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Case Series

Gastrointestinal stromal tumours: a series of 5 cases with review of literature

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common malignant mesenchymal lesions of the gastrointestinal tract originating from the interstitial cells of Cajal. They are characterized by overexpression of the tyrosine kinase receptor, protein product of c-KIT gene (KIT). In this case series we retrieved from our database, a total number of 5 patients, admitted and operated in the surgical department of Gauhati Medical College and Hospital and histopathologically diagnosed as GIST in the Pathology department of Gauhati Medical College and Hospital. The age range of the patients was 25 to 55 years, with mean age of 43.6 years. Out study population consisted of 2 males and 3 females. Out of 5 cases, 1 occurred in the stomach, 2 in jejunum, 1 in ileum and 1 involved the ileocaecal region; 2 were diagnosed as Malignant GIST and 3 as Benign. The differential diagnoses for spindle cell GISTs are leiomyoma, leiomyosarcoma, intra-abdominal desmoid fibromatosis, schwannoma, inflammatory myo-fibroblastic tumor and solitary fibrous tumor and that for epithelioid GIST include neuroendocrine carcinoma. Knowledge of the differential diagnoses of mesenchymal lesions of the gastrointestinal tract is important to accurately diagnose both GIST and non GISTs as the management approach is very different.

Keywords: GIST, Histopathology, CD-117

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common malignant mesenchymal lesions of the gastrointestinal tract originating from the interstitial cells of Cajal. They are characterized by overexpression of the tyrosine kinase receptor, protein product of c-KIT gene (KIT).

They are more common in the fourth to sixth decade of life with sporadic presentation or as part of syndrome complex. Mitotic activity and tumor size are important prognostic parameters of the risk of aggressive tumors.[1]

CASE SERIES

A total of 5 cases of GISTs were reported during the 1-year study period. All cases of diagnosed GISTs with available formalin fixed paraffin embedded tissue were selected from the departmental pathology records. Nature of the specimen was excisional biopsy in all 5 cases. Tissues for excision biopsy were received in 10% buffered formalin, processed routinely with haematoxylin and eosin staining and diagnosed based on the histopathological examination.

The patient characteristics (age and sex) and tumor characteristics (site, type, necrosis and mitotic activity) were analyzed in these cases. The age range of the patients was 25 to 55 years, with mean age of 43.6 years. Out of 5

cases, 1 occurred in the stomach, 2 in jejunum, 1 in ileum and 1 involved the ileocaecal region; 2 were diagnosed as malignant GIST and 3 as benign. All the cases are elaborated in tabulated form in Table 1.

Table 1: Details of all 5 cases of GIST.

Variables	Case 1 (5363/21)	Case 2 (195/22)	Case 3 (5680/22)	Case 4 (6514/22)	Case 5 (8207/22)
Age (years)	50	50	38	25	55
Sex	Female	Male	Female	Female	Male
Clinical presentation	Mass	Mass	Intussusception	Mass	Mass
Site	Ileum	Jejunum	Jejunum	Ileocaecal	Stomach
Size (cm^3)	25×20×12	10×5.5×5	4.5×3×2	14×10×3	25×20×12
Histologic type	Spindle cell type	Mixed (spindle>epithelioid type)	Mixed (epithelioid>spindled)	Spindle cell type	Spindle cell type
Histologic grade	Low grade	High grade	High grade	Low grade	Low grade
Mitotic rate (hpf)	≤5/50	5-10/50	>/5/50	≤5/50	≤5/50
Necrosis	Absent	Present	Present	Absent	Absent
IHC for CD117	Positive	Positive	Negative	Positive	Positive
Follow up	Doing well	Doing well	Expired within 7 days of OT	Doing well	Doing well

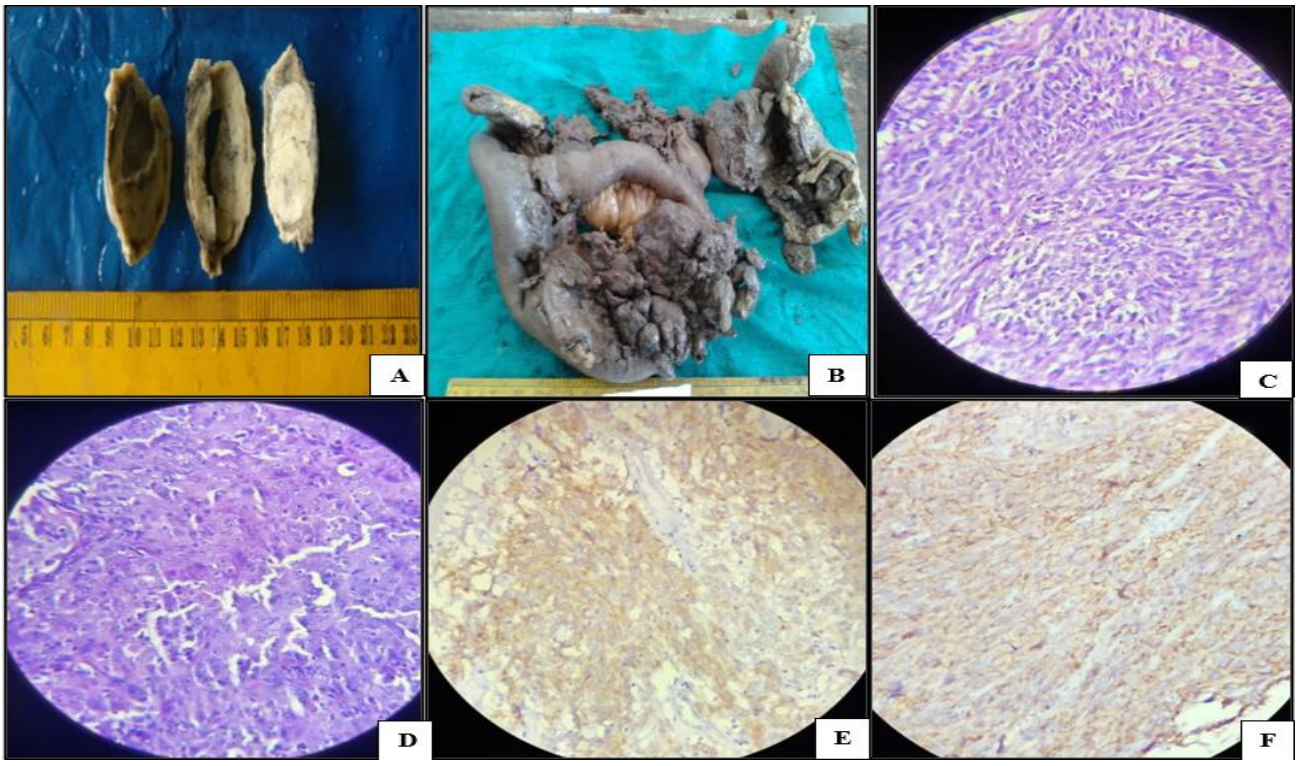

Figure 1: (A) Gross image of a case of GIST occurring in the stomach; (B) gross image of a case of GIST occurring in the ileo-caecal region; (C) HPE (at 40X) GIST with spindle cell morphology; (D) HPE (at 40X) GIST with epithelioid cell morphology; (E and F) IHC for CD117 (at 40X) showing diffuse cytoplasmic positivity.

Table 2: Review of literature and comparison of the results of this case series with other concurrent studies.

Review	Year	P	N	Mean age	Gender		Tumor site		Tumor size (cm)		Tumor focality		Tumor type			Tumor grade		Mitotic count (50 HPF)		Necrosis	IHC (CD-117+)
					M	F	GI	Extra GI	≤10	>10	U	M	Epith-elioid	Spin-dled	Mixed	Low	High	</= 5	>5		
Ahmed et al[22]	2008	204	185	64.4	87	98	174	11	-	-	-	-	-	-	-	-	-	-	-	-	183
Lak-shmi et al[23]	2010	84	92	-	-	-	92	0	61	31	-	-	4	71.9	23.6	9	70.4	-	-	-	87
Vij et al[24]	2011	223	121	50.4	-	-	108	13	-	-	-	-	20	78	23	-	-	80	22	68	114
Yacob et al[25]	2015	60	150	-	95	55	150	0	92	58	-	-	-	105	-	73	42	-	-	-	135
Li et al[26]	2015	55	112	68	64	48	112	0	88	24	-	-	13	82	17	-	-	65	47	-	97
Alq-usous et al[27]	2016	84	42	56.8 (M), 51 (F)	25	17	36	6	29	13	-	-	6	23	13	35.7	51.5	-	-	17	42
Krish-nappa et al[28]	2016		29	59.7	17	12	26	3	-	-	-	-	1	22	6	6	7	-	-	16	22
Jumn-iensuk et al[29]	2018	127	76	61.18	38	38	71	5	54	22	70	4	6	57	13	62	14	55	16	24	75
Tepeo-ğlu et al[30]	2018	160	65	61.75	31	34	65	0	56	9	65	0	2	44	19	41	17	52	13	18	59
Prese-nt study	2023	12	5	43.6	2	3	5	0	2	3	5	0	0	3	2	3	2	3	2	2	4

Note: Year- year mentioned is the year of published articles, P- period of study in months, N- number of cases in the study, Mean age in years, U- unifocal, M- multifocal.

DISCUSSION

In a study examining the Surveillance, epidemiology, and end results (SEER) registry, the incidence of GIST is reported to be 0.32 per 100,000 per year, and the prevalence is reported to be 1.62 per 100,000 per year during a 15-year period.[2] GISTs commonly occur in the age group of 40-60 years with few cases presenting in the paediatric age group. GISTs most commonly arise in the stomach (60%), followed by jejunum and ileum (30%), duodenum (5%), colorectum (4%), and esophagus or appendix (1%).[3-9] Patients can present with bleeding, perforation, obstruction or may be asymptomatic, i.e; identified incidentally on endoscopy, radiology or autopsy. Majority of GISTs are sporadic, but have also been identified in association with neurofibromatosis type 1 (NF1), Carney triad and Carney Stratakis syndrome.[10-16]

Carney triad is caused by non-hereditary Succinate dehydrogenase complex subunit C hypermethylation. It is characterized by a constellation of gastric GIST, extra-adrenal paraganglioma, and pulmonary chondroma; and Carney-Stratakis syndrome is characterised by autosomal dominant germline mutation of SDH complex. It comprises a constellation of gastric GIST and paraganglioma. These GISTs are characterized by occurrence at relatively younger age, female gender predilection, multifocality, presentation in gastric antrum, slow growth, frequent metastases, do not harbor *KIT* or PDGFRA mutations, lack of response to imatinib treatment, and, infrequently, a fatal outcome.[17-20] GISTs arising in patients with NF1 typically present with multiple tumors involving the small bowel and are clinically benign.[16]

Macroscopically, GISTs are well circumscribed tumour masses and on cut section are fleshy pink or tan-white with areas of haemorrhage, necrosis and cystic degeneration. GISTs are monotonous tumors that can be divided into three principal subtypes depending on the morphology. Spindle cell type (70%) - composed of spindle cells arranged in short fascicles with syncytial cell borders, pale eosinophilic fibrillary cytoplasm and elongated nuclei. Paranuclear vacuolization and extracellular deposits of dense, collagen (skeinoid fibers) are also seen. Epihelioid cell type (20%)- composed of epithelioid cells arranged in nests and sheets with pale eosinophilic to clear cytoplasm and round nuclei. Mixed type (10%)- comprises of mixed spindle and epithelioid cell morphology. GISTs are variably cellular and can have sclerotic, collagenous, or myxoid stromal changes. Immunohistochemistry for CD 117 (KIT) shows positivity in 90% of GISTs with DOG 1 showing positivity for 1/3rd of CD 117 negative cases showing that it is a promising new marker with even greater sensitivity and specificity for GIST. CD 34 shows positivity in 50-90% of GIST. At the molecular level, GISTs occur due to mutations in KIT and PDGFRA which result in expressed proteins with constitutive oncogenic signaling in the absence of their ligands. KIT and PDGFRA are mutually exclusive. Wild type GISTs are succinate dehydrogenase deficient and typically occur in younger females.[21]

The differential diagnoses for spindle cell GISTs are leiomyoma, leiomyosarcoma, intra-abdominal desmoid fibromatosis, schwannoma, inflammatory myofibroblastic tumor and solitary fibrous tumor.[21] Leiomyoma and leiomyosarcoma are composed of spindle cells with sausage-shaped nuclei, brightly eosinophilic cytoplasm, and distinct cell borders. Intra-abdominal desmoid fibromatoses are composed of myofibroblastic cells arranged in long sweeping fascicles set in an eosinophilic collagenous matrix.

Inflammatory myofibroblastic tumors are composed of atypical myofibroblastic cells of spindle cell morphology with vesicular tapering nuclei and well-defined cell borders arranged in fascicles and admixed with a prominent lymphoplasmacytic infiltrate. Schwannomas are composed of bland spindle cells with fibrillary cytoplasm and wavy nuclei. Solitary fibrous tumors are composed of bland spindle cells with scant cytoplasm and short nuclei arranged in characteristically pattern-less architecture with staghorn vessels. The differential diagnoses for epithelioid GIST include neuroendocrine neoplasms. Neuroendocrine neoplasm consists of monomorphic cells with round nuclei, salt and pepper chromatin and scant cytoplasm with variable mitoses according to which they are graded. Management of GISTs include surgical resection and use of tyrosine kinase inhibitors as adjuvant therapy. GISTs harbouring CD 117 mutation are best sensitive to TKIs whereas those with no mutation for CD 117 and PDGFRA are the least sensitive. According to the 2007 and 2010 NCCN and EORTC guidelines, risk assessment for GISTs is determined by tumor size, anatomic site, and mitotic activity in order to determine which patients will receive adjuvant TKI therapy.[31-33]

CONCLUSION

GISTs are the most common malignant mesenchymal lesions of the gastrointestinal tract. Knowledge of the differential diagnoses of mesenchymal lesions of the gastrointestinal tract is important to accurately diagnose both GIST and non GISTs as the management approach is very different. Judicious use of immunohistochemistry and molecular study can be undertaken as ancillary methods to arrive at the diagnosis. Identification of the type of mutation in GIST can guide in the treatment as well as prognosis of patients. The histopathological and immunohistochemical evaluation of all the cases correlates well with the prognosis of patients highlighting the role of pathologists as integral to the management of GIST. The limitation of the study is it is a retrospective case series. Molecular analysis of GISTs could not be undertaken in this case series due to lack of infrastructure and financial constraint.

Recommendations

Comparative assessment of the histopathological assessment of GISTs both before and after targeted therapy can be undertaken. Molecular analysis of GIST can shed better light on the use of targeted therapy and development of new drugs to achieve a better cure rate even in aggressive cases.

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