Case Report

Gastrointestinal stromal tumors — a clinicopathological study

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Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumors of the GIT. These develop within the wall of the GIT and occur throughout the GIT from oesophagus to rectum. The KIT mutation results in activation of the tyrosine kinase receptors allowing its detection by immunohistochemistry and helps in confirming the histologic diagnosis of GIST. GISTs are categorized into distinct risk categories and prognostic groups based on tumor size, number of mitoses per 50 high power fields and the anatomic location of the tumor. The present study is of a retrospective, case series nature. Data was retrieved from Pathology archives and Department of Cancer Registry, Malabar Cancer Centre. There were a total of 11 cases in the present study. In our study, almost 20% GISTs occurred below the age of 50 years. Jejunum and ileum were the commonest sites. Majority of tumors were located in submucosal or intramural locations. All were of spindle cell morphology and CD117 was the most useful antibody, being strong diffuse positive in 70%.

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Gastrointestinal stromal tumors (GISTs) are a heterogeneous group of tumours. These are the most common primary mesenchymal tumors of the gastrointestinal tract. These tumours develop within the wall of the gastrointestinal tract. GISTs are known to occur throughout the GIT from oesophagus to rectum[1,2]. The most common site for a GIST is stomach, which is followed by the small intestine (excluding duodenum)[3,4]. About 85-90% of the GISTs harbor a mutation of KIT (CD117). cKIT is a tyrosine kinase receptor which is normally expressed by the Interstitial cells of Cajal located in the wall of the gut. These cells coordinate the autonomic nervous system of the gut and the smooth muscle cells to regulate motility and peristalsis. The remaining 5 to 15% GISTs contain PDGFRA mutations[5,6].

The KIT mutation results in the activation of the Tyrosine kinase receptors. This can be detected by IHC and helps in confirming the histologic diagnosis of GIST[4,5,7,8]. GIST is mostly seen in the elderly, and the median age ranges between 58 and 66 years[4,5,7,9,10]. No definite gender predilection has been reported. Histologically, most of the GISTs show a spindle cell appearance (75 to 80%).Epithelioid cell or mixed morphology is seen in a minority of cases[7,11,4]. Small intestinal GISTs are twice as likely to behave as clinically malignant tumors compared to gastric GISTs. Most GISTs of the colorectumare very aggressive and advanced tumors with a poor prognosis[12,13].

GISTs can also occur outside the gastrointestinal tract, in the omentum, mesentery and retroperitoneum. Then these lesions need to be distinguished from other mesenchymal tumors seen in these sites, especially from benign and malignant smooth muscle tumors.

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GISTs are categorized into distinct risk categories and prognostic groups based ontumor size, number of mitoses per 50 high power fields (HPFS) and the anatomic location of the tumor[4,11]. Based on these factors, GISTs belong to a Very low risk, Low risk, Intermediate risk and High risk categories.

Surgical excision is the mainstay of therapy for GISTs. Targeted therapy with Imatinibmesylate show spectacular results especially in patients with unresectable, recurrent and even metastatic tumors.Imatinib binds to KIT and inhibits the intracellular signalling pathways.

Materials and Methods

The present study is of a retrospective, case series nature. The variables taken into consideration are age, sex, anatomic site, tumor size, mitotic count, histomorphology, immunohistochemical expression, risk category and follow-up status. The entire course of this study was carried out in the Department of Oncopathology, Malabar Cancer Centre, Thalassery.

Data was retrieved from Pathology archives and Department of Cancer Registry, Malabar Cancer Centre. Consecutive patients diagnosed from January 2012 to December 2016 were included in the present study. Risk stratification and categorisation into prognostic groups were based on tumor site, size of the tumor and mitotic count per 50 hpf, with a risk of progression classified into low risk, intermediate risk and high risk categories[12]. The data collected was entered in Google Forms and EpiInfo software was used for the analysis of results. Descriptive statistical tools like mean and Standard Deviation were used for continuous variables and frequency and percentages used for categorical variables.

Observations

A total of 11 cases were included in the audit. Majority of cases were diagnosed in the sixth and seventh decades and the mean age was 62 years. Over 70% of the patients were males. The average size of tumors was 6.5 cm and sizes ranged from 2.75 to 9.5 cms. Symptoms varied from vague abdominal pain, abdominal mass, heart burn, bleeding per rectum, hematemesis and anemia. Grossly,

majority of the tumors were submucosal or intramural, nodular bulging masses, many with central ulceration. Some were polypoid and protruded into the lumen. Jejunum and ileum was the commonest site (50%), while almost 30% were located in the stomach. On histological examination, 80% cases showed spindle cell morphology. Cases with epithelioid morphology were not seen. Immunohistochemically, CD117 was the most useful antibody, being strong diffuse positive in 70%. In 10% cases in our series were diagnosed as extra gastrointestinal GISTs (EGISTs). Using the elaborate algorithm, developed by Miettinen and Lasota[11], all the gastric GISTs in our study were assigned low risk (Group 3a). Based on Miettinen and Lasota's proposal 40% small intestinal GISTs in our study were assigned group 2 (low risk), 20% were assigned group 3a (moderate risk) and the remaining 40% were assigned high risk for disease progression in jejunal and ileal GISTs. All patients in our series underwent resection. All the patients who underwent treatment by surgery and Imatinib have not reported any recurrences or metastatic disease

Discussion

The mean age in our series is comparable to that reported in Western and even Asian literature where mean ages of gastric and small intestinal GISTs have varied from 58 to 70 years[7,9,10,13]. GISTs in all locations occur in the elderly, l0% GISTs occur in patients below 40 years of age[11]. In our study, almost 20% GISTs occurred below the age of 50 years. Studies have shown no gender predilection, although some studies demonstrate a mild male predominance ie, 52 to 55% in GISTs in all locations[10,12]. In our study, over 70% of the patients were males. The average size of tumors in our study was 6.5 cm and sizes ranged from 2.75 to 9.5 cms. Various studies have reported sizes ranging from a few millimeters to greater than 20 cms for small intestinal, and a few millimeters to greater than 40 cms for gastric GISTs[11]. In a series of gastric GISTs, the mean size for gastric GISTs was 6 cms[11]. In two separate studies, mean tumour size was 4.6 cms and 7.02 cms respectively[9,10]. Symptoms in our cases were variable; the commonest were vague abdominal pain, abdominal mass, heart burn, bleeding per rectum, hematemesis, anemia etc. Grossly, majority of the tumors were submucosal or intramural, nodular bulging masses, many with central ulceration. Some were polypoid and protruded into the gastric lumen. Similar, gross appearances have been described by other studies[11].

In our series, small intestine (jejunum and ileum) was the commonest site, (50%), while almost 30% were located in the stomach. According to various international studies, 59 to 61% GISTs occur in stomach[3,9,11], about 30% in the jejunum and ileum, and 4 to 5% occur in the duodenum. Colorectal GISTs comprise 4 to 5%[10,11]. Compared to the international data, location in stomach was slightly less common in our series while location in small intestine was slightly higher.

On histological examination, almost 80% cases showed spindle cell morphology while cases with epithelioid morphology were not seen. Various international studies have reported the epithelioid type to comprise between 20-25%, with mixed tumors comprising the remaining 5 to 10% cases[4,5,11].

Immunohistochemically, CD117 was the most useful antibody, being strong diffuse positive in 70%. We have limited experience with DOG1 (Discovered on GIST-1) since we acquired this antibody only in 2016. DOG1 IHC done on paraffin blocks retrieved demonstrated diffuse positivity in 100% of the cases in which it was done. We intend to use DOG1 in all future cases as this antibody has proved to be a very sensitive marker for GISTs. Published Western literature shows that CD117 positivity is seen in 95% (gastric) to 98% (small intestinal) GISTs. It has been seen that most spindle cell GISTs shown positivity for CD34[7,11]. A study from China showed CD117 positivity in 94.5%[10].

Around 10% cases in our series were diagnosed as extra gastrointestinal GISTs (EGISTs). While EGISTs definitely represent bona fide and true GISTs, and demonstrate CD117 immunohistochemical expression as well as GIST-specific KIT mutations, their incidence in most series is extremely low, around 1%[11]. The current thinking is that most of the cases of so called EGISTs are actually detachments or metastases from GISTs of primary GIT origin[11]. Accurate surgical details or radiological films are not available in many cases. Therefore, many of the so called EGISTs could actually represent involvement of retroperitoneum, omentum, mesentery etc by gastrointestinal stromal tumors. Studies have looked for parameters that can clearly identify bona fide EGISTs. Matrix metalloproteinases (MMPs), which are molecules that are implicated in metastasis by various malignant tumors, have been investigated for their role in contributing to the ability of EGISTs to metastasize. However, we have not carried out this in the present study.

The evaluation of prognosis is essential in GIST. Every GIST carries a risk and potential for malignant behavior and there is increasing reluctance to label any GIST as benign. However, this risk varies from very low to very high[7,11]. Earlier studies showed that about 50% primary localized GISTs relapsed within the first five years (local recurrence within the peritoneal cavity or liver metastases) while a much greater percentage of GISTs relapsed within ten years, and that if relapse occurred, prognosis was almost invariably poor[15,16]. It is not practically possible to divide GISTs into benign or malignant categories based on morphology alone and the emphasis shifted to determining criteria which could assess the risk of GISTs to behave in a malignant fashion. Several schemes were developed to define criteria which can stratify the risk of malignant behavior and by which GISTs can be assigned to definite risk categories (low, intermediate, high) or groups[11,15,17]. Tumor size and number of mitoses per 50/HPFs emerged as the major criteria. It also became clear that location was extremely important, with non-gastric GISTs harboring a much higher risk for malignant behavior compared to gastric GISTs of comparable size and mitotic activity[9,11]. Other histologic factors including cellularity, coagulative necrosis, mucosal invasion etc have been suggested[9,11]. Currently, the risk stratification is based on the consensus proposal[17] and the risk prediction algorithm[11]. In a recent study from Turkey which looked at 249 cases, 47% cases belonged to the high risk category[18]. Other recent studies from Asia have also risk stratified GISTs based on the above criteria.

Using the elaborate algorithm, developed by Miettinen and Lasota[11], all the gastric GISTs in our study were assigned low risk (Group 3a). Based on Miettinen and Lasota's proposal[11], 40% small intestinal GISTs in our study were assigned group 2 (low risk), 20% were assigned group 3a (moderate risk) and the remaining 40% were assigned high risk for disease progression in jejunal and ileal GISTs.

The primary treatment of GISTs is surgical excision with adequate negative tumor margins. All patients in our series underwent resection. All the patients who underwent treatment by surgery and Imatinib have not reported any recurrences or metastatic disease. Although surgical excision is the mainstay of therapy for GISTs, targeted therapy with Imatinib mesylate (Gleevec) which binds to KIT and inhibits intracellular signaling, has shown spectacular results especially in patients with unresectable, recurrent and even metastatic tumors. Adjuvant treatment is recommended if the chances of recurrence are greater ie, large tumor size, location other than gastric, high mitotic rate etc. Treatment is recommended

for at least a year after surgery, while for tumors which are highly likely to recur, treatment is recommended for up to three years after surgery. Newer drugs, such as Sunitinib are also coming up and may be effective in patients who become resistant to Gleevec. The role of surgery in patients with recurrent or metastatic GISTs who were responding to Imatinib is currently a subject for additional research.

To summarize, our series of 11 cases show that the demographic features and clinical presentation are similar to that of other similar studies. The prevalence of Jejunal and Ileal GISTs are more common in the present series, in contrast to a Gastric location being the most common site in several other studies. The histomorphology, Immunohistochemical features and responses to treatment were similar to what has been described by various similar series.

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