MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.4.394.400

OPEN ACCESS

Key Words
Gastrointestinal stromal tumor, immunohistochemistry, malignancy

Corresponding Author
Sucharitha Pathivada,
Department of Pathology ACSR Government Medical College Nellore, AP, India
hi.itssuchi@gmail.com

Author Designation
[1]Associate Professor
[2-4]Assistant Professor
[5]Professor and HOD

Received: 30 January 2024
Accepted: 25 February 2024
Published: 24 March 2024

Citation: Kande Srinivasulu, Swarupa Rani Ragi, Shaik Raja Husne Kalam, Sucharitha Pathivada and B. V. Sai Prasad, 2024. A study of gastrointestinal stromal tumors in a tertiary care hospital. Res. J. Med. Sci., 18: 394-400, doi: 10.36478/makrjms.2024.4.394.400

A Study of Gastrointestinal Stromal Tumors in a Tertiary Care Hospital

[1]Kande Srinivasulu, [2]Swarupa Rani Ragi, [3]Shaik Raja Husne Kalam, [4]Sucharitha Pathivada and [5]B.V. Sai Prasad

[1,2,4]Department of Pathology ACSR Government Medical College, Nellore, AP, India
[3]Department of Pathology Government medical college, Kadapa, AP, India
[5]Department of Pathology, ACSR Government Medical College, Nellore, AP, India

ABSTRACT
The gastrointestinal stromal tumors (GISTs) are neoplasms of mesenchymal origin, they represent 0.3% of neoplasm in the digestive tube. They are defined by the expression of CD117, a tyrosine kinase receptor of the growth factor. Aim of this study is to know the clinical, pathological immunohistochemical characteristics of patients who attend the hospital of ACSR Government Medical College, Nellore during June 2021-May 2023. Fourty nine cases of GIST were found, in all cases, clinical data and the macroscopic aspect were studied microscopy and immunohistochemical characteristics were also checked. These cases are more frequent in women, in a proportion of 1.4:1, with an average age of 52-year-old. The treatment was full surgery, in 4 of them, a lymphadenectomy was done metastasis was found in one case. The average size of the tumors was 8 cm. The predominant histological pattern was fusocellular (81.5%), followed by epithelioid patterns (7.4%) and mixed (11.1%). The main locations were the stomach (48.1%), small intestine (40.7%), rectum (5.6%), omentum (3.7%) mesentery (1.9%). The malignant potential according to Fletcher's criteria were very low malignant potential (20.5%), low malignant potential (25%), intermediate potential (20.5%) high malignant potential (34.1%). All cases were positive for CD117.

INTRODUCTION

These are neoplasms made up of spindle cells and epithelioid and occasionally pleomorphic cells, which originate from interstitial cells of Cajal (ICC), with mutations in the receptor tyrosine kinase genes, which distinguish them from other tumors. In the decades from 30-50 of the 20th century, these tumors were classified as leiomyomas or leiomyosarcomas and tumors with epithelioid features were designated as leiomyoblastomas or epithelioid leiomyosarcomas. Dudley cols in 1942 and Rabinovich *et al*. in 1949 considered that these neoplasms had a benign evolution. In counterpart France and Brenes in 1950, as well as Martin in 1960, they saw that some of these tumors were malignant and also suggest their myoid nature[1]. In the decade from 60-70, electron microscopy (EM) showed the absence of muscle differentiation. The term gastrointestinal stromal tumor (GIST) was introduced by Mazur and Clark[2] in 1983, working with immunohistochemistry (IHC) and ME techniques, determining that they did not have smooth muscle cell characteristics, whereas GIST was occasionally protein positive. S-100 proposes a Schwannian origin from the myenteric plexus. In 1984, Herrera *et al*[3]. confirmed the neural nature of an intestinal malignancy by calling it plexosarcoma and because it coincided with a publication of a similar tumor with neuroendocrine differentiation by Walker and Dvorak these tumors were classified within the GIST, but considering a possible neuroendocrine differentiation[1].

In 1987, Barker and Rudolfe[4] succeeded in cloning the c-kit, using somatic human-mouse hybrid cells, locating the gene on chromosome 4. 2 years later, d'Auriol *et al*[5]. located the gene in the 4q11-q12 region. In 1990, the mesenchymal nature of the tumor was confirmed by IHC, given that between 60% and 70% were positive for CD34 (hematopoiesis progenitor cell antigen) this is being the first relatively specific marker of the GIST. Kindblom *et al*[6]. argued that the GIST was related to the ICC, the myenteric plexus they form a network located in the plexus of Auerbach, regulating the communication between neurons and muscle fibers act as a pacemaker controlling peristalsis, muscle contraction possibly as mediators of neurotransmitters[7]. Histogeneti cally, ICC has a mesenchymal origin they differ from an intestinal precursor cell which also gives rise to smooth muscle cells. The expression of c-kit proto-oncogene and the precursor cell factor receptor would be necessary for the proliferation and differentiation of the precursor cells toward ICC[8]. The absence of neuroendocrine differentiation of ICC, evidenced by EM, excludes that these cells have a bifunctional, neural muscular capacity[9]. Kitamura *et al*[10]. discovered the increased function by mutation of the c-kit proto-oncogene and over-expression of CD117. Later, Lasota *et al*[11]. demonstrated that c-kit mutations and positivity for c-kit occurred only in GIST. In addition, the interaction between c-kit and its ligand factor precursor cells (stem cell factor) that binds to the intracellular receptor is vital for cell survival, proliferation differentiation.

Heinrich *et al*[12]. reported that the possibility of a second receptor involved in the pathogenesis of GIST was raised, especially in those lacking mutations in c-kit found a second in the platelet-dependent epidermal growth factor alpha (PDGFRa) receptor. In 2001, Joensuu *et al*[13]. described the first case of GIST, treated with imatinib, designed for the treatment of chronic myeloid leukemia, but which can act on proteins with tyrosine kinase activity, such as c-kit receptors and PDGFRa receptors. The aim of this study was to describe the clinical pathological aspects and IHC of the neoplasms diagnosed as GIST in ACSR Government Medical College hospital, Nellore during June 2021-May 2023 period .

MATERIALS AND METHODS

Review of cases of mesenchymal tumors of the digestive system, during the period from June 2021 to May 2023 which had lamellae and paraffin blocks, to make additional histological sections if required; similarly, they had studies of IHC, for CD117, anti-smooth muscle actin (AAML) S-100 protein (PS-100). From the microscopic study and IHC of the mesenchymal tumors, 49 were found which fulfilled the GIST criteria. The microscopic study also allowed obtaining data regarding histological pattern, number of mitosis, histological type, state of the borders, necrosis and differentiation. From the anatomopathological report, data were obtained on the clinical diagnosis, age and sex of the patient size and location of the tumor with all this information, an overview of the risk factors was formed, which determine the malignant behavior of these neoplasms.

RESULTS AND DISCUSSIONS

In 49 cases of GIST. Clinical diagnosis of tumor found in 25 cases (51%), of probable GIST in 20 (41 %), gastric Ca in 3 cases (6%), perforation of 1 case (2%) acute abdomen in 1 case (2%). The average age of the group was 52 years, with limits between 24 years the least and 82 years the highest. Regarding sex, 25 cases (54%) were women and 24 (47%) were men. Regarding localization, 26 cases (48%) were in the stomach, 5 (9%) in the duodenum, 8 (15%) in the jejunum, 9 cases (17%) in the ileum, 3 (6%) in the rectum, 2 (4%) in omentum 1 (2%) in the mesentery. When correlating the location with the age group, it was found that, in 22cases (44%), it was between 21 and 50 year old, 24 cases (46%) between 51 and 75 year old 5 (9 %%) >75 year old. Table 1 The size of the tumors could only

be obtained in 44 of the 54 cases and ranged from 1 cm the least to 30 cm the greatest, with an average of 8 cm, nevertheless, tumors of 1 cm only there were 1 (2%) and tumors >10 cm. 13 (30%) (Table 2). (Fig 1) showing the the macroscopic appearance of gastrointestinal stromal tumors (GIST). Ten cases were biopsies or cases of revision of lamellae, therefore there is no data on the size of the tumor. Regarding the mitosis index for 50 high-gain fields (CGA, by its abbreviation in Spanish), we found <2.32 cases (59%); >2 <5 mitosis for 50 CGA, 9 (17%), >5 <10 mitosis for 50 CGA, 6 (11%) and >10 mitosis for 50 CGA, 7 (13%) (Table 3). Regarding the histological type, the fusiform variety (Fig. 2) was present in 42 cases (82%), the epithelioid form in 3 cases (6%) mixed type (Fig. 3) in 5 cases (10%). Regarding the borders, 39 cases (78%) had rounded edges and 10 (21%) had infiltrating edges. In the cases with infiltrating edges, 5 tumors were gastric, 2 of jejunum, 1 of ileum 1 of mesentery. Two more cases corresponded to biopsies it was not possible to determine the characteristics of the infiltration.

In the IHC study of the 49 cases, all were positive for CD117 (Fig. 4) and the reactions for AAML and PS-100 were negative. In two cases, lymphadenectomy was performed in one case of high-grade jejunum GIST, there was metastasis to a regional lymph node. GISTs are heterogeneous in terms of molecular signature and differ in their natural history and management . This analysis is the study from India elaborating on the diversity appreciated in previous datasets across the world. GIST is neoplasms of mesenchymal origin, constituting a group of lesions characterized immunohistochemically by expressing in >90% of cases the transmembrane receptor derived from the stem cell, with activity on the receptor tyrosine kinase known as CD117 or c-kit. The incidence of GIST is 10-20 cases per 10,00,000 inhabitants. It occurs around 50 years with an average of 55-65 years. In our cases, the youngest was 22-year-old and the oldest 81-year-old, with an average of 54 years, which agrees with that reported in the literature. It is most commonly located in the stomach (50%-60%), followed by the small intestine (20%), colon and rectum (10%) esophagus (<5%). Occasionally, they are located in omentum, mesentery, retroperitoneum, pancreas gallbladder[14]. In our tumors, it was in descending order: the stomach (48.1%), small intestine (40.8%), rectum (5.6%), omentum (3.7%) mesentery (1.9%).

The symptoms depend on the size of the GIST; thus, gastric tumors present with abdominal pain or hemorrhage. In GIST of the small intestine are pain, hemorrhage or signs of obstruction[15]. In the Mexican population, Medina *et al*[16]. found that the main symptoms are abdominal pain (56%), digestive tract hemorrhage (38.7%) anemia (34.1%), vomiting (16.1%), abdominal distension (12.9%), weight loss (12.9%)

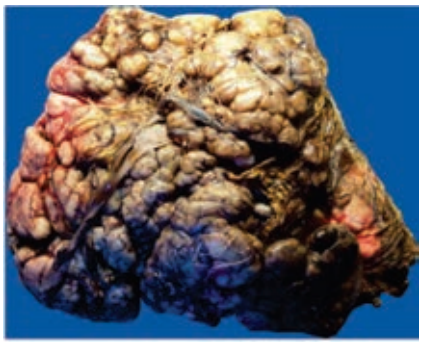

Fig. 1: Gross morphology: the macroscopic appearance of gastrointestinal stromal tumors (GIST)

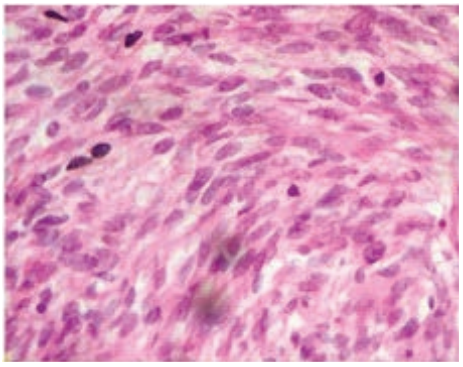

Fig. 2: Microscopic image of gastrointestinal stromal tumor with a fusocellular pattern and a mitosis figure in the central part of the HE ×200 image

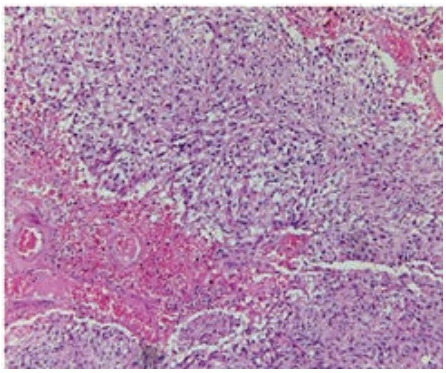

Fig. 3: Microphotography showing a mixed image of gastrointestinal stromal tumor, a fusocellular pattern and an epithelioid HE ×400

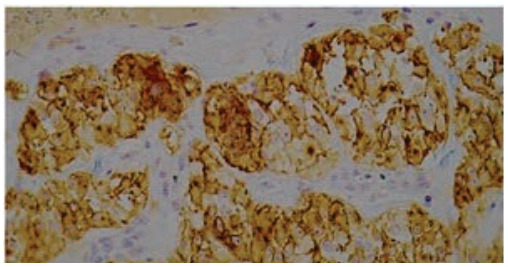

Fig. 4: Positive immunohistochemistry for CD117 in an epithelioid-type gastrointestinal stromal tumor

Table 1: Age and location of tumors

Age groups	Locations						
	Stomach	Duodenum	Jejunum	Ilium	Rectum	Epiplon	Mesentery
<20 years							
21-50 years	8	4	4	5	1		
51-75 years	13	1	4	3	1	2	
>75 years	3			1	1		1
Total	26	5	8	9	3	2	1

Table 2 Size and staging of neoplasias in 42

Cases				
Location	<2 cm	2 cm <5 cm	>5 cm <10 cm	>10 cm
	T1	T2	T3	T4
Stomach		5	6	6
Duodenun		4		
Yeyunum	1		1	1
Ilium	1	2	3	5
Rectum	1		1	
Epiplón		2	2	
Mesentery				1
Total	3 (7%)	13 (32%)	13 (32%)	13(32%)

Table 3: Index of mythosis for 50 fields of great increase

Location	<2 to 2	2 to <5	>5 to <10	>10
Stomach	18	3	2	3
Duodenun	5			
Yeyunum	5	1	1	1
Ilium	3	3	2	1
Rectum	1	1	1	
Epiplón		1		1
Mesentery				1
Total	32 (59.3%)	9 (16.7%)	6 (11.1%)	7(12.9%

postprandial fullness (6.5%). The reported size of the tumors is between 0.3 cm the smallest and 38 cm the oldest. We found that the largest tumor was 30 cm and the smaller than 1 cm with an average of 8 cm. As for gender, they occur more frequently in men; however, in our casuistry, the woman was mostly affected in a 1.2:1 ratio.

Within the organ affected by the tumor, it may have an intramural, submucosal, suberosa location. When cut the surface is of variable color depending on the degree of hemorrhage, its color may be grayish, whitish, reddish, or brownish. They are usually fleshy looking solids, with cystic or necrotic areas[17]. Of our cases, 13 had necrosis, 10 of which measured >10 cm and 3 <10 cm. Histologically, GIST presents different cell morphologies: spindle cells (77%), epithelioid cells (8%) the mixed form (15%)[14]. The proportion found in our casuistry was spindle cells (81.5%), cell epithelioid (7.4%) mixed variety (11.1%). Fusocellular tumors are composed of cells with a fusiform nucleus, scarce eosinophilic or pale cytoplasm a fibrillar aspect. They grow without a defined pattern, fusocellular, verticillate, storiform, or palisading, like peripheral nerve tumors. In the cases of this report, we found two with neurofibroma-like pattern, one with a storiform pattern the other with cellular pleomorphism. Epithelioid tumors have extensive, eosinophilic, oncocytic, or clear cytoplasm, they can present perinuclear glycogen the histological pattern can be organoid, trabecular, alveolar or insular. Mixed tumors show transition between the epithelioid and spindle cell fields. Between 80% and 100% of GISTs show mutations in one or both tyrosine kinase receptors, which are the kit gene and PDGFRa. Tyrosine kinase is detectable by IHC with CD117 antigen, which produces a strong and diffuse staining cytoplasmic. Our cases were all positive (54/54) to CD117.

A small proportion of GIST is negative for CD117, in this situation, a marker that is independent of the kit or PDGFRa mutations has been described it is a protein of the calcium and chlorine regulatory channel called DOG 1 (Anoctamin 1). It is an antibody with greater sensitivity to CD117 but with relative specificity, since it has been positive in several carcinomas and some sarcomas[18,19]. Negative cases of DOG and kit can be diagnosed with the protein kinase theta, which is expressed in all GISTs regardless of their mutational status[20]. The mutation of the kit gene is an early event in GIST, with the mutation of exon 11 being the most common. Secondary mutations are also found in exons[13,14,17] or[18]. Studies of mutations are necessary when GISTs do not react to CD117[19,21].

Approximately 10% of GISTs do not detect mutations in c-kit or PDGFRa and it is called wild-type (WT); in spite of not detecting these mutations, the tyrosine kinase is activated. In the GIST of the WT variety, several oncogenic mutations have been described, such as BRAF, which encodes a serine/threonine protein kinase, which plays an important role in the regulation of the cell cycle and oncogenic modification of cellular responses to growth signals via Mitogen-activated protein kinase[22]. Between 2005 and 2006, Miettinen and Lasota[23] added the location parameter to the Fletcher[24]

classification, finding that the intestinal GIST of the jejunum and ileum with a similar size and mitosis activity to the gastric ones are more aggressive. In our cases, there are few examples and we do not have data on the evolution after surgery, of the GIST reported here, to reach these conclusions (Tables 2 and 3). However, in Mexico, Medrano *et al*[25]. found, in a study of 66 cases of GIST, that the variable that showed statistical significance in survival was localization in intestinal lesions, the survival was lower.

In 2010, the International Union Against Cancer (UICC)[26] presented a new classification TNM: T1 tumor <2 cm, T2 tumor >2 cm >5 cm, T3 tumor >5 cm <10 cm T4 tumor >10 cm. According to this classification, our cases behaved as follows: T1, 3 cases (6.8%); T2, 14 cases (31.8%), T3, 14 cases (31.8%) and T4, 13 cases (29.6%) (Table 2). The same UICC ensures the histological grade according to the number of mitoses by 50 CGA: low grade, when the mitosis count is <5 per 50 CGA high grade, when the count is >5 mitosis per 50 CGA. Regarding the histological grade, our cases presented the following behavior: low grade 41 cases (75.9%) and high grade 13 cases (24.1%) (Table 3). The prognostic factors to be considered in the GIST are several and include localization tumors that originate in the small intestine and rectum have a worse prognosis[24]. Peritoneal or hepatic metastases are of worse prognosis. Small tumors, incidental in the serosa, have a favorable course[27]. Other factors are tumor size, number of mitoses per 50 CGA, spontaneous or iatrogenic rupture of the tumor, affected surgical margins, necrosis, nuclear atypia, muscle, or mucosal invasion[28]. Ki 67 >10% is associated with poor prognosis[31]. In the Mexican population, Martínez *et al*[29]. found that the expression of p53 is greater in lesions of the intestine than in the stomach. Ki 67 >10% is associated with poor prognosis[30].

The treatment of choice is complete surgical resection, lymphadenectomy is not necessary since lymphatic dissemination is unlikely[31]. Lymphadenectomy was performed in 4 of our cases one of them identified metastases in 1 lymph node. GIST is resistant to radio- and chemo-therapy and has recurrence or metastasis in 20%-50% of patients with resectable tumors, nevertheless, imatinib, in the postoperative period, has managed to improve recurrence-free survival. With imatinib, the best results are given when there is a mutation of exon 11 and greater resistance with mutations of exon 9 and the PDGFRa gene. When there is resistance, second-generation chemotherapy drugs such as sunitinib or regorafenib can be used[32]. The application of micro-RNA (myRNA) in the treatment of GIST is under the study they are agents that can provoke an immune response[17]. The miRNA, which is small single-stranded RNA encoding 19-22 nucleotides, has the ability to regulate gene expression by translational inhibition or degradation of messenger RNA[33].

CONCLUSIONS

In a recent study it showed that prevalence of mutation testing among patients with GIST continues to be low at the level of primary care centres. Mutational analysis testing helped us personalise treatment patterns in a significant proportion of patients attending our GIST clinic. This highlights the importance of mutational analysis for therapeutic decision-making, impacting the prognosis of patients as well as the family. Novel TKIs could be incorporated into our armamentarium of management of GIST. The geographical variations can be understood better if dedicated support groups and collaborations work synchronously, as entities continue to be 'rare' if active testing is lackinga[34]. Early diagnosis and radical resection of the primary lesion are the most appropriate treatment for healing . Main treatment used was surgical resection however do not have data on the subsequent evolution of patients.

REFERENCES

1. Herrera, G., 2003. Historical perspective: A jurney through evolution of classification schemes, in US-CAP Companion Meeting Syllabus.
2. Mazur, M.T. and H.B. Clark, 1983. Gastric stromal tumors reappraisal of histogenesis. The Am. J. Surg. Pathol., 7: 507-520.
3. Herrera, G.A., H.P.D. Moraes, W.E. Grizzle and S.G. Han, 1984. Malignant small bowel neoplasm of enteric plexus derivation (plexosarcoma). Light and electron microscopic study confirming the origin of the neoplasm. Dig. Dis. Sci., 29: 275-284.
4. Barker, P.E. and F.H. Rudolfe, 1985. Human c-kit oncogen of human chromosome 4. Am. J. Genet., Vol. 37.
5. d'Auriol, L., M.G. Mattei, C. Andre and F. Galibert, 1988. Localization of the human c-kit protooncogene on the q11-q12 region of chromosome 4. Hum. Genet., 78: 374-376.
6. Kindblom, L.G., H.E. Remotti, F. Aldenborg and J.M. Meis-Kindblom, 1998. Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am. J. Pathol., 152: 1259-1269.
7. Min, K.W. and I.S. Seo, 2003. Intestitial cells of Cajal in the human small intestine: Immunochemical and ultrastructural study. Ultrastruct. Pathol., 27: 67-78.
8. Maeda, H, A. Yamagata, S. Nishikawa, K. Yoshinaga, S. Kobayashi and K. Nishi, S. Nishikawa, 1992. Requirement of c-kit for development of intestinal pacemaker system. Development, 116: 369-75.

9. Wang, L., H. Vargas and S.W. French, 2000. Cellular origin of gastrointestinal stromal tumors. Arch. Pathol. Lab. Med., 124: 1471-1475.
10. Kitamura, Y., S. Hirota and T. Nishida, 2003. Gastrointestinal stromal tumors (GIST): A model for molecule-based diagnosis and treatment of solid tumors. Cancer Sci., 94: 315-320.
11. Lasota, J., M. Jasinski, M. Sarlomo-Rikala and M. Miettinen, 1999. Mutations in exon 11 of c-kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Am. J. Pathol., 154: 53-60.
12. Michael, C.H., L.C. Christopher, A. Duensing, L. McGreevey and J.C. Chang *et al.* 2003. PDGFRA activating mutations in gastrointestinal stromal tumors. Science, 299: 708-710.
13. Joensuu, H., P.J. Roberts, M. Sarlomo-Rikala, L.C. Andersson and P. Tervahartiala *et al.,* 2001. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N. Engl. J. Med., 344: 1052-1056.
14. Miettinen, M. and J. Lasota, 2001. Gastrointestinal stromal tumors-definition, clinical, histological, immunohistochemical and molecular genetic features and differential diagnosis. Virchows Arch., 438: 1-12.
15. Ueyama, T., K.J. Guo, H. Hashimoto, Y. Daimaru and M. Enjoji, 1992. A clinicopathologic and immunohistochemical study of gastrointestinal stromal tumors. Cancer, 69: 947-955.
16. Medina, F.H., J.J.Aguilar and Z.J. Medina, 2009. Tumores del estroma gastrointestinal. Analisis de factores pronósticos en un grupo de pacientes mexicanos. Gac. Med. Mex., 146: 91-96.
17. Miettinen, M. and J. Lasota, 2006. Gastrointestinal stromal tumors: Review on morphology, molecular pathology, prognosis and differential diagnosis. Arch. Pathol. Lab. Med., 130: 1466-1478.
18. González-Cámpora, R., R.R. Asensio, A. Vallejo-Benítez, D. Marcilla-Plaza and M. Biscuola *et al.,* 2017. Tumores del estroma gastrointestinal: Breve actualización y consenso de la seap-seom sobre diagnóstico patológico y molecular. Rev. Esp. Patol., 50: 89-99.
19. Quiroga, I.B., P.T. Togores, M.A.S. García, J.M.P. Casajús, C.G. Ortega, N.R. Dawid and A.S. Muñoz, 2013. Tumores del estroma gastrointestinal (GIST): Serie del hospital central de la defensa gómez ulla. Sanidad Militar, 69: 173-181.
20. Duensing, A., N.E. Joseph, F. Medeiros, F. Smith and J.L. Hornick *et al.,* 2004. Protein Kinase C theta (PKCtheta) expression and constitutive activation in gastrointestinal stromal tumors (GISTs). Cancer Res., 64: 5127-5131.
21. Blay, J.Y., 2009. New paradigms in gastrointestinal stromal tumour management. Ann. Oncol., 20: 18-24.
22. Agaram, N.P., G.C. Wong, T. Guo, R.G. Maki and S. Singer *et al.,* 2008. Novel v600e braf mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosomes Cancer, 47: 853-859.
23. Miettinen, M., J.F. Fetsch, L.H. Sobin and J. Lasota, 2006. Gastrointestinal stromal tumors in patients with neurofibromatosis 1. Am. J. Surg. Pathol., 30: 90-96.
24. Fletcher, C.D.M., J.J. Berman, C. Corless, F. Gorstein and J. Lasota et al., 2002. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum. Pathol., 33: 459-465.
25. Guzmán, R.M., N.K.M. Bautista, J.R. Silverio and G.G. Ávila, 2015. Factores pronósticos de recurrenciay supervivencia en tumores del estroma gastrointestinal. experiencia del hospital de oncología centro médico nacional siglo xxi, instituto Mexicano del seguro social. Elsevier BV, Gaceta Mexicana Oncología, 14: 259-267.
26. Sobin, L.H., M.K. Gospodarowicz, C.H. Wittekind, 2010. TNM Classification of Malignant Tumours. 7th Edn., Wiley-Blackwell,, Chichester, West Sussex, UK., ISBN-13: 9781444332414, Pages: 309.
27. DeMatteo, R.P., J.J. Lewis, D. Leung, S.S. Mudan, J.M. Woodruff and M.F. Brennan, 2000. Two hundred gastrointestinal stromal tumors. Ann. Surg., 231: 51-58.
28. Newman, P.L., C. Wadden and C.D.M. Fletcher, 1991. Gastrointestinal stromal tumours: Correlation of immunophenotype with clinicopathological features. J. Pathol., 164: 107-117.
29. Martínez-Consuegra, N., J. Baquera-Heredia, B. León-Bojorge, A. Padilla-Rodríguez and H.C. Ortiz, 2006. Expresión de p53 y Bcl-2 como marcadores pronósticos y de localización anatómica en tumores del estroma gastrointestinal (GIST). Estudio clínico-patológico e inmunohistoquímico de 19 casos. Rev. Gastroenterol. Mex., 71: 269-278.
30. Liang, Y.M., 2012. Prognostic significance of pten, ki-67 and cd44s expression patterns in gastrointestinal stromal tumors. World J. Gastroenterol., 18: 1664-1671.
31. Koelz, M., J. Lense, F. Wrba, M. Scheffler, H.P. Dienes and M. Odenthal, 2011. Down-regulation of miR-221 and miR-222 correlates with pronounced Kit expression in gastrointestinal stromal tumors. Int. J. Oncol., 38: 503-511.
32. Duensing, S. and A. Duensing, 2010. Targeted therapies of gastrointestinal stromal tumors (GIST)-the next frontiers. Biochem. Pharmacol., 80: 575-583.

33. Haller, F., A. von Heydebreck, J.D. Zhang, B. Gunawan and C. Langer *et al.,* 2009. Localization- and mutation-dependent microrna (miRNA) expression signatures in gastrointestinal stromal tumours (GISTs), with a cluster of co-expressed miRNAs located at 14q32.31. J. Pathol., 220: 71-86.

34. Baa, A.K., S. Rastogi, S. Fernandes, S. Shrivastava and R. Yadav *et al.,* 2023. Insights into the medical management of gastrointestinal stromal tumours: Lessons learnt from a dedicated gastrointestinal stromal tumour clinic in north India. Ecancermedicalscience, Vol. 17 10.3332/ecancer.2023.1497