Gastrointestinal stromal tumors

A clinicopathological study

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ABSTRACT

الأهداف: تقييم العروض التقديمية السريرية والخصائص المناعية الكيميائية لـ GIST ومقارنتها بالبيانات المنشورة دوليًا.

الطريقة: تم دراسة 36 مريضا تم تشخيص إصابتهم بـ GIST بين يناير 1997م وديسمبر 2015م بأثر رجعي في مستشفيين من الدرجة الثالثة. تم تنفيذ IHC مستقبلا عندما لم يتم القيام به في البداية.

النتائج: كان متوسط عمر المرضى 54 عام (المدى، 81–17 سنة). في الغالب، وجدنا أن الإناث أكثر اصابه بالورم و نسبة الذكور إلى الإناث كانت 1:1.7. أكثر الأعضاء تأثراً كانت هي المعدة (63.8%) يليها الأمعاء الدقيقة (25%) ومنطقة القولون والمستقيم (8.4%)، وكان الألم البطني الأكثر شيوعا في 33.3% من المرضى يليه نزيف الجهاز الهضمي في 30.5%. لوحظ أن معظم GISTs المعدة في المراحل المبكرة في العرض: المرحلة الأولى والثانية (60.8%) ، بينما في GISTs غير المعدي كانت مرحلة الورم متقدمة: المرحلة الثالثة والرابعة (69.3%). تم العثور على خصائص IHC الإيجابيه لكل حالات ال GIST بالترتيب التنازلي حسب الانتشار وهي 88.9% لـ vimentin و83.3% لـ CD117 و77.8% لـ CD 34 و63.9% لـ Ki67 و38.9% لـ SMA و27.8% لـ desmin و19.4% لـ S100.

الخاتمة: توضح أورام انسجة الجهاز الهضمي في دراستنا ميزة مشابهة للبيانات الدولية المنشورة. ومع ذلك، توجد اختلافات طفيفة من حيث الميزات السريرية والكيمياء المناعية.

Objectives: To evaluate the clinical presentations and immunohistochemical (IHC) properties of gastrointestinal stromal tumors (GISTs) and to compare them to internationally published data.

Methods: Thirty-six patients diagnosed with GISTs between January 1997 and December 2015 were retrospectively studied in 2 tertiary hospitals. Immunohistochemical staining was carried out prospectively when it has not been completed fully at the beginning.

Results: The median age of patients was 54 years (range; 17-81 years). Predominantly, we found more females were affected. The male to female ratio was 1:1.7. The most frequently affected organs were the stomach (63.8%) followed by small bowel (25%) and colorectal region (8.4%). Abdominal pain was the most frequent presentation in 33.3% of the patients then gastrointestinal (GI) bleeding in 30.5%. Most of the gastric GISTs were at early stages at presentation: stage 1 and II (60.8%), while in non-gastric GISTs, the tumor stage was advanced: stage III and IV (69.3%). The IHC characteristic of GIST in descending order showed positivity for vimentin (88.9%), CD117 (83.3%), CD34 (77.8%), Ki67 (63.9%), SMA (38.9%), desmin (27.8%), and S100 (19.4%).

Conclusion: Gastrointestinal stromal tumors in our study demonstrates a major similar feature as the published international data. However, minor differences do exist in terms of clinical features and immunohistochemistry.

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The most common mesenchymal tumor of the gastrointestinal tract is gastrointestinal stromal tumors (GIST), with an overall incidence of 10 to 20 per million people. The recognition of the interstitial cells of Cajal as the likely precursor cells, identification of mutations in c-KIT and platelet-derived growth factor receptor-a (PDGRF-a) were key to understanding GIST biology.[1-3] The symptoms and signs of the tumor are not disease-specific. Therefore, about half of the patients with GISTs have metastases at the time of diagnosis. The clinical signs and symptoms are usually related to the presence of a mass or GI bleeding.[4] We assessed the clinicopathological features of a series of cases of GIST encountered in two-major hospitals in our geographical area (Eastern Province of Saudi Arabia) and compared our findings to the published data.

Methods. This was a retrospective study conducted to assess the clinicopathological features of GISTs. A total of 36 patients diagnosed with GISTs between January 1997 and December 2015 were included. The majority of specimens were surgically resected tumors (31/36 cases). The remaining specimens were tumor biopsies (5/36 cases) obtained by endoscopy. Hematoxylin and eosin (H and E) stained tumor slides were reviewed and classified utilizing the National Institutes of Health (NIH) criteria.[4] The clinical, follow up data and immunohistopathological features were obtained from the patients' medical records. This study received ethics committee approval (consent was waived due to the nature of the study) and the tenets of the Declaration of Helsinki was followed.

Samples from each specimen were formalin-fixed and then paraffin-embedded and sectioned at a thickness of 4 microns. Sections were then deparaffinized in xylene, hydrated in descending grades of alcohol and stained with H and E. Then, they were immunohistochemically stained for CD117 (c-kit), CD34, SMA (smooth muscle actin), desmin, S100 protein, vimentin and Ki-67. The IHC staining was performed in a Ventana Benchmark automated immunostainer as per the manufacturer's instructions (Ventana Medical Systems Inc., Strasbourg) using the labeled streptavidin-biotin (LSAB) method with 3,3'-diaminobenzidine (DAB) as the chromogen.

Tumors were histologically classified as very low risk, low risk, and intermediate or high-risk based on NIH Consensus Guidelines for Grading of GIST.[4-6]

Statistical analysis. Data were analyzed using the SPSS, version 16.0, statistical analysis program (SPSS, Inc., Chicago, IL). Descriptive statistics, namely, mean (± SD), were used for all continuous variables depending on their normal distribution. For categorical variables, frequency and percentages were reported. Comparisons between 2 variables were done by Student's t-test for the independent parametric variables and the chi-square test for the dichotomous variables. For all tests, significance was defined as $p<0.05$.

Results. The patients' demography data showed of the 36 patients with GISTs, the majority were women (63.8%) with overall median age of 54 years (**Table 1**).

The most common clinical presentation was abdominal pain (33.3%), followed by gastrointestinal (GI) bleeding (30.5%). The most common sites of primary GIST were gastric in origin in 23 patients (63.8%) while extragastric GIST found in 13 patients (36.2%) with frequency in descending order from the small intestine (25%) then colorectal area in 3 patients (8.4%) and the esophagus in one patient (2.8%) (**Table 1**).

The overall tumor size was 7.78 cm, the majority of patients presented with large tumor size: 5-10 cm in 35.1% of the patients (**Table 2**). Microscopic mitoses rate in high-power fields (HPFs) were observed to be predominantly low with 5/50 in 28 cases (77.8%) then 6-10/50 HPFs in 4 cases ((11.1%) and more than 10 HPFs in only 4 cases (11.1%) (**Table 2**).

Table 1 - Clinical characteristic of 36 patients diagnosed with gastrointestinal stromal tumors (GISTs).

Variables	n (%)
Gender	
Male	13 (36.2)
Female	23 (63.8)
Male to female ratio	1:1.7
Age	
Mean (±SD)	53.89 (15.05)
Median (range)	54.0 (17-81)
Nationality	
Saudi	33 (91.6)
Non-Saudi	3 (8.4)
Presenting symptoms	
Abdominal pain	12 (33.3)
Abdominal mass	9 (25.0)
Gastrointestinal bleeding (GI)	11 (30.5)
Upper GI bleed	7 (19.4)
Lower GI bleed	4 (11.1)
Weight loss	2 (5.6)
Intestinal obstruction	2 (5.6)
Tumor site	
Gastroesophageal junction	1 (2.8)
Stomach	23 (63.8)
Small intestine	9 (25.0)
Colon	2 (5.6)
Rectum	1 (2.8)

In accordance with the proposed approach for defining the risk of aggressive behavior in GISTs, most of our patients had intermediate (47.2%) or high risk (38.9%) (**Table 2**).[5,6]

Immunohistochemistry (IHC) staining (**Table 3**) showed the most commonly positive receptor was vimentin in 88.9% of cases, followed by c-kit (CD117) in 83.3%, CD34 in 77.8%, Ki67 in 63.9% and SMA in 38.9% of cases. Desmin was negative in 72.2% and S100 and 80.6% of cases.

As per the American Joint Committee on Cancer (AJCC) Staging System for GIST (7th edition, 2010), the staging of the tumors was sub-grouped based on their anatomic locations (gastric and non-gastric GISTs) and mitotic rates. All tumors with lymph nodes or other metastases were considered AJCC stage IV.[5] Most of the gastric GISTs were in early stages of presentation with 60.8% of the patients in stage I and II, while in non-gastric GISTs, the tumor stages were advanced stage III and IV in 69.3% of patients (**Table 3**).

Due to the higher incidence of advanced stages in our cases, with only 13.9% of our patients classified as low-risk and the majority either intermediate or high-risk, surgery was achievable in 86.2% of the patients. However, in only 44.5% of our patients (n=16) surgery alone was curative, while 41.6% of patients (n=15) were treated surgically followed by targeted therapy with Imatinib (Gleevec). In 13.9% (n=5) of patients were not candidates for surgical resection due to advanced disease with metastases, out of those 4 patients (11.1%) were treated with targeted therapy alone, and one patient (2.8%) declined treatment. Curative primary surgical resection achieved in 15 patients with negative margin ranging from 2 mm to 5.5 cm, while one patient required reoperation for positive margin. Metastatic liver GIST found in 5 patients with one underwent palliative resection of the primary gastric lesion but none of our case underwent liver resection.

Discussion. Gastrointestinal stromal tumors can arise at any age; however, more than 80% are reported in individuals older than 50 years, with the average age of 63 years. The reason for the younger age group in our study (median: 54 years) compared to the reported data was the fact that we have a younger population in general. The most frequent tumor location was the stomach in all reported studies. In a recent systematic review including all published population-based studies on GISTs, the most common primary tumor location was the stomach in 55.6% of 9747 reported GISTs, followed by, in descending frequency, the small bowel in 31.8%, the colorectal area in 6%, and the esophagus in 0.7% of cases.[7] Other locations were reported in 5.5% of cases. Similarly, in our study, the frequency of the anatomical location of GISTs in descending order was the stomach (63.8%), small bowel (25%), colon (5.6%), esophagus (2.8%) and rectum (2.8%) (**Table 1**).

The reported data regarding specific symptoms in various studies were dependent on the categories and definitions used. Among the most common symptoms

Table 2 - Pathological characteristics of gastrointestinal stromal tumors

Pathological characteristics	n (%)
Tumor sizes (cm)	
<2	3 (8.3)
2-5	11 (30.6)
>5-10	13 (36.1)
>10	9 (25.0)
Mean overall tumor size (cm)	7.78
Microscopic mitoses/HPFs	
5/50	28 (77.8)
6-10/50	4 (11.1)
>10/50	4 (11.1)
Risk stratification‡	
Very low risk	0
Low risk	5 (13.9)
Intermediate risk	17 (47.2)
High risk	14 (38.9)

HPF - high-power fields, ‡as per the proposed approach for defining risk of aggressive behavior in gastrointestinal stromal tumors[5]

Table 3 - Gastrointestinal stromal tumors immunohistochemical features and tumor stage.

Characteristics	Positive (n=36)		*P*-value
Immunohistochemical features			
Vimentin	32 (88.9)		
CD117	30 (83.3)		
CD34	28 (77.8)		
Ki67	23 (63.9)		
SMA	14 (38.9)		
Desmin	10 (27.8)		
S100	7 (19.4)		
	Gastric GIST (n=23)	**Non-gastric GIST (n=13)**	
Tumor stages			
Stage IA	5 (21.6)	1 (7.7)	0.37
Stage IB	8 (34.8)	0	0.05*
Stage II	1 (4.4)	3 (23.0)	0.054
Stage IIIA	2 (8.8)	0	0.91*
Stage IIIB	1 (4.4)	5 (38.5)	0.05*
Stage IV	6 (26.0)	4 (30.8)	0.77

Values are presented as number and percentage (%).
*Fisher Exact test. GIST - gastrointestinal stromal tumors

Table 4 - Published studies in gastrointestinal stromal tumors immunohistochemistry.

Authors	Country (year)	Number of patients	CD117 (c-KIT) n (%)	CD34	Ki67	SMA	Desmin	S-100	Vimentin
Tryggvason et al[11]	Iceland (2005)	57	57 (100)	44 (80.0)	NA	3 (5.5)	3 (5.5)	0 (0)	NA
Kim et al[12]	Korea (2005)	747	699 (93.6)	597 (80.2)	NA	209 (28.1)	NA	153 (20.0)	NA
Chan et al[13]	Hong Kong (2006)	47	44 (93.6)	38 (80.1)	NA	13 (27.7)	NA	9 (19.0)	NA
Steigen & Eide[14]	Norway (2009)	102	99 (97.1)	85 (85.8)	NA	NA	NA	NA	NA
Alghamdi et al*	Saudi Arabia (2017)	36	30 (83.3)	28 (77.8)	23 (63.9)	14 (38.9)	10 (27.8)	7 (19.4)	32 (88.9)

Values are presented by number and percentage (%). *present study, NA - not available

reported, abdominal pain, gastrointestinal bleeding and intestinal obstruction were the most common; however, several other nonspecific complaints were also observed. We observed similar findings in clinical presentations with abdominal pain (33.3%) and GI bleeding (30.5%) being the most common mode of presentation. However, abdominal mass was the reason for presentation in 25% of the cases. Lower GI bleeding presented in 4 patients due to colorectal GIST in three patients and small bowel GIST in one patient (**Table 1**).

According to the NCCN taskforce guidelines for GISTs, tumor biopsy for suspected GISTs should only be considered in the case of suspicion of alternative diagnoses or when neoadjuvant is contemplated. However, if the lesion is accessible through an endoscopic approach, then this mode of biopsy is preferred to the percutaneous approach.[8] By contrast, if the lesion is small and surgically resectable, or if prior biopsy carries a serious risk for complication, then surgical resection without preceding biopsy is acceptable.

In general, gastric GISTs have more favorable prognosis at similar stages compared to that of other anatomical locations. Gastric GISTs equal to or less than five cm in size with five mitoses per 50 HPFs or less have a reported low risk for metastasis, whereas those originating from the small bowel (irrespective of size or mitoses) or gastric GISTs with more than five cm diameter more than 5 mitoses per 50 HPFs have moderate to high risk for metastasis.

Data from studies reporting NIH risk groups showed that very low-risk GIST groups were the least frequent (15%), while low-, intermediate- and high-risk groups accounted for 30%, 22%, and 33% of the cases.[5,6] Similarly, in our study, 5 cases (13.9%) were in the low-risk group, 17 cases (47.2%) were in the intermediate-risk group and 14 cases (38.9%) were in the high-risk group. There were no very low-risk cases in our study (**Table 2**).

Most reported GISTs were local disease when first detected, and overt metastases were found in approximately 10%-20% of cases.[6] Most reported metastatic GISTs were found in the abdominal cavity and the liver, while other rare sites such as bones have occurred. In our study, 10 cases (28%) were stage IV at the time of their presentation. This represented a higher incidence than the published data and reflected the need for a high index of suspicion and awareness among physicians and patients in our area (**Table 3**).

Hirota[9] demonstrated mutations in the c-Kit proto-oncogene in GISTs associated with the expression of Kit protein (also known as CD117). Currently, the diagnosis of GISTs is usually established by demonstrating positive staining for both CD 117 and CD34. However, equally important is the demonstration of negative results for S-100, desmin, CK and LCA to rule out other differential diagnoses.[10]

A comparison of various studies to the present one is depicted in **Table 4**. Our study showed the prevalence of positive and negative receptors including c-kit and CD34 and other IHC expression compared to other populations.[11-14]

A cure is possible in patients with surgically margin-negative resection in resectable GISTs. Therefore, it is important to establish risk-stratification schemes to aid in estimating recurrence-free survival and to reduce the complications of unnecessary overtreatment with adjuvant systemic chemotherapy. Hence, low-risk patients have a favorable outcome by complete surgical resection with no need for adjuvant chemotherapy. Targeted therapy with tyrosine kinase inhibitors has revolutionized the outcome of completely resected tumors, resulting in prolonged responses in patients who had advanced disease.[15-17] Due to the higher incidence of advanced stages in our cases, with only 13.9% of patients classified as low risk and the majority as either intermediate or high risk, surgery was achievable in 31 (86.1%) of the patients. However, in only 16 (44.5%) of our patients, surgery alone was curative, while 15 (41.6%) patients were treated surgically followed by adjuvant chemotherapy. Five (13.9%) patients

were not candidates for surgical resection because of advanced disease. In those patients were the surgical intervention is not possible, the targeted therapy poses a survival-benefit therapeutic option were offered in four of our patients.[17] All our cases did not pose any diagnostic dilemma hence DOG1 receptor detection was not done as the importance of this receptor in c-KIT negative specimens. Therefore, it was considered cost-ineffective.[18-20] The only report in the literature regarding GISTs emanating from our region did not report the prevalence of all receptors, giving the present study a unique status as a reference for comparison.[21]

In conclusion, GISTs are a rare type of tumor in the Eastern Province of Saudi Arabia. Unfortunately, no accurate epidemiological data are available. Although there are no specific trends, nevertheless, GISTs are more commonly seen in middle-aged women and in younger populations compared to other countries. Furthermore, we observed more advanced tumor stage in our patients population. Finally, GIST characteristics in our community demonstrate similarities to the reported international data with respect to clinical and pathological characteristics, however, our study shows some unique findings that can serve as a reference for clinicians in our area.

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