Saudi Arabia. *Saudi Med J* 2010; 31: 437-441.

Elshenawy YM, Ganote CE, Al-Abadi MA. Fatal abdominal sarcomatosis secondary to gastrointestinal stromal tumor with bland histology. *Saudi Med J* 2009; 30: 1469-1472.

Al-Salam S, El-Teraifi HA, Taha MS. Could imatinib replace surgery in esophageal gastrointestinal stromal tumor. *Saudi Med J* 2006; 27: 1236-1239.