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ORIGINAL ARTICLE

Immunophenotyping of Gastrointestinal Mesenchymal Tumours in Lagos, Nigeria

Immunophénotypage des tumeurs mésenchymateuses gastro-intestinales Lagos, Nigeria

F. B. Abdulkareem*†, O. Rotimi‡, S. O. Elesha†, A. A. F. Banjo†

ABSTRACT

BACKGROUND: **Gastrointestinal stromal tumour (GIST) represents only 1% of all malignant tumours of the gastrointestinal tract (GIT) but it is the most common gastro-intestinal mesenchymal tumour (GMT) with majority arising from the stomach and small intestine.**

OBJECTIVE: **To determine the prevalence of GIST using immunophenotypic characteristics.**

METHODS: Materials were formalin fixed paraffin embedded blocks of GMT diagnosed in Lagos Nigeria between January 1995 and February 2007. Sections were stained with CD117, CD34, SMA, S100 and Desmin antibodies at the research Laboratory of The Leeds General Infirmary, United Kingdom following standard procedure.

RESULTS: **Thirty-two cases of GMT (aged 10–78 years with a mean age of 46 and M: F=1.3:1) were analyzed. GIST accounted for 13 (40.6%), smooth muscle tumours 7(22%), vascular three(9.3%), de-differentiated liposarcoma two (6.2%), and unclassified (3%) of the GMT cases. Immuno-staining was not done for six cases of lipoma (18.7%). GISTpatients had a mean age of 45.4years with a M: F of 1.6:1; 54% was located in the stomach. Histologically, spindle cell type predominated accounting for 46% followed by mixed (31%) and epithelioid types (23%). Only 30.7% the GIST were suspected before immuno-staining.**

CONCLUSION: **Gastrointestinal stromal tumour is the most common gastro-intestinal mesenchymal tumour in Lagos with a male preponderance. The most common site is the stomach. The immunophenotypic characteristics are comparable with gastrointestinal stromal tumours reported from other parts of the world. WAJM 2009; 28(6): 358–362.**

Keywords: **Gastrointestinal tract; Tumour; Stromal tumour; Immunophenotyping; Nigeria Lagos.**

RÉSUMÉ

CONTEXTE: *les tumeurs stromales gastro-intestinales (GIST) ne représente que 1% de toutes les tumeurs malignes des voies gastro-intestinales (GIT), mais c'est la plus courante gastro-intestinales tumeurs mésenchymateuses (GMT) à la majorité provenant de l'estomac et l'intestin grêle.*

OBJECTIF: *Déterminer la prévalence des GIST en utilisant les caractéristiques immunophénotypiques.*

MÉTHODES: *Les matériaux ont été fixés au formol paraffine embarqués blocs de GMT diagnostiqué à Lagos au Nigeria, entre Janvier 1995 et Février 2007. Les articles ont été colorés avec CD117, CD34, SMA, S100 et des anticorps Desmin au Laboratoire de recherche de L'Infirmerie générale Leeds, Royaume-Uni suite à la procédure standard.*

RÉSULTATS: *Trente-deux cas de l'heure GMT (âgés de 10-78 ans avec un âge moyen de 46 et M: F = 1.3:1) ont été analysés. GIST représentaient 13 (40,6%), les tumeurs du muscle lisse 7 (22%), vasculaires trois (9,3%), de-liposarcome différencié deux (6,2%), et non ventilé (3%) des cas GMT. Immunocoloration n'a pas été fait pour les six cas de lipome (18,7%). GISTpatients avaient un âge moyen de 45,4 années avec un M: F de 1,6:1, 54% a été localisé dans l'estomac. Histologiquement, cell type de broche comptables prédominé pour 46%, suivie par des unités mixtes (31%) et les types épithélioïdes (23%). Seuls 30,7% des GIST étaient soupçonnés avant d'immuno-fluorescence.*

CONCLUSION: *tumeur stromale gastro-intestinale est la plus courante gastro-intestinales tumeurs mésenchymateuses à Lagos avec une prédominance masculine. Le site le plus commun est l'estomac. Les caractéristiques immunophénotypiques sont comparables aux tumeurs stromales gastro-intestinales signalés dans d'autres parties du monde.* ***WAJM 2009; 28(6): 358-362.***

Mots-clés: *tractus gastro-intestinal; tumeur; tumeurs stromales; immunophénotypage, Nigeria Lagos.*

†**Deparments of Morbid Anatomy, College of Medicine, University of Lagos, P.M.B.12003, Surulere, Lagos, Nigeria** ‡**Histopathology & Molecular Pathology, Leeds General Infirmary, Leeds, LS1 3EX, UK**

***Correspondence:** **Dr. Fatimah B. Abdulkareem,** Dept of Morbid Anatomy, College of Medicine University of Lagos, P.M.B.12003, Surulere, Lagos, Nigeria E-mail: biade64@yahoo.co.uk

Abbreviations: CD, cluster differentiation; **GIST,** gastrointestinal stromal tumour; **GIT,** gastrointestinal tract; **GMT,** Gastrointestinal mesenchymal tumour; **SMA,** smooth muscle antigen.

INTRODUCTION

Gastrointestinal stromal tumour (GIST) represents only 1% of all malignant tumours of the gastrointestinal tract (GIT).[1–3] It is however the most common mesenchymal tumours of the GIT with majority (47–60%) arising from the stomach and small intestine and a small number in other parts of the GIT.[1] Extraintestinal GIST (EGISTs) with similar immunohistochemical clinical characteristics have been reported in areas such as vulvo-vaginal, recto-vaginal septum, omentum, and retroperitoneum.[4]

GIST presents as solitary submucosal nodule and occurs commonly between the sixth and seventh decade of life in all races with no significant sex predilection.[1–3] Patients present with upper GIT bleeding and other non-specific GIT symptoms.[1,4] Histologically seen as spindle, epithelioid or pleomorphic cell tumour, size larger than 5cm and/or with, mitoses of greater than five per 50 high power fields in a tumour predict malignant behaviour.

Classified formerly as smooth muscle tumour, ultra-structural and molecular studies have shown that GISTs specifically express c-KIT gene (CD 117); a proto-oncogene, and growth factor for stem cell. It has tyrosine kinase activity and its product is called CD117.[1–3,5] This c-kit mutation or PDGF receptor alpha is expressed in all GISTs but not in true smooth muscle and neural tumours and has become a very important tool in the differentiation of GIST from other GMT. Positive CD117 staining in a GMT is said to be diagnostic for GIST. CD34 is another important diagnostic marker, detected in about 70% of GISTs, and has been shown to be associated with a malignant phenotype. The expression of CD44 has been demonstrated to correlate with a better prognosis.[1]

GISTs share morphological, immunophenotypical and genetic characteristics with the interstitial cells of Cajal (ICCs), the pacemaker cells of the GIT and have immunophenotypical and ultra structural features of both smooth muscle and neuronal differentiation, and regulate peristalsis.[6] Both GISTs and ICC express the tyrosine kinase KIT oncoprotein and expression of KIT is specific and required for the diagnosis. It has thus been suggested that GIST probably arises from the interstitial cells of Cajal which exhibit both myeloid and neural features and express c-Kit proto-oncogene.[7,8]

The response of the tumour to a selective tyrosine kinase inhibitor of ABL, KIT, and PDGFR; Imatinib mesylate (STI-571, Gleevec) has been found to be remarkable in patients with metastatic or advanced disease[1–3,9,10] providing clinical benefit in about 85% of patients with advanced GIST.

GIST has been described and reported from several parts of the world but there is a dearth of studies from Africa in general and Nigeria in particular. Recent report has shown that GIST does occur in Nigeria[11]. Six patients with confirmed diagnosis of GIST have benefited from an ongoing Glivec (imatinib mesylate) international patient-assistance programme therapy for Philadelphia/bcr-abl-positive chronic myeloid leukaemia (CML) and CD117-positive GIST patients at Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.[11] The aim of this study was therefore to determine the prevalence of GIST among all mesenchymal tumours of GIT in Lagos, Nigeria and also to describe its immuno-histochemical characteristics.

SUBJECTS, MATERIALS, AND METHODS

The materials for the study included formalin fixed paraffin embedded blocks of all cases of GMT diagnosed from Lagos University Teaching Hospital Histopathology laboratory and three other private laboratories (The Specialist Laboratory, Histolab Diagnostics and Seramoses laboratory) in Lagos over 12 years (January 1995–February 2007).

Ethical clearance was obtained from the research and ethics committee of the Lagos University Teaching Hospital (LUTH). All the tissue blocks of GMT were taken to the histopathology department of The Leeds General Infirmary (LGI) in the United Kingdom where the immuno-staining was done. Sections were stained with H&E to confirm diagnosis and select the best block for immuno-stain. All cases confirmed to be lipomas were not processed for immuno-staining while the remaining was sectioned on super-frost slides for staining with a panel of five antibodies (CD117, CD34, Desmin, SMA, and S100).

The sections were de-parafinized in xylene for ten minutes (after overnight incubation in 37º oven), dehydrated in alcohol for five minutes; followed by antigen retrieval using either pressure cooking or trypsinization. Pressure cooking was utilized for antigen retriever in all cases except for desmin for which typsinization was used. To prevent non-specific binding, all sections were treated with 100microliters of casein for five minutes. The sections were incubated with the primary antibodies diluted according to specification by the manufacturer for one hour (CD117–1:250; CD34–1:100; SMA–1:500; S100–1:1000; Desmin-two drops pre-diluted). The sections were then treated with two drops of the secondary antibody (anti-Rabbit envision – PO by Dako) for thirty minutes and 1:100 solution of three, three – diameno-benzidine (DAB). At intervals the sections were washed with TBA in between application of the casein and antibodies for five minutes. The slides were then washed, counter stained with Meyers' haematoxylin for one minute, dehydrated in alcohol and cleared in xylene before mounting.

The pathologists examined the slides histologically first individually and later jointly on multiheaded microscope. The opinion of the soft tissue pathologist was sought in cases that were not straight forward. The final diagnosis was based on the H & E stained and immunostaining characteristics. Diagnosis of GIST was based on positivity for both c-KIT and CD34; positivity for desmin and smooth muscle actin was the criteria for diagnosis of smooth muscle tumour; vascular tumour was based on only CD34 positivity while de-differentiated liposarcoma was based on positivity for S100.

RESULTS

A total of 43 cases of GMT were identified from the archives of the four laboratories, out of which 11 were excluded due to either incomplete clinical records or loss of tissue blocks. The remaining 32 cases constituted the

materials for the study. Their ages ranged from 10–78 years with a mean of 46. Majority of the cases were in the 31–60–year age group. There were 18 males and 14 females giving a male to female ratio of 1.3:1 (Table 1).

Of the 32 patients, there were six cases of lipoma diagnosed by only H & E and were excluded from immuno-histochemistry. These accounted for 18.7% of all the mesenchymal tumours with mean age of 48.2 years and equal sex incidence. All except one of the lipomas were located in the large intestine; the other one was located in the small intestine.

Twenty-six cases were further analyzed based on the result of the immuno-histochemistry and H & E features. Thirteen (41%) cases were positive for C-KIT (CD117) and CD 34 and thus classified as gastrointestinal stromal tumour. Seven (7%) cases were positive for both Desmin and SMA and thus classified as smooth muscle tumours (SMT); four of these were leiomyoma and three were leiomyosarcoma. Three (9.3%) cases were positive for only CD34 and were categorized as haemangioma. Two(6.2%) cases were diagnosed based on the H & E and positivity for S100 as de-differentiated liposarcoma. The remaining one case was negative for all the antibodies and categorized as unclassified GMT (Table 2).

The GIST cases occurred between the ages of 23 and 76 years with a mean of 45.4 years. There were eight males and five females with a male: female ratio of 1.6:1 (Table 3). Majority were located in the stomach with seven(54%) cases , three(23%) cases in the large bowel while one case each in the small intestine and omentum, and one was a liver metastasis (primary – unknown). Histologically, spindle shaped cells predominated in six(46%) cases, epithelioid in three(23%) cases while mixed spindle and epithelioid variety were seen in four(31%) cases. The mitotic count was greater than 10 per 50 high power fields in four (31%) cases.

Only four (30.7%) of the 13 cases of GISTs were suspected at diagnosis by routine H & E staining; the remaining cases were diagnosed as either tumour of smooth muscle six (46%), skeletal muscle one (7.6%), vascular one (7.6) or fibroblastic origin one (7.6%).

Table 1: Distribution of Patients with Gastrointestinal Mesenchymal Tumours by Age and Sex

Age group(years)	Frquency Number(%)		
	Male	Female	Total
0–10	1(5)	0(0)	1(3)
11–20	0(0)	1(7)	1(3)
21–30	3(17)	1(7)	4(12.5)
31–40	3(17)	4(29)	7(22)
41–50	3(17)	2(14)	5(16)
51–60	2(11)	4(29)	6(19)
61–70	4(22)	0(0)	4(12.5)
>70	2(11)	1(7)	3(9)
Unspecified	0(0)	1(7)	1(3)
Total	**18(56)**	**14(44)**	**32(100)**

Table 2: Immunophenotypic Categorization of Gastrointestinal Mesenchymal Tumours in Lagos, Nigeria

Immuno-phenotypic Category	Number (%)
Gastrointestinal stromal tumour (GIST)	13(41)
Smooth Muscle tumour	7(22)
Lipoma	6(19)
Vascular tumour	3(9)
Liposarcoma	2(6)
GMT –unclassified	1(3)
Total	**32(100)**

DISCUSSION

Of all the GMT analyzed, GIST was the commonest accounting for 41%. This concurs with other previous studies from various parts of the world which have established that GIST is the most common mesenchymal tumour of the GIT with frequencies varying from 60–80%.[10, 12–17] Next to GIST is smooth muscle tumours (SMT) in form of leiomyoma and leiomyosarcoma accounting for 22% in this study. This is comparable to the findings from other parts of the world.[17-19] In the USA, Perez et al recorded 18% of 1873 GMTs as smooth muscle neoplasm and GIST accounting for 82%.[18] Also in a Chinese Study by Wang *et al,* GIST was the most common accounting for 60.5%; followed by smooth muscle tumours 15.7%.[17] Orosz *et al* in Hungary reclassifying GMT in 463 patients recorded 245 to be GIST, 81 were leiomyogenic while 25 were neurogenic tumours.[19]

Most GMTs before the advent of immunohistochemistry and electron microscopy were initially presumed to be of smooth muscle origin; labeled leiomyoma/leiomyosarcoma when composed primarily of spindle shaped cells and leiomyoblastoma when composed of epithelioid variety.[16,20–21]

GIST was also known by various names such as smooth muscle tumour of uncertain malignant potential (STUMP), gastrointestinal autonomic nerve tumour (GANT) and gastrointestinal pacemaker cell tumour (GIPACT) which confirms the uncertainty surrounding its histogenesis and clinical behaviour.[12–14] It is thus possible that earlier studies which did not consider molecular characteristics must have mis-diagnosed this tumour. In Calabar, South-East Nigeria, a case of gastric epithelioid leiomyoma presenting with spontaneous haemoperitoneum was

Table 3: Clinical and Histological Parameters of 13 Cases of Gastrointestinal Stromal Tumour (GIST)

	Age	Sex	Site	Presenting Complaint/ Clinical Diagnosis	Pre-immuno Diagnosis	CD117	Desmin	CD34	SMA	S100
1.	23	M	Rectum	Rectal mass	Embryonal rhabdo-myosarcoma	Positive	Negative	Positive	Negative	Weakly positive
2.	33	F	Rectum	Rectal Tumour	Leiomyo Sarcoma	Positive	Negative	Positive	Negative	Negative
3.	40	M	Stomach	Stomach Cancer?	GIST	Positive	Weakly Positive	Positive	Negative	Weakly Positive
4.	30	F	Colon	Colonic Tumour Malignant?	Leiomyoma	Positive	Negative	Positive	Negative	Positive
5.	48	M	Small Intestine	Intestinal Obstruction	Sclerosing Haemangioma	Weakly Positive	Negative	Weakly Positive	Negative	Negative
6	27	M	Stomach	Left Hypochondrial Mass attached to Posterior Wall of Stomach	Leiomyoma? GIST	Positive	Negative	Positive	Negative	Weakly positive
7	39	M	Stomach	Recurrent Leiomyoma	Leiomyosarcoma	Positive	Negative	Positive	Negative	Negative
8	76	F	Stomach	Intra-abdominal Mass attached to greater curvature of stomach	Leiomyoma	Positive	Negative	Positive	Negative	Negative
9	50	F	Stomach	Gastric Mass	Leiomyosarcoma	Positive	Negative	Positive	Negative	Negative
10.	60	F	Omentum	Huge Omental Mass ? metastatic	GIST	Positive	Negative	Positive	Negative	Negative
11	51	M	Liver Nodule	? Metastatic Nodule	Metastatic Fibrosarcoma	Positive	Negative	Positive	Negative	Negative
12	47	M	Stomach	Gastric Outlet Obstruction	GIST	Weakly Positive	Negative	Positive	Negative	Negative
13	66	M	Stomach	Upper GIT Bleeding, Submucosal Mass	Malignant probably Leiomyosarcoma	Positive	Negative	Positive	Negative	Negative

reported.[22] Although no immunostaining was done, the clinical presentation and histological characteristics of this tumour as described by the authors fit what is now known as GIST.[22] This probably was epithelioid type of GIST.

This present study followed the recommendation of the consensus standard histological and immuno-histochemical analysis of GIST by using the five recommended antibodies; CD117, CD34, S100, desmin and smooth muscle actin and has been utilized by other workers doing similar study.[17–19] All the 13 cases were positive for c-KIT and CD34. Three of the 13 cases were also weakly positive for S100 while only one was weakly positive for desmin. Previous studies have reported that GIST can be positive for desmin in 2–13.4% and S100 in 5–10.2% of cases.[23, 24] Positive staining for SMA in 32% of cases has been reported while other studies have associated high positivity for SMA with lower survival.[25]

The mean age of GIST in this study was 45.4 corroborating previous studies which have established that GIST is rare below 40years with the peak age incidence in the fifth and sixth decade.[12]

Several studies have recorded a mean age of 50-65.8years.[24–28] The male: female ratio of 1.6:1 for GIST cases in this study compares well with previous study in which a slight male predominance has been reported[26] although other studies have recorded no significant sex difference.[13,24]

The most frequent location of GIST in this series was the stomach accounting for 54% which concurs with previous studies that have reported the stomach or upper GIT as the most common site with frequencies varying between 40–70%.[13, 17, 24–29] It however contrasts with the finding of Fernandez *et al* who reported 52.9% of their series located in the jejunum or ileum and only 29.4% were gastric.[26] Also in contrast to previous studies which indicated that the small intestine is the next common site for GIST, our study showed that the next common location was the large intestine.[13, 17, 24–25]

Histologically as established in the literature, the spindle cell type is the most common in this series but unlike most studies was followed by the mixed type; the epithelioid type being the least common1.[7,24]

Only 31% of cases of GISTs were diagnosed before immunohistochemistry (i.e. 70% of cases were misdiagnosed) which contrast the finding of Tzen et al in Taiwan who reported that only 35% of GISTs were misdiagnosed if immunohistochemical analysis of CD117 expression was not performed.[28] However yet about 15% are likely to be misdiagnosed if genetic analysis is not done.[28]The various mutations associated with GIST are KIT exons 8, 9, 11, 13, 17 but exon 11 is the most common (75%)[29]. All PDGFRA mutations were found to be gastric tumours with epithelioid morphology[29]; a type which is said to represent gastric tumours of low or no malignant potential. Molecular genetic analysis was not done in our series.

In summary, GIST is the most common GMT tumour in Lagos, Nigeria, accounting for 41% of GMT cases. The mean age of the patients was 45.5 with a slight male preponderance. The most commonest site is the stomach (54%) and only 30.7% were suspected before immuno-staining. The immunophenotypic characteristics are comparable with GISTs reported from other parts of the world.

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