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Histopathological and Immunochemistry Characteristics of Gastrointestinal Stromal Tumors at Two Sub-Saharan Hospitals

Bbosa Brian, Francis Basimbe*, Niyonzima Nixon and Emmanuel Othieno

Department of Surgery, Mother Kevin Postgraduate Medical School, Uganda Martyrs University, Uganda

Abstract

Introduction: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal system. Histopathological and immunochemistry examination takes an important part in confirming the types of GISTs, to choose appropriate therapeutics for patients. Patients demographics, anatomic sites, histopathology and immunochemistry characteristics of GISTs are unknown in St Francis Hospital Nsambya (SFHN) and Uganda Cancer Institute (UCI).

Objectives: This study aimed to explore the demographics, anatomic sites, histopathological and immunochemical characteristics of GISTs in St Francis Nsambya Hospital and Uganda Cancer institute.

Methodology: A cross sectional study was conducted. The study population included patients with a histological diagnosis of GISTs who presented between 2018 to 2021 in both facilities. Clinical, pathological and immunochemistry data was collected and analyzed.

Results: A total of 146 records/blocks of patients were reviewed and out of these only Histology and immunochemistry was done on 81 blocks/patients. Majority of the patients were aged 40 to 59years, (42%) and had a median age of 57 years with IQR (45-65). There was a male predominance of 51.9%. The commonest tumor site was the stomach, (81.5%). The commonest histological type was spindle cell (79%) followed by mixed (11.1%) then epithelioid 8 (9.9%). Most of cases in our study were benign (80.1%) and mitotic count ≤ 5/50 HPF in 71.6% cases. All cases with low mitotic rate were mostly benign with a p value of <0.0001.

Conclusion: We found GISTs were more common in male gender, stomach being the commonest site and 19% of GISTs were below 40 years. Spindle cell was the commonest histologic type and most of them were CKIT positive. Malignancy was correlated with non-spindle cell type and high mitotic rate.

Keywords: CD117 • Stem cell factor receptor

Abbreviations: GIST: Gastrointestinal Stromal Tumor; C-KIT: Tyrosine Kinase Receptor; UCI: Uganda Cancer Institute; SFHN: St Francis Hospital Nsambya

Introduction

Gastrointestinal stromal tumors are rare tumors and represent commonest mesenchymal tumors arising with in the gastrointestinal tract. They account for 2% of all GI tumors. Their origin was first attributed to cajal's cells, in mesodermal tissue but in now days been recognized that GISTs arise from multipotential mesenchymal stem cells [1].

Globally the incidence of GISTs is estimated to be approximately 10 – 20 per million people, per year. Malignant possibility is 10 – 20%. However, the incidence of GISTs shows a wide variation across geographical locations. Over 90% of GISTs occur over age of 40 years, with a median age of 63 years and no significant sex difference has been noted.

***Address for Correspondence:** Francis Basimbe, Department of Surgery, Mother Kevin Postgraduate Medical School, Uganda Martyrs University, Uganda; E-mail: basimbef@yahoo.co.uk/driman84@gmail.com*

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GISTs arise most commonly within the wall of the stomach (65-70%) and small intestine (30-45%), and are seen far less frequently in the esophagus, colon, and rectum. The clinical symptoms of GIST are non-specific and varied such as abdominal pain, gastrointestinal bleeding, gastric ulcer, and accidental discovery upon imaging examination.

Within the GIST category, cellular features demonstrate a broad morphological pattern, spindle cell (60-70%), epithelioid (30-40%) characteristics or a combination of both in variable proportion. GISTs are KIT expressing and KIT (tyrosine kinase receptor CD117) -signaling driven mesenchymal tumors. Many GISTs have an activating mutation in either KIT or PDGFR (Platelet derived growth factor receptor alpha) [2].

A panel of immunohistochemical markers is used to aid in correct diagnosis. A total of 91 to 98% of GISTs stain positively for KIT (CD117), which is a major factor in the initial identification of GIST and therefore is often the inclusion criterion into many reported series. Staining of GISTs for other standard laboratory immunomarkers is more variable, including CD34 (70%), smooth-muscle actin (35%), S-100 (10%) and desmin (5%) [3].

The diagnosis of GISTs is established using histopathology, immunochemistry (IHC), identification of disease specific mutations characteristic to these neoplasms. But in our setting, the above isn't met due to several factors like costs of investigation, loss to follow up, low level of suspicion.

There have been some international studies of gastrointestinal tract tumors on histopathology and immunohistochemistry, but few data have been

found in sub-Saharan Africa. No study has been published for GIST tumors in east Africa, Uganda. Observation in the pathology units and endoscopy units of St Francis Nsambya hospital and Uganda Cancer Institute has shown an increase in detection of GISTs thus the need to know the demographic factors, anatomic locations, histopathological and immunochemistry characteristics for better management.

The aim of the study was to establish the anatomical locations, demographic factors of patients with GIST tumors of gastrointestinal tumors, histopathological and immunohistochemistry characteristics of GIST tumors in st Francis Nsambya hospital and Uganda cancer institute. The demographic factors, histopathological characteristics and proportion of C – KIT positive GISTs in patients with GIST tumors of gastrointestinal tract in st Francis Hospital Nsambya and Uganda cancer institute was also studied [4].

Methods

Cross-sectional study was carried out, information and blocks were collected from pathology and endoscopy departments of st Francis Nsambya hospital and Uganda cancer institute.

Sampling technique

Entry point was the pathological and endoscopy departments of both centers, we sampled all available cases. We retrieved 146 records of patients diagnosed as GISTs confirmed by histology from 2018 to 2021. 45 cases from St Francis Hospital Nsambya and 101 cases from Uganda Cancer Institute. Names of patients were obscured and blocks coded. Of the 146 cases retrieved, 35 cases had no blocks as these were referrals to the centers and their blocks were taken back to the initial site, 20 cases had blocks without tissues as these were endoscopic samples where the tissue was used in the first assessment. 10 cases had other diagnoses and wasn't typical of GISTs on histology. 81 cases met the criteria for the study [5].

On 81 blocks histology and immunochemistry was done at UCI by a team of pathologists. The pathologist examined the slides first individually and later jointly with the principle investigator on multithreaded microscope. Histological cell type was categorized as spindled (>75% of the tumor), epithelioid (>75% of the tumor), or mixed cell type (both spindle and epithelioid at least 25% of the tumor). Mitotic count was done and described as high if mitotic count > 50/HPF or low count ≤ 5/HPF. Assessment of neoplasia was done and described as either benign or malignant. A total of 81 cases were used from both centres [6].

Dependant variables for this study were immunochemistry, histopathological characteristics of gastrointestinal stromal tumor. The independent variables included age, sex, geographical distribution, anatomical sites. The study included all patient records/blocks which indicated a diagnosis of GIST as retrieved and reconfirmed by histology from both pathology departments of both centres from 2018 to 2021. Data collection included all the available patient records and blocks in the pathology and endoscopy departments of St Francis hospital Nsambya and Uganda cancer institute (from 2018 to 2021).

Data extraction was done by the principle investigator and 3 research assistants (trained laboratory assistants).

Hematoxylin and Eosin protocol

1. Completely dewax in two changes of xylene for 2 minutes in each
2. Hydrate with (100%, 50%) alcohol to water for 1 minute in each
3. Stain in hematoxylin (nuclear stain) for 4 minutes.
4. Rinse in water
5. Blue in running tap water for 5minutes
6. Rinse in 95% alcohol for 1 minute
7. Stain in Eosin for 2 minutes
8. Rapidly rinse in 2 changes of 95% of alcohol for 3 seconds in each
9. Rapidly dehydrate in 100% alcohol for 3 seconds.
10. Clear in xylene for 1 minute
11. Mount in D.P.X

Immunochemistry

For immunohistochemical studies, we used archival formalin-fixed, paraffin-embedded (FFPE) tissues from those GIST samples and examined them using immunohistochemistry for 1-2 representative tumor blocks from each case.

Immunohistochemistry procedure: We used 3-μm-thick slides for immunohistochemical studies. Primary antibodies for CD-117 (Ventana pathway Anti -c- KIT (9.7) primary antibody) was used to find protein expressing. Immunostaining for CD-117 was performed by an automated staining machine (BENCHMARK XT) under the manufacturer's guide. Immunostaining was defined as positive (labeled [+]) if ⩾10% of tumor cells were stained and as negative (labeled [–]) if <10% of tumor cells were stained [7-10].

Data analysis

The data extracted from records and blocks with data collection tool was entered into computer using Epi Data, and exported STATA 14 for data cleaning and analysis. Descriptive statistics were used to summarize the independent and Dependant variables. For continuous variables expressed as median, interquartile range due to skewed data, and categorical variables expressed as frequency and percentage. To determine the demographic characteristics, anatomic sites, histopathological patterns and immunochemistry, the number of each category was divided by overall sample size and hence percentages were got. Fischer exact test was used to test the difference in the proportions of independent variables across the Dependant variables at bivariate analysis. For multivariate analysis a simple modified Poisson regression analysis was used to obtain unadjusted prevalence ratios. Factors that achieved *P*-values of <0.2 were used to build a multivariable model. Backward elimination was used to obtain final model which included age and region. The modified poisson was preferred because the proportion of outcome was more than 10% of the entire sample which will lead to exaggerated association if odds ratio were used [11-13].

Results of the analyzed data were presented in form of tables, pie chart and bar graph. Administrative clearance to conduct the research was obtained from the department of surgery St Francis hospital Nsambya, management of Uganda cancer institute, UMU faculty of medicine and approval from institutional Research and Ethics committee (IREC). The aim and method of carrying out the research was clearly explained to the departments and safety of records/blocks was maintained. No client consent was required since it was retrospective chart and block review.

Results

A total of 146 records/blocks of patients diagnosed with GISTs confirmed by histology from 2018 to 2021 were retrieved. Out of these 81 blocks/patients were included in the study.

Demographics

Majority of the patients were aged 40 to 59years, 34 (42%). Just over half of the patients were male, 42 (51.9%) (Table 1 and Figure 1).

Anatomic sites and histopathological characteristics

The commonest tumor site was the stomach, 66 (81.5%). Majority of the tumors were upper GI tumors, 70 (86.4%). spindle, 64(79%), benign, 65 (80.2%). A total of 58(71.6%) tumors had a mitosis count greater or equal to five (Table 2) (Figures 2 and 3).

Immunochemistry characteristics

Majority were C-KIT positive, 73 (90.1%).

Bivariate analysis of demographic, histopathological and immunochemistry characteristics

There was no significant difference in the distribution of age across the

Table 1. Demographic characteristics.

Variables	Frequency N=81	Percent
Age in Years		
Median (IQR)	57 (46 - 65)	-
<40years	16	19.8
40-59years	34	42
60+years	31	38.3
Sex		
Male	42	51.9
Female	39	48.1
Geographical location		
Central region	32	39.5
Western/Southern	15	18.5
Eastern	17	21
Northern	17	21

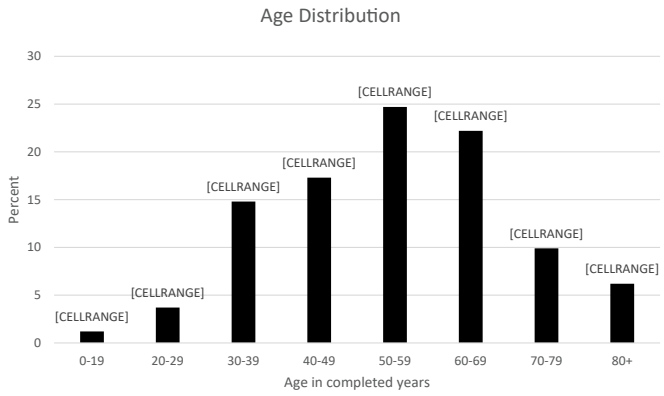

Figure 1. A bar showing age distribution.

Table 2. Anatomic sites and histopathological characteristics.

Variables	Frequency N = 81	Percent
Anatomic site		
Esophagus	2	2.5
Stomach	66	81.5
Duodenum	2	2.5
Jejunum and Ileum	2	2.5
Colon	3	3.7
Rectum	4	4.9
Anus	2	2.5
Anatomic site category		
Upper GI	70	86.4
Lower GI	11	13.6
Histopathological patterns		
Spindle	64	79
Epithelioid	8	9.9
Mixed	9	11.1
Mitosis count		
Median (IQR)	3 (2 - 7)	
<=5	58	71.6
>5	23	28.4
Neoplasia		
Benign	65	80.2
Malignant	16	19.8

upper and lower GI tumors (*P*=0.365). Majority of the benign tumors were in 60 years and above age group while majority of the malignant tumors were in those aged 40 t0 59years of age (*P*=0.074). Five out of 8 (62.4%) of the C-KIT

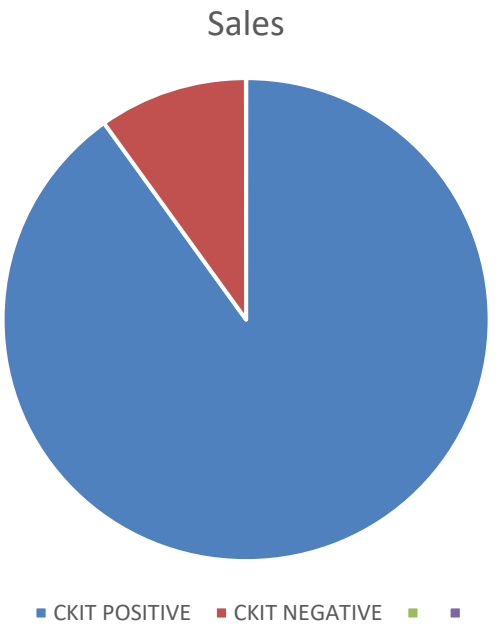

Figure 2. Pie chart showing immunochemistry characteristics.

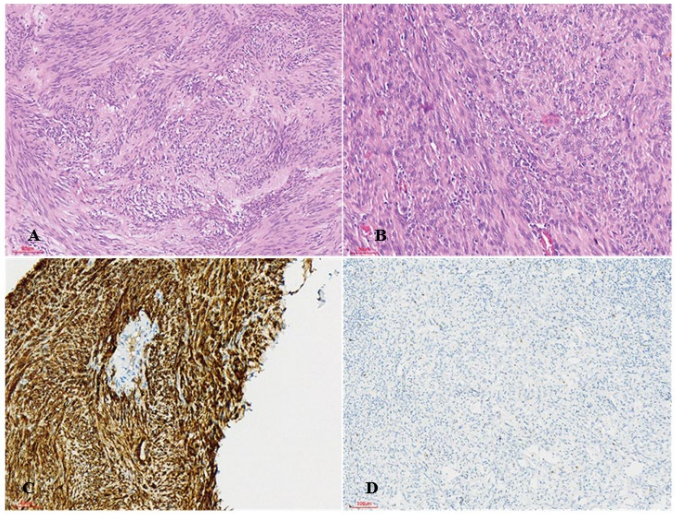

Figure 3. Shows the appearances of the different histopathological and immunochemistry patterns. Histopathological and immunochemistry patterns; A) Spindle, B) Mixed, C) CKIT Positive and D) CKIT Negative 200X.

negative tumors were in the 60+years age group while majority, 32 (43.8%) of the C-KIT positive tumors were among the 40-59years age group. There was no significant difference in the sex across the anatomic site (*P*=0.751), malignancy (*P*=0.784) and immunochemistry (*P*=0.472). All the 16 (100%) malignant tumors had mitotic counts greater than 5, while only 7 (10.8%) benign tumors had a mitotic count greater than five (*P* < 0.001) (Table 3).

Multivariate analysis

Age and geographical location that had p-values less than *P*=0.2 (standard inclusion criteria for multivariable analysis) were include in the modified Poisson regression analysis. Modified Poisson regression analysis was chosen because it is ideal for outcome proportions greater than 10% where the odds ratios exaggerate the associations. At bivariate analysis, patients from eastern appeared to be 4.7 times more likely to have lower GI tumors than people from the central region. After controlling for age however this association did not remain significant Adj. PR: 4.11 (95% CI: 0.77-21.89), *P*=0.098) (Table 4) [14-17].

Table 3. Bivariate analysis of Demographic, histopathological and immunochemistry characteristics.

Variables	Anatomic site		*P* value	Neoplastic		*P* value	Immunochemistry		*P* value
	Upper GI	Lower GI		Benign	Malignant		C-KIT +ve	C-KIT -ve	
Age category									
<40years	12 (17.1)	4 (36.4)		14 (21.5)	2 (12.5)		15 (20.5)	1 (12.5)	
40-59years	30 (42.9)	4 (36.4)		23 (35.4)	11 (68.8)		32 (43.8)	2 (25)	
60+years	28 (40)	3 (27.3)	0.365	28 (43.1)	3 (18.8)	0.074	26 (35.6)	5 (62.5)	0.443
Sex									
Male	37 (52.9)	5 (45.5)		33 (50.8)	9 (56.3)		39 (53.4)	3 (37.5)	
Female	33 (47.1)	6 (54.5)	0.751	32 (49.2)	7 (43.8)	0.784	34 (46.6)	5 (62.5)	0.472
Geographical location									
Central region	30 (42.9)	2 (18.2)		25 (38.5)	7 (43.8)		29 (39.7)	3 (37.5)	
Western/Southern	14 (20)	1 (9.1)		14 (21.5)	1 (6.3)		13 (17.8)	2 (25)	
Eastern	12 (17.1)	5 (45.5)		15 (23.1)	2 (12.5)		16 (21.9)	1 (12.5)	
Northern	14 (20)	3 (27.3)	0.123	11 (16.9)	6 (37.5)	0.195	15 (20.5)	2 (25)	0.88
Anatomic site									
Upper GI	70 (100)	0 (0)		56 (86.2)	14 (87.5)		62 (84.9)	8 (100)	
Lower GI	0 (0)	11 (100)	-	9 (13.8)	2 (12.5)	1	11 (15.1)	0 (0)	0.59
Histopathological patterns									
Spindle	56 (80)	8 (72.7)		52 (80)	12 (75)		58 (79.5)	6 (75)	
Epithelioid and mixed	14 (20)	3 (27.3)	0.691	13 (20)	4 (25)	0.445	15 (20.5)	2 (25)	0.672
Mitosis count									
<=5	49 (70)	9 (81.8)		58 (89.2)	0 (0)		50 (68.5)	8 (100)	
>5	21 (30)	2 (18.2)	0.72	7 (10.8)	16 (100)	<0.001	23 (31.5)	0 (0)	0.098
Neoplastic types									
Benign	56 (80)	9 (81.8)		65 (100)	0 (0)		57 (78.1)	8 (100)	
Malignant	14 (20)	2 (18.2)	1	0 (0)	16 (100)	-	16 (21.9)	0 (0)	0.346
Immunochemistry characteristics									
C-KIT positive	62 (88.6)	11 (100)		57 (87.7)	16 (100)		73 (100)	0 (0)	
C-KIT negative	8 (11.4)	0 (0)	0.59	8 (12.3)	0 (0)	0.346	0 (0)	8 (100)	-

Table 4. Multivariate analysis.

Variables	PR (95% CI)	*P* value	Adj. PR (95% CI)	*P* value
Age category				
<40years	1	-	1	-
40-59years	0.47 (0.13-1.66)	0.241	0.59 (0.16-2.18)	0.425
60+years	0.39 (0.10-1.54)	0.177	0.51 (0.12-2.09)	0.348
Sex				
Male	1 (1.00-1.00)	-	-	-
Female	1.29 (0.43-3.92)	0.651	-	-
Geographical location				
Central region	1	-	1	-
Western/Southern	1.07 (0.10-11.02)	0.957	0.95 (0.09-10.28)	0.967
Eastern	4.71 (1.01-21.96)	0.049	4.11 (0.77-21.89)	0.098
Northern	2.82 (0.52-15.46)	0.231	2.19 (0.39-12.27)	0.373
Histopathological patterns				
Spindle	1	-	-	-
Epithelioid and mixed	1.41 (0.42-4.79)	0.58	-	-
Mitosis count				
<=5	1	-	-	-
>5	0.56 (0.13-2.42)	0.438	-	-
Malignancy				
Benign	1	-	-	-
Neoplastic	0.9 (0.21-3.81)	0.889	-	-

Discussion

Demographics

In our study setting, a median age of 57 was attained which supports the fact that GISTs occur in elderly. In sub-Saharan Africa, studies done in Nigeria by Ogun GO, et al. [12] and Ayandipo, et al. had a median age of 57 and 57.6 also, a study done in S.A by Baker et al which compares fairly to our study. Also, other studies done in Korea, Japan, Vietienam by Kim et al, Miettinen M, et al., [9] Nguyen C, et al. [2] stated around the same median age.

All above studies had outliers with range of around (10 to 87). The above is in contrast with many studies that had median age of greater than 60 years [18-21]. It may be because of sample size (>200) and others were systematic reviews. GISTs rarely occur below the age of 20 years, in our study a total 1.2% was documented and supported 1.4% of study population done by also had 1 patient.

Majority of patients were aged 40 to 59, thus supports the observation that GISTs rarely occur in the young population. In our study, 19% GISTs occurred below the age of 40 years. This may suggest an earlier onset in our setting. In contrary to literature which states 90% of GISTs occur above age of 40. In our study setting we had a male predominance though literature doesn't have a correlation between age and GISTs. Several studies were in line with above. Several other studies reported a ratio of 1:1. Also, in countray other studies reported a female predominance. Majority of cases were from central region and this may be attributed because both centres are in that region.

Anatomic sites

The commonest anatomical site was stomach which may be because most of our samples were endoscopic samples but it is also in line with literature. Though two studies of Antonescu and Bhalgami, et al. which found slightly more in the small intestine than stomach. Our study also showed that GISTs were more predominant in the stomach followed by colorectal (8.6%) and small intestines which was a consistent finding in most of the literature.

Tumor site is of significance for risk stratification and as gastric tumors have a better outcome than non gastrisc tumors, appendix V for risk stratification table. The lower percentages in colorectal, small instestines may still be attributed to the few surgical cases involved in the study. But also, literature has lower percentages in oesophagus, colon, anus but a percentage close to 30% in small intestines. Upper GI GISTs 70 are more common than lower GI GISTs in our setting because stomach is most predominant site. GISTs in all locations occur in the elderly, less than 10% gastric GISTs occur in patients below 40 years of age.

Histopathological characteritics

The commonest histological type in our study setting was spindle cell followed by mixed then epithelioid. It is in line with most literature. Studies done in Nigeria by Ayandipo, et a., Abdulkareem et al. also show spindle cell was the most commonest histologic type (75.9%, 46%), followed by mixed spindled and epithelioid type (20.3%, 31%) and epithelioid type (3.7%, 23%). These observations were in line with most of the studies in Asia. On the contrary, a study conducted in the USA, Antonescu et al. found that majority were spindle type (84%), followed by epithelioid cell type (16%).

However, the study of Klieser et al. in Europe found that the majority were spindle type (61.2%), while the epithelioid cell type (19.4%) was equally found with the mixed spindled-epithelioid cell type (19.4%). Most of GISTs in both categories upper and lower GI are spindle cell tumors. Spindle cell tumor carries a better prognosis as most are benign. In our study most of cases had a low mitotic count and were benign and most of cases with high mitotic count were malignant which is supported by Miettinen M, et al., [9]. who found that mitotic activities are the most powerful prognosticators integrated with tumor size.

Also, a symposium article by Badalamenti G, et al. [1] reported the estimated annual incidence is 10-20 cases per million, of which 20%-30% were malignant which is closer to our study. Most histological pattern with malignancy was non-spindle type which is also in line with literature.

Immunochemistry characteristics

In this study CD117 (C KIT) positive was predominant which is supported by most of literature with range 91 to 98%. Immunochemically negative GISTs accounted for 8.9% which would be explained by retrospect archived samples collected in our study which would explain the low values, as protein/receptor degradation is inevitable over time. It is also stated that approximately 15% of GISTs do not display a definable KIT or PDGFRA mutation. These are classified by convention as wild-type GISTs. They represent a variety of different genomic changes but are not clinically distinct from mutant KIT or PDGFR.

In our study, all lower GI GISTs were CKIT positive compared to Upper GI GISTs but it wasn't statistically significant probably because of the smaller sample size for collection. This is in contrary with Korean study that showed C KIT positivity was high in the stomach (94.2%) and small intestine 94.6% while relatively low in colorectum (85.0%) and oesophagus (81.2%). Upper GI GIST had a higher proportion of CKIT positivity than lower GI as it documented elsewhere. But in our setting, it may also be because most of samples are endoscopic. Most of spindle cell GISTs were CKIT positive than non-spindle cell GISTs probably because most of samples were spindle cell and this is in contrast with literature that says that most immunoreactivity is found in epitheloid GISTs.

Conclusion

Most GISTs in our setting are spindle cell tumors and CKIT positive as it is in other parts of the world but a greater proportion of GISTs less than 40 years (19%) was noted. In our setting malignancy was also correlated with non-spindled cell type and high mitotic count. The commonest site was stomach and cases had a slight male predominance.

Recommendation

Immunochemistry is vital in diagnosis we will recommend SFNH to acquire immunochemistry services. Since we have greater proportion of tumors below 40, we recommend genetic testing for familial conditions related to GISTs (Carney's triad and Carney-Stratakis, neurofibromatosis). Since majority of GISTs are CKIT positive, we recommend molecular studies on the available blocks CKIT mutations so as to institute molecular targeted therapy (imatinib) as adjuvant or neoadjuvant. Acquisition of Endoscopic ultrasound guided biopsy in SFNH so that enable measurement of tumor size and also improving quality of biopsy taken.

Conflict of Interest

The authors declare no conflict of interest.

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