



An insight into gastro intestinal stromal tumors: A review article

P.Manimekhala¹, L Aruna², O Sirisha³, V.Vijaya Sreedhar⁴

1- Associate professor 2- Assistant professor 3- Senior Resident 4- Professor & HOD. Upgraded Department of Pathology, Osmania General Hospital, Hyderabad

Corresponding Address: Dr.P.Manimekhala, Associate professor, Upgraded Department of Pathology, Osmania General Hospital, Hyderabad. Email: manimekhalarao@gmail.com

Abstract:

Gastrointestinal stromal tumours account for less than 1% of all gastrointestinal tumours. Gastrointestinal stromal tumours (GISTs) are a subset of mesenchymal neoplasms of the gastrointestinal tract. They are the most common mesenchymal neoplasms of small intestine. They have been the subject of great interest over the past decade as a much deeper understanding of the underlying molecular biology of this tumour type which expresses CD 117 (KIT) – a proto oncogene protein which led to the therapeutic options principally the use of tyrosine kinase inhibitors. Recent times have witnessed a significant change in the molecular aspects and Immunohisto chemistry of GIST. They play an important role in the context of diagnostic, prognostic and therapeutic management. This review article is an attempt to list out these developments.

Key words: Gastrointestinal stromal tumour; tyrosine kinase; CD117; IHC; PDGFRA

Introduction:

The term stromal tumor was first introduced by Mazur and Clark in 1983 to define a group of gastric mesenchymal tumors that were not clearly differentiated by immunohistochemistry and ultrastructure and that were previously thought to be derived from smooth muscle of the gastrointestinal wall. Gastrointestinal stromal tumour is now defined as specific kit expressing and KIT signaling driven mesenchymal tumours of the gastrointestinal tract¹. These neoplasms are immunoreactive for CD117 which is a polyclonal antibody that recognises the type III tyrosine kinase KIT, which in turn is encoded by protooncogene CKIT. The identification and treatment of GIST has become more important after introduction of targeted treatment with KIT tyrosine kinase inhibitor Imatinib mesylate, ST1571 commercially known as Gleevec (Novartis Pharma Basel, Switzerland).

Histogenesis of GISTs: GISTs are KIT positive spindle cell, epithelioid or rarely pleomorphic mesenchymal tumours with characteristic histologic features and occurring anywhere in the GI tract or abdomen. By this definition, a large majority of GI mesenchymal tumours are GISTs. Previously GIST comprised a great majority of tumours formerly

diagnosed as leiomyomas, leiomyosarcomas, leiomyoblastomas [1,2]. Gastrointestinal autonomic nerve tumours (GANTs) are now understood as ultrastructural variants of GIST based on their histological and immunohistochemical similarities.

Demography: Review of literature has not shown any association with geographic location, ethnicity, race or occupation. Adults between the 6th and 8th decade are primarily affected. However cases have been reported in all age groups including children [1,2]. GISTs are extremely rare in children and only a few isolated cases have been reported in literature [1,2]. However tumours classified as GISTs in infants most likely represent inflammatory myofibroblastic tumours [2], particularly in KIT negative tumours. In the study by Senthil Rajappa et al [1], the peak age of incidence was 50 years, a decade lower than the western counterparts and most of the GISTs were indolent in behavior. Most of the studies show no specific sex predominance but few have noted a male preponderance [2]. GISTs occur at every level of the tubular gut and may be located primarily in the omentum, mesentery and retroperitoneum [3]. Studies indicate that in the gastrointestinal tract, the most common location is stomach (70%) followed by small intestine (20-30%) [3], large intestine (10%),

esophagus(5%) and elsewhere(5%). Extra GI GISTs are often located in mesentery, omentum and retroperitoneum. However most often GISTs in extra gastrointestinal tract represent metastasis from a primary in the GI tract. In the Indian scenario, the study of GI+STs by Lakshmi VA etal [2] revealed equal incidence in stomach and small intestine. Most of GISTs were of high risk category implicating a late diagnosis in most of the cases. 70% of the patients are symptomatic while 20% are asymptomatic and 10% are detected at autopsy [3]. The symptoms and signs are not disease specific and hence 50% have metastases at the time of diagnosis [3,4]. Hematogenous metastases develop in the liver and rarely in bones and lungs [4,5]. Raremetastases to the peripheral soft tissues such as arm, axilla and abdominal wall have also been reported [4,5].

Small GISTs are typically detected incidentally during radiologic examination or surgery for unrelated conditions. The most common presentation is mass per abdomen or bleeding. Symptoms related to site include dysphagia in the esophagus, biliary obstruction around the ampulla of vater or even intussusception in the small bowel [4]. Most of the western studies have revealed bleeding from GI tract to be the commonest symptom which may be due to ulceration of the overlying mucosa followed by mass lesion which may present as fullness [4,5]. Few cases may go unnoticed as they are asymptomatic. Hence it is mandatory to thoroughly investigate if the upper and lower GI endoscopy are normal in a patient who presents with bleeding.

Cell of origin: The cell of origin was of much debate until recent times. Previously they were diagnosed as leiomyomas but after much research into it's histomorphology, electron microscopy, immunohistochemistry the cell of origin was proved to be the interstitial cell of cajal or their stem cell precursors located around the myenteric plexus and in the muscularis propria throughout the gastrointestinal tract [5]. They show a remarkable variability in their differentiation pathways namely either to smooth muscle cells or to neural cells or to cells exhibiting feature of both smooth muscle and neural cells which can be confirmed by electron microscopy.

Pathogenesis: Mutually exclusive mutations in CD 117(KIT) or Platelet derived growth factor alpha(PDGFR α) and tyrosine kinase receptor mutations are observed in more than 80% of GISTs and are central to the pathogenesis of sporadic GIST [6]. These mutations are somatic and are present only in tumour tissue whereas similar constitutional mutations are present in all cells of the body and are inheritable in familial conditions. CD117 and

PDGFRA may be negative due to the presence of activating mutations of the gene. In such cases, DOG1 plays an important role in the diagnosis of GISTs.

C KIT protein and GIST connection: C KIT is a transmembrane growth factor receptor for a stem cell factor and is expressed strongly in hematopoietic stem cells i.e melanocytes, mast cells, germ cells and Interstitial cells of Cajal(ICC) [7]. Activating mutations of C KIT and PDGFRA permit the phosphorylation of the receptor tyrosine kinase perpetuating the receptor initiated signal and causing activation of the down stream effectors. The end result is an increase in cellular proliferation and decrease in apoptosis leading to neoplasia [8]. Four different regions of C KIT have been found to be mutated in sporadic GISTs – Exon 11, Exon 9, Exon 13 and Exon 17. Except Exon 17 mutations, all the other mutations are sensitive to imatinib therapy [9]. Three regions of PDGFRA are mutated in sporadic GISTs – Exon 18, Exon 12 and Exon 14. PDGFRA mutations are more commonly associated with gastric GISTs and show predilection for epithelioid morphology [10,11].

Familial GISTs [12]: Germline mutations in C KIT and PDGFRA have been documented which are inherited in autosomal dominant pattern. The familial conditions associated with GIST are : Carney triad [12].(Pulmonary chondroma, Paraganglioma and GIST), Carney stratakis syndrome [12] (Multiple GISTs), Neurofibromatosis – 1 [13].

Pediatric GISTs: Being extremely rare, they usually present during the second decade of life with a marked female predominance. They are most commonly located in the stomach and have an epithelioid morphology. The presence of multiple tumour foci is another distinctive feature in pediatric GISTs. They rarely have KIT/PDGFR α mutations [14]. Additionally, comparative genomic hybridization studies have shown that most pediatric GISTs that lack KIT or PDGFRA mutations have minimal, large scale chromosomal changes compared with adult GISTs. For risk stratification and prognosis, the system used in adults does not appear to be useful in pediatric GISTs. Although many patients may develop recurrence or metastasis, in general, pediatric GISTs follow an indolent course.

Pathology: They have a wide clinico-pathologic spectrum ranging from minute incidental nodules to large tumours. Grossly, majority of GISTs form solid, well circumscribed firm mass., Pedunculated, externally attached, exophytic mass or a sessile, small intraluminal polyp and sometimes as an intramural mass. Different gross patterns can be observed. They include hemispherical submucosal or serosal nodules, large cystic tumors, pseudodiverticles, and rarely,

plaque-like masses. Small to medium-sized gastric GIST typically form a well-delineated spherical or hemispherical mass beneath mucosa pushed into the lumen to form a smooth-contoured elevation. Some small intestinal examples form asymmetric dumbbell-shaped masses with a smaller intraluminal and a larger externally bulging components.

Large GISTs in the stomach and intestines often form an externally bulging masses, whose extensive extra-GI component can mask the tumor origin from the stomach or intestines. Duodenal GISTs involving the periampullary region can extend to the pancreatic head region immediately adjacent to external wall of duodenum and clinically and radiologically simulate a primary pancreatic tumor. Small GISTs of the colon rectum can bulge inward forming an intraluminal polyp. Larger rectal GIST often grow into the rectovaginal septum in women and are attached to the prostate in men, sometimes clinically simulating a prostatic tumor

The surface appears granular and rubbery. They are circumscribed and unencapsulated. The surface is characteristically grey in colour. Malignant GISTs tend to be white in colour because of increased cellularity and are more likely to show areas of hemorrhage, necrosis and myxoid degeneration. Preoperative radiologic studies by CT scan or MRI are very helpful in determining the tumour configuration and its extension and relation with adjacent organs [14]. Extra gastrointestinal GISTs commonly present as spherical nodules with smooth surfaces and in rare instances, innumerable pea-sized nodules are studded throughout the peritoneum [14].

Histopathology: The histopathology of GISTs varies according to the site. In the western literature [15], most of them have a combined morphology-spindle and epithelioid cell pattern followed by spindle cell and epithelioid pattern. the cell borders vary from distinct to syncytial pattern; the former is more common in epithelioid pattern while the latter tends to predominate in spindle cell pattern. The nuclei typically have an evenly dispersed chromatin but some tumours contain prominent nucleoli in varying numbers of cells. mitotic counts vary largely in number from 0-20 per 50 high power fields. High mitotic counts per se are rare in GISTs and is one of the most important histological predictors of malignancy.

Gastric GISTs [15]: They are composed of either spindle cells or epithelioid, the epithelioid variant is more common in gastric GISTs. Spindle cell GISTs may have a sclerosing, palisading vacuolated, hypercellular or sarcomatous patterns while epithelioid GISTs show sclerosing, dyscohesive, hypercellular

and sarcomatous patterns. Perinuclear vacuolization is a common feature of gastric GISTs and is sometimes common throughout the tumour [15]. Epithelioid GISTs in stomach correspond to previously designated leiomyoblastomas of the stomach. They are typically composed of polygonal cells with round nuclei and ample cytoplasm varying from eosinophilic to amphophilic and clear with focal nuclear pleomorphism.

Small intestinal GISTs: These tumours are composed of spindle cells and nearly half of them contain microscopically distinctive, round, oval or elongated eosinophilic and PAS positive aggregates of extracellular collagen fibres – Skenoid fibres – have been found as a statistically favorable prognostic factor [15]. If an epithelioid pattern is encountered in small intestinal GISTs there is a significant association with malignant potential.

GISTs in other sites: Most GISTs of sites other than stomach and small intestine have a spindle cell pattern and have the same cytological features as small intestinal GISTs.

Immunohistochemistry: GISTs are generally CD 117 positive and C KIT or PDGFRA mutation driven mesenchymal tumours of the gastrointestinal tract [16]. CD 117 positivity is seen in most cases of GIST (95%) regardless of its site and biologic behavior. Staining pattern may be cytoplasmic, membrane and paranuclear region (Golgi pattern). CD 117 is the best diagnostic marker, but 5-10% of GISTs are negative, in such cases DOG1 may play a role.

CD 117: It is an antibody specifically targeted against \KIT receptor. The best KIT antibodies currently available for formalin fixed and paraffin embedded tissue are polyclonal because monoclonal antibodies react inconsistently with GIST.. In GIST tumoral cells may show cytoplasmic, membrane and paranuclear pattern or a combination of the three. Staining intensity may be quite variable showing a diffuse, focal or patched distribution [17].

Paranuclear staining pattern: This staining pattern has been recognised as a KIT mutation marker and an indicator for treatment with imatinib [18]. The reason for this paranuclear staining pattern is that in GISTs with KIT mutations, protein maturation and targeting towards the cell are not carried out correctly, so it is confined to cytoplasmic vesicles [19].

CD117 negative GISTs: The frequency of CD 117 negative GISTs in literature varies between 5-10% according to selection criteria, yet is particularly high in the subset of GISTs with PDGFRA mutations and epithelioid phenotype [20].

CD34: Approximately 70-80% of GISTs are positive for CD34, the hematopoietic progenitor cell antigen

also expressed in endothelial cells, subsets of fibroblasts and many neoplasms related to these cell types. The frequency of CD34 positivity varies with site: GISTs of esophagus and rectum are nearly consistently positive while positivity at other sites is relatively inconsistent [20]. 30- 40% for SMA, 5% for S100 protein and 1-2% for Desmin or Keratin.

Platelet derived growth factor alpha(PDGFR α): In a normal digestive tract, PDGFR α immunoreactivity is present in ganglion cells, neural cells and schwann cells but not in ICC. In GISTs, PDGFR α expression can be nuclear, cytoplasmic or paranuclear pattern or a combination of the three. It has been observed that in KIT mutated tumours, the intensity of PDGFR α staining is lower than in those with mutated PDGFR α mutations. The lack of specificity, ubiquity and technical problems have pushed the marker into a second plane [21].

Protein kinase C theta: The association between PKC expression and GIST was identified in molecular studies of sarcomas [22]. PKC is involved in lymphocyte activation, in signal transduction of striated muscle and in neuronal differentiation. In GISTs, the staining pattern is cytoplasmic, diffuse and granular. The important consideration of PKC is that it is expressed in GISTs regardless of the mutational status [23]. whether there is a KIT mutation or a

PDGFR α mutation making it a specific marker in doubtful cases [24].

DOG1: Named as Discovered on GIST(DOG1), it encodes for the transmembrane protein - FLJ10261 located on chromosome 11 and is positive in normal interstitial cells of cajal [25]. In GISTs, the staining pattern varies from cytoplasmic to membranous with strong and diffuse intensity. DOG1 expression on GISTs seem not related to the presence of mutations as screening for mutation in most of the exons did not reveal any mutations. It's specificity is much greater than CD117. Taking into consideration it's high specificity and sensitivity, it should be added in to the IHC panel for evaluating GISTs.

Other markers in the panel of GISTs include IGF1R, S-100, Smooth muscle actin(SMA) which show variable positivity in GISTs and Desmin which shows Negativity in GISTs.

Differential diagnosis: GISTs show a variety of differentiation spectrum ranging from fully differentiated tumours with myxoid, neural or ganglionic plexus phenotype [26]. The differential diagnosis includes Leiomyoma, Schwannoma, Solitary fibrous tumor, Desmoid tumour, Inflammatory myofibroblastic tumour and inflammatory fibroid polyp. A confident diagnosis of GIST can be made based on a panel of immunohistochemistry.

Panel of immunohistochemistry of GISTs and other tumors considered into its differential diagnosis:

Histopathological Diagnosis	PANEL OF IMMUNOHISTOCHEMISTRY					
	C-KIT	Smooth muscle actin	Desmin	S100	CD34	Keratin
Tumor Type						
GIST	+++	+	-	-	+++	-
Leiomyoma	-	+++	+++	-	+ -	+ -
Leiomyosarcoma	-	+++	+ to +++	-	+	+
Schwannoma	-	-	-	+++	-	-
Fibromatosis	-	++	-	+	-	-
Carcinoma	-	+ to ++	-	-	-	+ to +++
Melanoma	+	-	-	+++	-	-

Prognostic factors [30]: Traditionally 3 key prognostic factors were taken into consideration i.e motitic rate > 5 per 50 HPF, size and site of the tumor .

Several studies have pointed out that besides traditional risk factors like tumor size, mitotic count and tumor location, CD 34 positivity and high KI-67

labeling index(>30%) have a worse prognosis than GISTs which show lesser values. Parallel to the controversy regarding their histogenetic derivation, the assessment of malignant potential in GIST remained a major controversial issue for decades ending up to now.

- Age: GISTs in children are clinically malignant.
- Site: Benign GISTs are more common in stomach. Malignant GISTs more common in small intestine.
- Probably Benign: Gastric tumors: Maximum diameter less than 5 cm, no more than 5 mitoses per 50 hpf. Intestinal tumors: Maximum diameter less than 2 cm, no more than 5 mitoses per 50 hpf.
- Uncertain or Low malignant potential :Intestinal tumours: Maximum diameter 2-5cm and no more than 5 mitoses per 50 hpf. Gastric tumours: Maximum diameter 5-10cm or no more than 5 mitoses per 50 hpf. Malignant: Gastric tumors: Maximum diameter over 10cm or more than 5 mitoses per 50hpf. Intestinal tumors: Maximum diameter over 5 cm or more than 5 mitoses per 50 hpf. Mitotic activity and tumor size: Mitosis > 5 per 50 HPF is a more powerful prognostic predictor than tumor size.
- Proliferative index: There is a good correlation between cell cycle regulatory proteins and prognosis. Ki67 analogue with > 10% of nuclear positivity showed an increased incidence of metastasis in few studies.
- Presence and type of KIT mutation [31]: This factor is important as a predictor of response to imatinib.

Risk stratification and clinical outcome [27]:

- **National Institute of Health(NIH) criteria/ Fletcher's criteria:** Tumour size and mitotic activity were used as sole parameters.

Risk category	Size(cm)	Mitotic index(50 hpf)
Very Low	<2	<5/50hpf
Low	2-5	<5/50hpf
Intermediate	<5	6-10/50hpf
	5-10	<5/50 hpf
	>5	>5/50 hpf
High	>10	Any index
	Any size	>10/50 hpf

Armed Forces Institute of Pathology (Miettinen's) criteria [28]: This is distinguished from NIH criteria by taking anatomic site into consideration and defines 8 prognostic subgroups taking size and mitotic activity into consideration.

Revised NIH consensus criteria [29]: In addition to size and mitotic count, nonradical resection of the

tumor and tumor rupture are regarded as factors associated with an adverse outcome.

Proposed UICC [29] (International union against cancer) system: The seventh edition of International union against cancer published at the beginning of 2010 included for the first time, a classification and staging system for GIST.

Management of localized and advanced disease:

Surgical resection with preservation of pseudocapsule is the primary therapy for localized disease [32]. In pre-imatinib era, patients with metastasis had a median survival of 18-24 months and responded poorly to all forms of chemotherapy.

Therapeutic implications of activating KIT mutations: Imatinib mesylate and sunitinib maleate are FDA approved 1st and 2nd line drugs in the treatment of GIST. nMutational analysis of primary tumours is not routinely recommended at this point of time. As per the National Consensus Cancer Network(NCCN) task force report, it may be performed in selected cases, such as to confirm the diagnosis of KIT positive tumours with atypical morphology/clinical features; in KIT negative tumours to differentiate GIST from other mesenchymal tumours.

Mechanisms of imatinib resistance [33]: 50 % of GISTs treated with imatinib mesylate demonstrate resistance within the first 2 years of treatment and often present as new nodules within the same lesion.

Conclusion:

During the past decade, basic and translation research advances have provided a detailed understanding of molecular pathogenesis of GISTs. We now however face challenges related to resistance to imatinib.

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Figures:

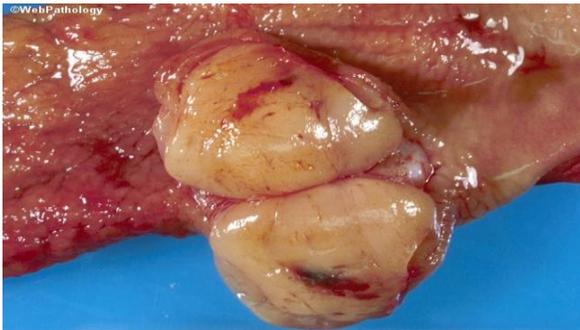


Figure 1: GIST in the stomach with a polypoid appearance



Figure 2: GIST in the small intestine with ulceration.



Figure 3: Cross section of GIST in the small intestine showing hemorrhages

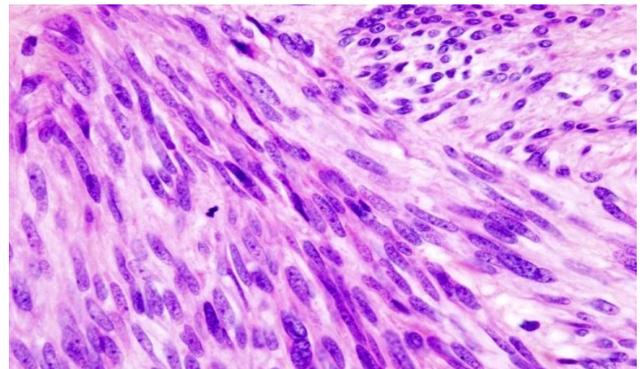


Figure 4: Photomicrograph of GIST showing spindle cell pattern, H&E – 400X

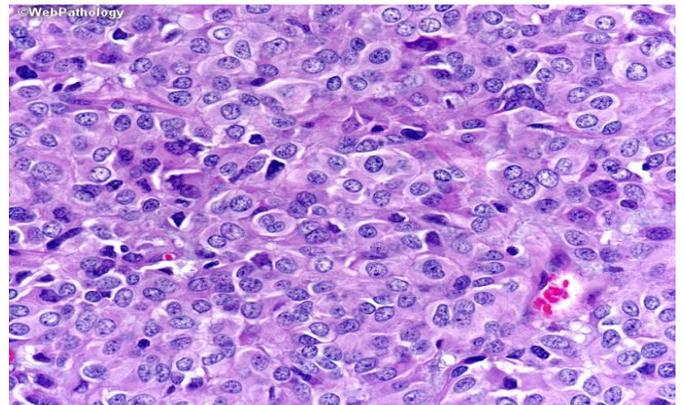


Figure5: Photomicrograph of GIST showing epithelioid pattern, H & E – 400X.

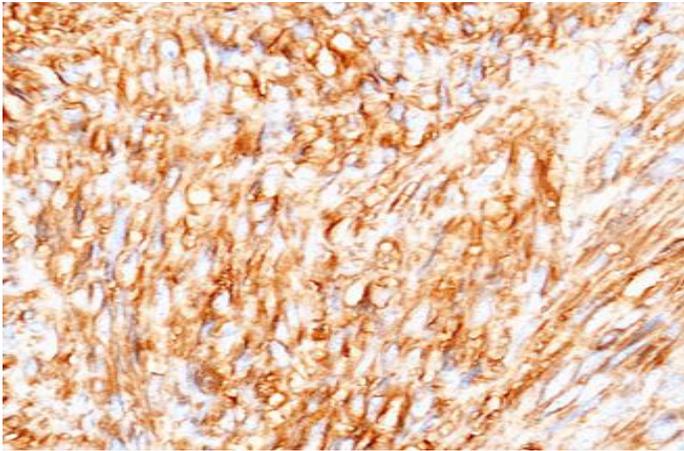


Figure6: Photomicrograph showing membranous positivity for CD117 in GIST, 400X

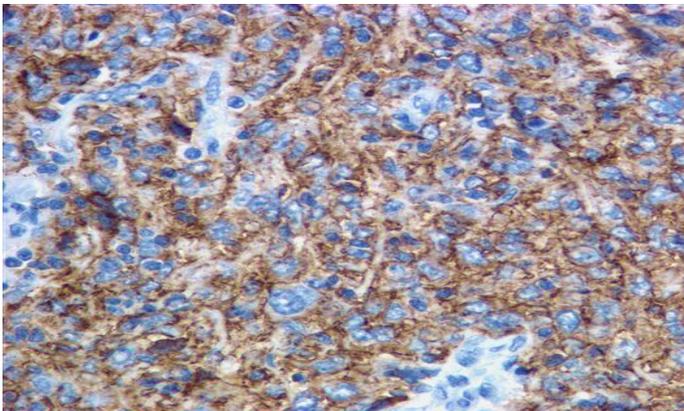


Figure7: Photomicrograph showing perinuclear positivity for CD117, 400X.

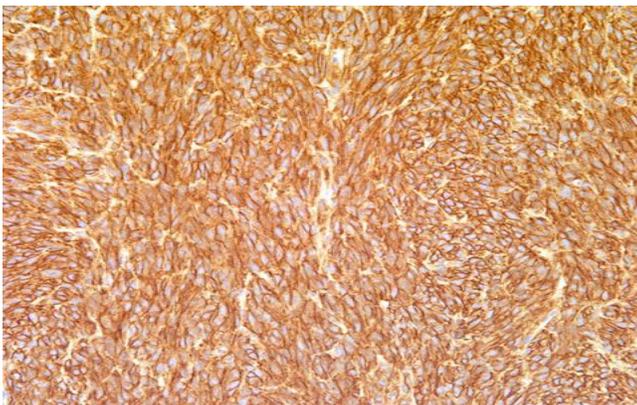


Figure8: Photomicrograph showing Cytoplasmic and membranous positivity for DOG1 in GIST

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