

Gastrointestinal Stromal Tumors: A Review

Farhat Abbas¹, Waseem Raja Dar^{2*}, Muzamil Latief², Summyia Farooq³, Manzoor Ahmad Parry², Peerzada Ziaulhaq⁴, Najeeb ullah Sofi² and Imtiyaz Dar²

¹Department of Pathology, Sher-i-kashmir Institute of Medical Sciences, Srinagar, India

²Department of Medicine, Sher-i-kashmir Institute of Medical Sciences, Srinagar, India

³Department of Pathology, Government Medical College, Srinagar, India

⁴Department of Radiology, Sher-i-kashmir Institute of Medical Sciences, Srinagar, India

Abstract

Introduction: Gastrointestinal tumors are rarest of the gastrointestinal tumors. They arise from interstitial cells of Cajal.

Objective: To review the current diagnosis and management of gastrointestinal tumors.

Material and methods: Pubmed was searched for 'gastrointestinal tumors' and relevant studies used for this review.

Conclusion: GISTs are one of the rarest tumors of GI tract. They are more common in middle aged males. Diagnosis involves radiology, histopathology and immunohistochemistry. Treatment is surgical and chemotherapy.

Keywords: Gastrointestinal stromal tumors; DOG 1; C-kit

Abbreviations: GIST: Gastrointestinal Stromal Tumors; PDGFRA: Platelet-Derived Growth Factor Receptor Alpha; NF1: Neurofibromatosis 1

Introduction

Gastrointestinal Stromal Tumors (GISTS) are one of the rare tumors of Gastrointestinal Tract (GI tract). These non-epithelial tumors are most common mesenchymal tumors of GI tract. Earlier believed to have a neuronal or smooth muscle origin are now however known to arise from special cells of GI tract called Interstitial Cells of Cajal (ICCS). ICCS are also known as pacemakers of GI tract as they give signals to tract muscles for contraction. These muscles on contraction propel the food through the tract [1,2]. An incidence of 1.5/100,000/year has been estimated for GIST [3]. The total number of cases in United States range from 4000 to 5000 (American Cancer Society).

Objectives

To review the current methods of diagnosis and management of GIST tumors and update the readers about recent research done on GISTS.

Material and Methods

A Pubmed search was made using the term 'gastrointestinal tumors' and relevant studies were used for collecting information regarding the current topic. The information was then presented under different subheadings for easier assimilation of the knowledge by the readers.

Discussion

GISTS are rare tumors accounting for less than 1% of all GI tumors. GISTS occur predominantly between 40-60 years of age. Median age of occurrence is around 60 years [4]. GISTS are more common in males. In pediatric age group GISTS have been found predominantly in girls. GI tract is the most common location contributing to more than 80% of GISTS. 50-70% of GI tract GISTS are located in stomach [5]. In GI tract these arise from the layer muscularis propria [6]. Other sites include retroperitoneal space, omentum and pelvis minor. Genetic syndromes have been associated with GISTS. These include familial

GIST, Neurofibromatosis type 1 and Carney Stratikis syndrome [7]. GISTS are associated with gene mutations. In 85% cases of GIST, tumor behavior is driven by kit mutations. C-kit receptor tyrosine kinase gene encodes for a transmembrane receptor. This is a growth factor receptor called stem cell factor. Mostly there is mutation in the C-kit gene itself; however some time there could be a defect in constitutive activity of C-kit enzyme pathway. Mutations occur in exons (9-17) of this gene. 10% GISTS have PDGFRA gene mutation, which is again a receptor tyrosine kinase gene. Mutations are seen in exons 12, 14 and 18 of PDGFRA gene. Rarely BRAF kinase mutations can be seen. The inhibition of this Tyrosine Kinases (TK) has revolutionized the therapy of these tumors as specific targeted treatment with TK inhibitors is now available [8-10]. The exquisite sensitivity of these tumors to the novel tyrosine kinase receptor inhibitors imatinib, mesylate and sunitinib has significantly changed management and prognosis of these tumors [11]. Some GISTS do not harbor C-kit or PDGFRA mutations, these carry wild type of mutations in all hot spots of C-kit and PDGFRA genes. Recent discoveries have highlighted mutations in though less common genes including NF1, SDH, CD34, nestin, SMA, caldesmon, calponin, vimentin and embryonic smooth muscle actin. 7 CD34 is ligand of tyrosine kinase encoded by C-kit. DOG1, a novel protein encoded by ANO1 (Anoctamin), is a calcium chloride regulated channel. It is also known as transmembrane protein 16A (TMEM 16A.12It). (DOG1) is a recently described mouse monoclonal antibody, and has more specificity and sensitivity compared with C-kit and CD34 for GISTS. It is expressed in C-kit positive as well as C-kit negative GIST [12].

***Corresponding author:** Waseem Raja Dar, Department of Medicine, Sher-i-kashmir Institute of Medical Sciences, Srinagar, India, Tel: +91-8261815278; E-mail: dwaseem.mw@gmail.com

Received February 09, 2016; **Accepted** February 25, 2016; **Published** February 27, 2016

Citation: Abbas F, Dar WR, Latief M, Farooq S, Parry MA, et al. (2016) Gastrointestinal Stromal Tumors: A Review. J Mol Imag Dynamic 6: 124. doi:10.4172/2155-9937.1000124

Copyright: © 2016 Abbas F, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Diagnosis

The dictum for GIST diagnosis involves clinical suspicion followed by radiological detection, histopathological correlation and finally immunohistochemical confirmation. Most GISTS are discovered when they are less than 4 cm in size and are asymptomatic. Symptomatic GISTS mostly present with GI bleeding, fullness, pain abdomen, palpable masses and obstructive features [13]. Metastasis is seen in liver in 65% of cases and in omentum in 25% of cases. Nodal metastases are rare in GIST [14]. Clinically age of the patient, family history and medical condition should be taken into consideration.

Imaging

On X-ray stomach GIST appears as a radioopaque shadow and intestinal gist shows an obstructive pattern. Small sized tumors have been accidentally discovered on endoscopy as submucosal process or masses. On barium studies GISTS appears to be like an intramural mass having smooth borders forming right or obtuse angles with adjacent bowel. Bull's eye and target lesion signs appear suggesting ulcerated mucosal surface. As the tumor grows it becomes an exophytic mass projecting into abdominal cavity. It can undergo necrosis and cavitation if it loses blood supply, eventually it will ulcerate and communicate with bowel lumen to form air fluid levels on barium studies [15,16].

Role of CT scan, MRI, PET scan

CT scans help to find the location, size and extent of spread of tumors. On contrast enhanced CT small tumors appear as homogenous intramural masses. Large tumors appear heterogenous with peripheral enhancement and low attenuation centre [17]. MRIs can also help to find the extension and spread of tumors. A useful diagnostic method is f-fluoro-deoxyglucose positron emission tomography [18]. It is used in rapid assessment of tumor spread, response to imatinib and development of imatinib resistance in patients [19]. In this method FDG sugar is injected into the blood and after half an hour the scan is done to see the radioactivity of the body [20].

Histopathology

Once a tumor is detected on imaging it's difficult to distinguish between GIST, other malignancies and some focus of infection so biopsy is needed to reach the final diagnosis. Endoscopic biopsy, Fine Needle Aspiration (FNA) biopsy or surgical biopsy can be done to find out the histopathological diagnosis of GISTS.

Macroscopically

Grossly the tumor appears like an exophytic serosal nodule ranging in size from 1-2 cm in asymptomatic cases to more than 20 cm in large symptomatic high risk tumors [21]. Specimen is homogeneous, grey white, nodular or lobulated, cystic, trabeculated with gelatinous areas of hemorrhage and necrosis.

Microscopically

Three types have been seen in GISTS. 70% of GISTS are spindle cell tumors. Spindle cells are uniform elongated cells having eosinophilic cytoplasm and ill-defined cell borders and uniform ovoid nuclei. 20% of tumors are of epitheloid morphology with cells having pale eosinophilic to clear cytoplasm and round nuclei. Rest of the 10% tumors are of mixed spindle cell and epitheloid morphology.

Immunohistochemistry

Molecular studies have shown that most GISTS express C-kit

and PDGFRA having gain of function mutation in these genes. Over 90% of GISTS are positive for C-kit. Expression of C-kit by GISTS has revolutionised the treatment using TK inhibitors like imatinib mesylate and sunitinib. Kinase mutation status helps to predict if the tumor can respond to TK inhibitors and prognosis after tumor resection. CD117 exhibits a diffuse, focal or mixed staining pattern. Other tumors which show CD117 positivity include kaposi sarcoma, melanoma and deep fibromatosis, so a more specific and sensitive marker should be present for diagnosing GIST. These markers can diagnose CD117 negative GIST and include DOG 1, nestin, protein kinase c, theta carbonic anhydrase II and succinate dehydrogenase. DOG1 is a new promising marker of GIST being more sensitive and specific than C-kit. DOG1 expression is not affected by treatment with TK inhibitors which make CD117 fade and eventually turn negative after prolonged treatment. It stains about one third of kit negative GISTS. In a study conducted by West et al; immunoreactivity for DOG1 GISTS samples was 97.8% reactive [12]. DOG1 antibody stains tumour cells and interstitial cells of cajal with no background staining. It is used as a specific marker of GIST [22]. However in desmoplastic melanomas, synovial sarcomas, leiomyosarcomas, basal-cell carcinomas, hepatocellular carcinomas, adenoid cystic carcinomas, bowel adenomas, esophageal, squamous cell carcinomas, gastric carcinomas and uterine-type retroperitoneal leiomyomas it shows spriadic positivity. However, given that between 36% and 50% of CD117-negative tumors are DOG1-positive; this antibody should be included in routine histochemical diagnosis of GISTS [23]. Together C-kit and DOG1 can define GISTS in 99% of cases.

An early marker of GISTS was CD34 but it's less sensitive and specific as compared to kit and DOG1. It's expressed in 50 to 80% of GISTS. Other markers include Ki 67, s-100 (positive in 6-28%), smooth muscle actin which is positive in 20-40% of cases, desmin(positive in 4-5% of cases)and vimentin. These markers however are less specific for GIST [24].

Prognosis and Treatment

Prognosis of GISTS depends on size of tumor and number of mitosis per 50 high power fields and depth of mucosal infiltration (Table 1) [25]. C-kit mutation in GISTS are associated with poor prognosis [26].

Mitotic Index	Size, cm	Risk of Progressive Disease (%)			
		Gastric	Duodenum	Jejunum and Ileum	Rectum
<5/50-HPFs	<2 cm	None	None	None	None
<5/50-HPFs	>2 to <5 cm	Very Low(1.9)	Low (8.3)	Low (4.3)	Low (8.5)
<5/50-HPFs	>5 to <10 cm	Low (3.6)	Insufficient data	Moderate (24)	Insufficient data
<5/50-HPFs	>10 cm	Moderate (12)	High (34)	High (52)	High (57)
<5/50-HPFs	<2 cm	None†	Insufficient data	High†	High (54)
<5/50-HPFs	>2 to <5 cm	Moderate (16)	High (50)	High (73)	High (52)
<5/50-HPFs	>5 to 10 cm	High (55)	Insufficient data	High (85)	Insufficient data
<5/50-HPFs	>10 cm	High (86)	High (86)	High (90)	High (71)

*Adapted from Miettinen M, Lasota RJ. Gastrointestinal stromal tumours: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23:70–8326. **Abbreviations:** GIST: Gastrointestinal Stromal Tumor ; HPF: high-power field.

Table 1: Risk stratification of primary GISTS based on mitotic index, tumour size, and anatomic site.*

In a study it has been found that deletions in kit codon 557/558 had worse prognosis than any other kit exon 11 mutations or deletions not involving codon 557/558 better Five year survival was seen in kit exon 11 point mutations or duplications [27]. DOG1 expression it is an important diagnostic tool in patients with kit negative [28]. The main goal of treatment is complete surgical resection of the tumor with negative resection margins and preservation of an intact pseudocapsule [29]. Chemotherapy in GISTS is given with tyrosine kinase inhibitors like imatinib or sunitinib. These agents act by blocking signals via C-kit and PDGFRA receptors. It is given preoperatively as induction therapy for irresectable or borderline resectable tumors or as adjuvant therapy in patients having high risk of recurrence and metastatic disease. Sunitinib is second line therapy which is given in imatinib resistant cases.

References

1. Graadt van Roggen JF, van Velthuysen ML, Hogendoorn PC (2001) The histopathological differential diagnosis Of gastrointestinal stromal tumours. *J Clin Pathol* 54: 96.
2. Mazur MT, Clark HB, Hashimoto K (1983) Gastric stromal tumors- Reappraisal of histogenesis. *Am J Surg Pathol* 7: 517-519.
3. Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A, Senthil K, et al. (2013) A gist of gastrointestinal stromal tumors. *World J Gastrointest Oncol* 5: 102-112.
4. Dematteo RP, Henrich MC, El-rafai WM (2002) Clinical management of GIST: before and after STI-571. *Hum pathol* 33: 466-477.
5. Sherif FN, Zaghrou AS, Markby EL (2008) Gastrointestinal Stromal Tumors (GIST) of the Stomach: Retrospective Experience with Surgical Resection at the National Cancer Institute. *Journal of the Egyptian Nat Cancer Inst* 20: 80-89.
6. Rebey HS, Aiad HA (2014) Immunohistochemical expression of DOG 1 as a diagnostic marker for gastrointestinal stromal tumors in comparison to C-kit. *J Am Sci* 10: 198-205.
7. Foo WC, Atzwanger BC, Alexander Lazar J (2012) Pathology of Gastrointestinal Stromal. *Clin Med Insights Pathol* 5: 23-33.
8. Gina Nakhla A, Hala NH, Mohammed F (2012) Immunohistochemical Study of Dog 1 Protein Expression in Gastrointestinal Stromal Tumors. *Ac J of Can Res* 5: 61-70.
9. Demetri GD, Von Mehren M, Blanke CD (2002) Efficacy and Safety of Imatinib Mesylate in advanced GISTS. *New Eng J Med* 347: 472-480.
10. Graham JS, Boyd K, Nowiki S (2014) A Retrospective Study Of Incidence of GIST in Scotland from 1995 to 1999. *J Clin Exp Pathol* 4: 196.
11. Simon S, Grabelus F, Ferrera L (2013) DOG 1 regulates growth and IGFBF5 in gastrointestinal stromal tumors. *Cancer Res Accr J CAN* 73: 3661-3670.
12. Liegl B, Jason L, Hornick (2009) Monoclonal antibody DOG1.1 shows higher sensitivity than kit in the diagnosis of GIST, including unusual subtypes. *Am J Surg Pathol* 33: 437-445.
13. Pierie JP, Choudry U, Muzikansky A (2001) The effect of surgery and grade on outcome of gastrointestinal stromal tumors. *Arch Surg* 136: 383-389.
14. DeMatteo RP, Lewis JJ, Leung D (2000) Two hundred gastrointestinal stromal Tumors. Recurrence patterns and prognostic factors for survival. *Ann Surg* 23: 51-58.
15. Pithorecky I, Cheney RT, Kraybill WG (2000) Gastrointestinal stromal tumors: current diagnosis biologic behavior and management. *Ann Surg Oncol* 7: 705-712.
16. Lehnert T (1998) Gastro intestinal sarcoma (GIST): A Review of post-surgical management. *Ann chir gynecol* 87: 297-305.
17. Hersh MR, Choi J, Garrett J (2005) Imaging gastrointestinal stromal tumors *cancer control* 12: 111-115.
18. Lach HC, Szczerbińska BK, Słomka M (2008) Gastrointestinal stromal tumors. epidemiology, clinical picture, diagnosis, prognosis and treatment. *Pol Arch Med Wewn* 118: 216-221.
19. Vermal A, Kumar S (2015) GIST: A Case Report with Historical Review and Recent Approach to Management. *IOSR Journal of Dental and Medical Sciences* 14: 30-35.
20. American Cancer Society Gastrointestinal Stromal Tumor Review Article 2014.
21. Won N (2011) Gastrointestinal stromal tumours-an update for histopathologists. *Histopathol* 59: 807-821.
22. Miettinen M, Sobin LH, Lasota J (2005) Gastrointestinal Stromal tumours of the stomach: A clinicopathologic, immunohistochemical and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 29: 52-68.
23. Ríos-Moreno MJ, Jaramillo S, Pereira Gallardo SA (2012) Gastrointestinal stromal tumours (GISTs): CD117, DOG-1 and PKC_ε expression. Is there any advantage in using several markers? *Pathol Res and Prac* 208: 74-81.
24. Sozutek A, Afsar CU, Gunaldt M (2014) Diagnostic and prognostic roles of dog1 and ki 67, in gist patients with localized or advanced /metastatic disease. *International journal of clinical and experimental medicine* 7: 1914.
25. Miettinen M, Lasota RJ (2006) Gastrointestinal stromal tumours pathology and prognosis at different sites. *Semin Diagn Pathol* 23: 70-83.
26. Liu XH, Bai CH, Xie Q, Feng F, Xu ZY, et al. (2005) Department of pathology changai hospital. *World j of gastroentology* 11: 3948-3952.
27. Woznaik A, Rutkowski P, Piskorz A (2012) Prognostic values of kit/pdgfra mutations gastrointestinal stromal tumors(GIST): polish clinical gist registry experience. *Ann Oncol* 23: 353-60.
28. Sozutek D, Yanik S, Akkoca AN (2014) Diagnostic and prognostic values of dog 1 and ki 67, in gist patients with localized or advanced metastatic disease. *International j of clinical and experimental medicine* 7: 1914-1922.
29. Erinn DK, Rubin BP (2011) Gastrointestinal stromal tumors: Molecular mechanisms and targeted therapies GAGE-Hindawi Access to Research. *Pathology Research International* 1-7.