Gastrointestinal Stromal Tumors in Northeastern Iran: 46 Cases During 2003-2012

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ABSTRACT

BACKGROUND

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. They are usually C-kit positive and seen slightly more common in men. These tumors are seen in the GI tract from the esophagus to the anus with occasional invasion or metastasis.

METHODS

In this retrospective study, we evaluated the prevalence of c-kit positive stromal tumors of the GI tract based on age, site of involvement, size of tumor, local invasion, and Immunohistochemical markers. The study was conducted in Mashhad University of Medical Sciences in Iran during 2003-2012.

RESULTS

Of the total 46 patients, 18 (39.1%) were men and 28(60.9%) were women with a mean age of 58.07 years (range: 18-93). Common sites of tumor were stomach, small intestine, esophagus and rectum, respectively. The number of mitoses per 50 HPF varied between zero and 160 mitoses. Overall, 23 cases had 5 mitoses 50/HPF (50%) and 23 tumors expressed <5 mitoses/50 HPF (50%). Local invasion and metastasis were observed in seven cases with extension to liver, pancreas, pregastric tissue, omentum, mesentery and appendix. Positive reaction for CD34, S100, actin and desmin was seen in 47.8%, 13%, 21.7%, and 4.3% of the patients, respectively.

CONCLUSION

Most patients were women. The prevalence of tumors in the esophagus was higher than the rectum. Invasion and metastasis did not correlate with mitotic rate, site and size of tumor. We suggest evaluation of genetic, racial and geographical or other unknown risk factors.

KEYWORDS
Gastrointestinal stromal tumors; GIST; Iran

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors of the gastrointestinal (GI) system and accounts for less than 1% of the tumors of the GI tract. GIST refers to a group of spindle or epithelioid cells or pleomorphic mesenchymal tumors of the GI system which express the protein Kit.[1] They originate from

neither the nervous nor the musculoskeletal system. Instead, they stem from interstitial cells of Cajal which are c-kit positive.[2,3]

The incidence rate is 40 per million with an annual incidence of 11-14 x 10^6. Malignant types of GIST occur with an incidence rate of 4 per million and comprise 20–30% of all soft tissue sarcomas. Overall, 0.1–3% of all malignant tumors are GIST. Yet, the precise incidence of benign types of GIST is difficult to determine since it requires surgical and pathological reports.[2,4,5] Typically, it develops in individuals above 40 years of age with an average age of 55–65 years. There is no significant difference in terms of frequency between men and women, although it is seen slightly more often in the former.[6] However, it is rare in children.[2]

Gastrointestinal stromal tumors may be found anywhere from the lower half of the esophagus to the anorectal area, but in 59–60% of cases they occur in the stomach.[2] Epithelioid forms of the tumor are typically found in the antrum, while the more malignant types occur in the body. Nevertheless, the prognosis of GIST found in the stomach is better than that of the small intestine, which constitutes the site for 30% of all GISTs, occurring especially in the jejunum. Duodenal GIST occurs more frequently in the second portion of the duodenum and can be mistaken for pancreatic tumors. The esophagus, mesentery, omentum, colon, and rectum account for only 10% of the GI sites where the tumor may be found. The disease may also has an autosomal dominant pattern of inheritance and it is found more frequently in patients with neurofibromatosis.[2,5]

More than 30% of GISTs have malignant features such as metastasis and infiltration.[5] Morphology alone may not be able to differentiate between indolent types of the tumor and the aggressive forms.[7]

Most GIST cells express both CD34 and CD117(c-kit receptor), with the later detected on 95% of tumor cells.[1,2,7] In the less than 10% of cases negative for the c-kit mutation, another tyrosine kinase receptor (i.e., platelet-derived growth factor) mutation is involved, which suggests the role of a different molecular mechanism.[8] The c-kit mutation is considered a marker which predicts response to treatment with imatinib.[4,7,9]

Although the tumor may be asymptomatic, it commonly presents with GI bleeding, which may be occult or severe, and may rarely cause pain, obstruction, perforation or a palpable mass.[2,7,10] Metastasis to the liver and soft tissue of the abdomen is common, whereas metastatic involvement of bone, peripheral soft tissues, lungs and the lymphatic system is a rare finding. However, the possibility of metastatic disease necessitates long-term follow-up of patients with GIST. Malignant types of the disease also involve the spleen, the pancreas and the transverse colon.[2] Resistance of tumor to chemoradiotherapy also emphasizes the importance of total surgical resection of the tumor without any involved surgical margins.

DOC-I and CD34, smooth muscle actin, and the S100 protein are found in 79-80%, 20-30%, and 10% of the tumors of the small intestine, respectively, despite the fact that very few tumors are desmin positive.[4,12,13]

Prognostic factors include size, location, mitotic rate, and perforation. Extra-gastric sites and perforation suggest a poor prognosis. Tumor size greater than 5 cm and those with more than 5 mitoses are at greater risk for relapse. At a given size and mitotic rate, GISTs found in the stomach have a better prognosis than those in the small intestine.[7]

Risk of metastasis is less than 5% when tumor size is less than 10 cm and contains <5 mitoses. However, the risk increases by 10-15%, if tumor size is more than 10 cm, but with few mitoses, or remains between 2 and 5 cm, but exceeds 5 mitoses/50 HPF. Intestinal GIST that is >5 cm has a moderate risk for metastasis independent of the mitotic rate. The risk is increased when the number of mitoses increases to more than five.[7]

We aimed to assess the prevalence of c-kit positive stromal tumors of the GI tract based on age, site of involvement, size of the tumor, local invasion, and immunohistochemical markers in the Mashhad, northeast Iran.

MATERIALS AND METHODS

This retrospective cross-sectional study was

done on patients with GIST in Mashhad, at the pathology and archives departments of Ghaem Hospital and Razavi Hospital, on samples sent to the referral laboratory of Moayyed during 2003- 2012.

All patients with an established diagnosis of GIST based on positive c-kit results were included. Of these patients, twenty-seven were diagnosed via surgery and nineteen had needle biopsy for diagnosis.

The paraffin blocks of the tumors from these patients were evaluated in pathology laboratories at university hospitals and the referral laboratory of Moayyed with the supervision of a GI pathologist.

15 out of 61 patients with GIST were excluded due to lack of sufficient data, and 46 patients were included in this study. The slides (prepared by hematoxylin and eosin staining) from each patient were evaluated according to the anatomical site of the lesion, and the macroscopic features of the tumor such as size, local invasion, necrosis and bleeding. All paraffin blocks were examined for the number of mitoses in areas with maximum cellular density in 50 sequential microscopic high-power fields (HPF). Moreover, immunohistochemical features including CD117, CD34, S100, and desmin were determined. Data were analyzed using SPSS software, version 11.

RESULTS

Of all 46 patients with GIST tumors, 18 (39.1%) were men and 28 (60.9%) were women. The mean SD age of the patients was 58.07 16.3 years (range: 18-93 years).

The tumors were found in the stomach, small intestine, esophagus, and rectum in 27 (58.7%), 10 (21.7%), 5 (10.9%), and 4 (8.7%) patients, respectively. The mean ± SD diameter of tumors was 6.24 4.66 cm, ranging from 2 to 25 cm. The mean size of the tumors based on location was 7.17 cm (range: 2-25 cm) in the stomach, 6.8 cm (range: 4-12 cm) in the small intestine, 2.4 cm (range: 2-3 cm) in the esophagus, and 4.62 cm (range: 3-5.5 cm) in the rectum.

Necrosis and hemorrhage occurred in 14 (30.4%) patients. The number of mitoses per 50 HPF varied between zero and 160 mitoses. Overall, 23 cases had 5 mitoses (50%)/50 HPF and 23 tumors (50%) expressed <5 mitoses/50 HPF.

Local invasion and metastasis were observed in 7 of the tumors with extension to the liver (two cases), pancreas, pregastric tissues, omentum, mesentery, and appendix.

According to the tumor markers, CD117 was positive in all 46 (100%) tumors, CD34 in 22 (47.8%), S100 in 6 (13%), actin in 10 (21.7%), and desmin in 2 (4.3%). Based on S100 protein marker, 13% of the GIST tumors in our study showed neural differentiation, while based on desmin marker, only 4.3% tended to show signs of differentiation towards smooth muscle cells (table 1).

DISCUSSION

GIST is one of the most common types of mesenchymal cell tumors of the GI system. The majority of such tumors express CD117, which plays a significant role in response to therapy and prognosis. Most frequent sites of GI involvement are stomach followed by small intestine. Tumor location and size as well as the mitotic rate are of significant importance in determining the likelihood of metastasis and the prognosis of the disease.

In our study, most patients were women and the average age was above forty. The results of two other studies were similar to ours with respect to the patients' age, but more patients were men in their study.[2,14]

Based on our findings the two most common sites of tumor involvement were stomach and small intestine, consistent with previous studies.[1,2,5] However, rectum was the third location of involvement in these studies followed by esophagus, the latter was the most common site of tumor involvement in our study. This could be attributed to risk factors such as genetics, race and geographical location or other unknown risk factors, which suggest the need for more extensive studies in Iran.

According to our data, tumor size varied between 6 to 24 cm. Miettinen reported the tumor size from small nodule to 40 cm with a mean size of 6 cm[2,4] while in Bucber`s study the smallest and largest tu-

Table 1: **Evaluation of tumors with local invasion or metastasis**

Primary location	Local invasion	Metastasis	Sex	Age(year)	Size(cm)	CD34	S100	Desmin	Actin
Small intestine	_	Liver	M	48	8	+	_	_	_
Small intestine	_	Liver	F	26	4	+	_	_	_
Stomach (body)	pancreas	_	F	48	3	+	_	_	_
Stomach	Around of stomach tissues	–	M	51	3	+	_	_	_
Stomach	omentum	_	M	66	2	_	_	_	_
Stomach	mesentrium	_	M	52	10	+	_	_	_
Small Intestine (jejunum)	_	Appendix	F	58	10	+	_	_	_

mor size was 1 and 20 cm, respectively.[14]

Almost half of the tumors found in the study showed >5 mitoses/50 HPF. Of these, seven had invasion or metastasis. Metastasis was not observed in other patients, even though these patients required longer follow-up period. The invasion and metastasis were lower than the previous reports where approximately 30% of the GISTs were reported as metastatic.[2,5]

The extent of necrosis was not a good differentiating factor between benign and malignant tumors, a fact which had been confirmed by previous studies. In immunohistochemical studies, the frequency of S100 protein and desmin were detected in 13% and 4.3%, respectively, was similar to other studies.[2,5] However, the frequency of CD34 marker had a lower prevalence than the 70-80% rate reported previously.

These findings showed that tumor size poorly correlated with its behavior so that a small-sized tumor may be associated with local invasion or even metastasis. In addition, tumors originating in the stomach or small intestine were more likely to be malignant and therefore, a longer follow-up period is recommended for such tumors. Conversely, a higher mitotic rate (>5 per 50 HPF) was not always associated with a malignant nature or liver metastasis, yet follow-up of such patients is also recommended. Finally, due to the complex nature of such tumors, further epidemiological studies with larger sample size are needed.[15]

In our study, most patients were women. The stomach was the most common anatomical site for GIST. In northeast Iran, the prevalence of esophageal GIST was higher than GIST found in the rectum. Lower prevalence of CD34 marker was also detected. Tumors with a high mitosis rate and increased size are not necessarily associated with metastasis, suggesting the need for further studies in order to identify factors associated with the extension of GIST. Therefore, genetic, racial and geographic or unknown risk factors should be evaluated in future studies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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