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Original Article

Gastrointestinal stromal tumor - a clinicopathological study and its theraputic outcome in a tertiary care hospital

Raiesh Kumar N*

Assistant professor, Department of pathology, Annapoorna medical college and hospitals, NH47, Sankari road, Seeragapadi, Salem. India.

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ABSTRACT

Objectives: The aim of the study is to determine the clinico-pathological features of primary gastrointestinal stromal tumors [GIST] and its therapeutic outcome in a Tertiary care Hospital, Tamil Nadu, India. Materials and methods: 16 patients with primary Gastrointestinal lymphoma[PGIL] diagnosed over a 6 year period from 2003 to 2008 were retrospectively and prospectively studied clinically and histopathologically they were classified using the Fletcher classification and a follow-up was till 2010 made for minimum three years from the date of diagnosis. Result: 16 patients (1.63%) were GIST arising out of 980 primary gastrointestinal malignancies, with a female to male ratio of 1.5: 1. All the patient were non vegetarians and majority of males were alcoholics and smokers. The mean age of the male patients was 46 years with age varying from 34 - 60 years, while for females, the mean age was 48 years, ranging from 40-70 years. Abdomen pain was the most common presenting symptom (70%), and the most common primary site was stomach (72.2%), followed by small bowl (16%), 95% of cases were CD 117 Positive. Surgery was considered in 90% of patients, liver was the main site of metastasis and the 3 years and the 4 years survival rate was 91% and 78% the use of Imatinib improved the rate of survival and post operative recurrence and the metastasis was decreased. Conclusion: Primary gastrointestinal stromal tumors constitute about 1.63 % of all gastricintestinal malignancies Abdomen pain was the common presenting symptom and stomach being the commonly involved site with female predominance. 95% of cases were CD 117 Positive The majority of the cases treated by surgery and the use of adjuvant imatinib had good prognosis with a 3 year and 5 years 91% and 78 % respectively.

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express CD34 and the KIT on their surface [4].

1. Introduction

GISTs (Gastro Intestinal Stromal Tumors) are a subset of mesenchymal tumors and represent the most common mesenchymal neoplasms of GI (Gastrointestinal) tract. Gastrointestinal Stromal tumors are KIT-expressing and KIT (tyrosine kinase receptor - CD117)-signaling driven mesenchymal tumors. [1]. They account for <1% of all GI tumors. Recently recognized that GISTs arise from multipotential mesenchymal stem cells [2]. However, GIST is a newly recognized tumor entity but the literature on these stromal tumors has swiftly expanded. In the past, these tumors were presumed to have elements of smooth

muscle (smooth muscle origin), so they were classified as

leiomyomas, leiomyosarcomas and leiomyoblastomas [3]. GISTs

Over 90% of GISTs occur in adults over 40 years old, in a percent of GISTs arise from the colon and rectum, and 5% are located in the esophagus.

The clinical signs and symptoms are related to the presence of a mass or bleeding [6]. Abdominal pain and bleeding are the common presenting symptoms. However, most of the patients present with vague symptoms, such as nausea, vomiting, abdominal discomfort, weight loss. Presently, the defining feature of GIST is the expression of CD117, a

* Corresponding Author: Dr.N.Rajesh kumar M.D., Assistant professor. Department of pathology. Annapoorna medical college and hospitals, NH47, Sankari road, Seeragapadi, Salem. India. E-mail: rajeshprnatesan @Gmail.com.

median age of 63 years. However, GIST cases have been reported in all ages, including children. The incidence between the sexes is the same, although a study reported that there is a slight predominance of males [5]. The most common location of GIST is stomach (50-60%) and small intestine (30%-40%). Five to ten

marker of KIT activation, which is sensitive although not entirely specific. Five percent of GISTs are known to be negative for CD117 (KIT protein), [7,8] although they resemble KIT-positive GISTs by cytomorphology.

Surgical resection of the local disease is the gold standard therapy. Its goal is complete resection of the disease with avoidance of tumor rupture [9]. Complete surgical resection is connected with 48-65% five year survival [10].

Imatinib, its efficacy as a tyrosine kinase was assessed in chronic myeloid leukemia [11]. The use of Imatinib mesylate in recurrent or metastatic, resectable or not GIST in prospective trial has shown response in 50% patients, and in approximately 75-85% patients have at least stable disease.

2. Material and Methods

A total of 16 patients with GIST diagnosed at Tertiary Care Hospital in Tamil Nadu, India over a period of 6 years were studied prospectively and retrospectively(2003 through 2008) and a follow up was made for a minimum three year till 2010. Medical records of all the patients were reviewed and clinical and pathological information was recorded in a structured questionnaire form. The laboratory and radiological work- up done. The demographics, clinical presentation and associated syndromes, the lab investigations and computed tomography (CT), magnetic resonance imaging (MRI) and endoscopy findings were collected. The immunohistochemical profile was performed using a panel of CD117, CD34, vimentin, desmin and S100. The main prognostic factors, such as size, mitotic index, rupture, metastatic lymph nodes details were collected and Fletcher's classification was used (Table 1). The type of resection performed was classified as R0 if there was no residual disease or microscopic involvement of surgical resection; R1 when there was residual disease; and R2 when there was macroscopic residual disease. In the evaluation of treatment outcomes, we analyzed overall survival and disease-free survival, survival after introduction of imatinib. Treatment with imatinib was ranked neoadjuvant when performed prior to surgery.

Estimated malignancy potential (Fletcher et al.).

Malignancyrisk	Size (cms)	Mitotic (50 hmf)
Verylow	<2	<5
Low	2-5	<5
Intermediate	<5	6-10
	5-10	<5
	>5	>5
High	>10	Anyindex
	Anysize	>10

3. Results

GIST comprised 16 of 980 of primary gastrointestinal tumors. The tumor was located in the stomach in the majority (72%) of patients followed by small intestine (16%), retroperitoneum (4%) and the colorectum (8%). There was a significant correlation between tumor size and mitotic index, with larger tumors having

higher mitotic index (p < 0.001). Mitotic index per 5 mm(2) correlated with high cellularity (p < 0.001), presence of necrosis (p < 0.001) and presence of mucosal invasion (p = 0.01). Expression of CD117 was seen in 94%, CD34 in 59%, SMA in 41%, S-100 in 33%, and desmin in 4% of tumors.

Four patients were males and eight were females. The female to male ratio was 1.5:1. The mean age for males was 46.2 years ranging from 34-60 years and for females the mean age was 48 years ranging from 40-70 years. GISTs ranged in size from 2 to 25 cms

Majority of the GISTs (44%) ranged in size from 5 to 10 cm and slightly fewer (30%) were >10 cm, which categorized the latter as definitely malignant and in the high-risk group. Majority of the GISTs (50%) grossly presented as mass lesions and the next most frequent presentation (31%) was polypoid lesions. The cutsurfaces were mainly firm to soft to fleshy and dark variegated, with 60% showing hemorrhage, 31% showing additional necrosis and 19% showing cystic change. In tumors <5 cm in size, these secondary changes were uncommon.

GISTs demonstrate variable histology, including sheet-like arrangement, short fascicles, whorls, storiform, and organoid patterns. Short fascicular arrangement was the most common pattern in both benign and malignant tumors followed by pure spindle cell morphology and very few cases had a pure epitheloid cell morphology. Mixed spindle and epitheloid cell morphology was found in few cases. Nuclear palisading was found in 20% of the cases reminiscent of nerve sheath tumors.

3.1.Imatinib therapy

In all, 16 patients in this study received imatinib therapy and follow-up was possible for periods of 3–5 years. One group had 6 patients who had received imatinib therapy for a period of 6 months following surgical resection, 2 of whom were of the highrisk category, three of the intermediate-risk category, and one of the low-risk category. In two of these 16 patients, imatinib was started only after metastasis was encountered. The rest of the 4 patients, the disease was stable for periods of 3–5 years. The second group had 6 patients who received imatinib therapy for periods longer than 6 months, four of whom were of the high-risk category.

In two of the high risk group had metastasis, following which imatinib therapy was started. one patients in the group that had inoperable disease received imatinib after diagnosis. The period of stable disease after imatinib therapy was mostly 1 year and in some of 2 and 4 years.

4. Discussion

In our study 16 cases were detected out of 980 gastrointestinal neoplasms and GIST is most common mesenchymal tumors seen in the gastrointestinal tract. Although it has been suggested that many E-GIST may represent metastasis from gastrointestinal primaries, in our study the GIST may arise d e novo in extragastrointestinal sites [12,14]. A few studies have evaluated the clinicopathological features of E-GIST [14,15].

GISTs vary greatly in size, ranging from <1 cm to more than 30 cm in diameter. The present study included one case incidentally-detected GIST and all were less than $2\,\mathrm{cm}$ in diameter. The median size of GIST was $10\,\mathrm{cm}$, which is slightly larger than what is reported earlier. The larger tumor size may reflect a combination of referral bias ofreporting centers and late presentation of patients.

In the present study, 4 (25%) GIST had high cellularity. Assessment of tumor cellularity in GIST of different sites is available in only a few studies [19–20]. One of small intestine GIST showed high cellularity which is slightly lower than that reported in literature [19, 20]. Colonic GIST are commonly of high cellularity [21, 22]. All colonic GIST in this study showed moderate to high cellularity. Spindle cell GIST were the most common, comprising 60% of tumors as is reported in other studies [17, 18, 23,24]. Almost 70% of the epithelioid tumors originated in the stomach. Other studies have reported similar frequencies [25]. In our study 26% of gastric GISTs were epithelioid type; other studies [26, 27] have reported slightly higher frequencies of 27% and 32%. A great majority of small bowel GIST were of spindle cell type n=28 (77.8%). Skenoid fibers were noted in 16.7% of small bowel GIST in the present study.

Other studies have reported higher rates of the presence of skenoid fibres ranging from 30% to 50%. This difference may be due to the higher frequency of larger and more cellular small intestinal tumors in the present study, as compared to those reported by other workers [20, 28].

Marked nuclear atypia was present in 22 cases in the present study, distributed evenly between spindle and epithelioid tumors. Nuclear atypia, seen in gastric GISTs, was comparable to the previous studies [26, 27]. Tumor necrosis was seen in tumors at all sites. More than 22% of gastric GIST and 32% small bowel GIST showed areas of necrosis. Other studies have shown similar frequency of necrosis ranging from 20% to 30% in GIST [17, 18, 24, 26,28]. The higher incidence of necrosis in the present study is likely to be due to higher proportion of larger tumors.

GISTs are usually divided into two broad groups, based on mitotic index of up to 5 and more than 5 per 50 high-power microscopic fields (HPF). Since the areas of high-power fields vary in different microscopes, the mitotic index reported in various studies is not comparable as only an occasional study has specified the exact area in which the mitotic figures were counted. However, it is now generally accepted that older denominator of 50 high-power fields should be replaced by 5 mm2 for GIST [7]. In the present study, the tumors with lower mitotic index (=5/5mm2) weremorefrequent(n =79, 65.28%) than those with higher mitotic index (>5/5 mm2). This finding is comparable varied widely in previous studies [24, 25, 29].

Tumors designated as GIST stained positively for CD117. It is usually accepted currently that all GISTs are not CD117 positive and CD117 negative tumors are usually associated with mutation of PDGFRA [30]. In the largest series of 1768 gastric GIST by Miettinen et al., 91% tumors were reported to be CD117 positive

[26]. 55% cases. Other studies have reported 36–92% positivity [17, 18, 23–25]. Gastric GIST has been reported to be more commonly positive for CD34 as compared to small bowel GIST [26, 28]. Immunopositivity for SMA showed an inverse relationship to CD34 expression as reported in occasional studies [7]. In the present study, SMA positivity We found that GIST comprise majority of mesenchymal tumors of the GIT and are also found in extra-gastrointestinal sites. We recommend a wide immunohistochemical panel including CD117, CD34, smooth muscle actin, desmin, S-100 and vimentin for classification and diagnosis of mesenchymal tumors of GIT.

The present study, 94.8% tumors morphologically designated as GIST stained positively for CD117. It is usually accepted currently that all GISTs are not CD117 positive and CD117 negative tumors are usually associated with mutation of PDGFRA [30]. In the largest series of 1768 gastric GIST by Miettinen et al., 91% tumors were reported to be CD117 positive [26].

In the evaluation of treatment outcomes, the overall survival and disease-free survival, survival after introduction of imatinib was good. Treatment with imatinib was ranked neoadjuvant when performed prior to surgery.

5.Conculsion

The current study showed that gastrointestinal stromal tumor is the commonest mesenchymal tumor in gastrointestinal tract. Primary GIST is commoner among females than males, the peak age being in the fifth decade. Abdomen pain is the common presenting symptom. The majority of patient were non vegetarians and most of them were mutton takers. Most of the male patients were alcoholics and smokers and female patients were non alcoholic and non smokers. The disease showed non specific symptoms which lead to a delay in the time of diagnosis. The commonest site was stomach followed by small intestine. 95% of cases were CD 117 Positive. Surgery was considered in 90% of patients, liver was the main site of metastasis and the 3 years and the 4 years survival rate was 91% and 78% the use of Imatinib improved the rate of survival and post operative recurrence and the metastasis was decreased.

The data presented here is an approximate assessment of the epidemiological features of primary GIST which are needed to undertake definite preventive and therapeutic measures.

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