Review / Derleme

Gastrointestinal stromal tumours (GIST)- Pathology and clinical applications of recent molecular advances --A perspective review.
Gastrointestinal stromal tümörler (GİST) - Patoloji ve yeni moleküler gelişimlerin klinik uygulamaları - Bir perspektif yorum.

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Abstract

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the GI tract. They occur most frequently in stomach (60-70%), or small intestine(SI) (25-30%). Rare sites include colon, rectum, appendix and esophagus (<10%). On histology their appearance varies from cellular spindle cell tumours to epithelioid to pleomorphic tumours. Traditionally, three criteria have been used to determine malignancy, which include site of origin (SI and rectal tumours are more aggressive than stomach tumours), tumour size(>5 cm) and mitotic rate.(>5/50 hpf).GISTs are characterized by gain of function mutation in c kit (CD117) proto oncogene most commonly involving exon 11. GISTs without c kit mutation show mutations in platelet derived growth factor receptor alpha(PDGFRα).Surgery has been the standard treatment for resectable GISTs, but metastatic and unresectable GISTs had a poor prognosis. Recent molecular advances have opened new vistas leading to the development of specific molecular targeted therapies which stabilize the disease and reduce the frequency of disease recurrence. This review summarizes our existing knowledge, recent advances regarding histogenesis, pathology, molecular biology, and targeted cancer therapies which has revolutionized the management of these diseases.

Key words : Gastrointestinal stromal tumours, c-kit,

Gastrointestinal stromal tumours (GIST)- Pathology and clinical applications of recent molecular advances --A perspective review.

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract. Before being recognized as a distinct entity, these tumours were presumed to have elements of smooth muscle origin or neural origin and were classified as leiomyomas, leiomyosarcomas, leiomyo-blastomas or schwannomas. Mazur and coworkers coined the term gastrointestinal stromal tumours to collectively refer to a group of mesenchymal tumours of neurogenic or myogenic differentiation which lacked immunohistochemical features of Schwann cells and did not have ultrastructural features of smooth muscle cells.[1]

Landmark work done by Hirota and colleagues in 1998 demonstrated c-kit(CD117) (Cluster designation 117) mutations in the pathogenesis of GISTs. GISTs also express CD34 on their surface. Subsequent work in 2003 by Heinrich discovered activating mutation in PDGFRα (platelet derived growth factor alpha) [2,3] GISTs were considered to originate from interstitial cells of Cajal, but are now believed to arise from multipotent mesenchymal stem cells.[4]

Epidemiology

Data regarding the incidence of GIST prior to 1990 is scarce since it was not a well-recognized entity till then. However recent estimates put the incidence at 10-20 million people / per year with a malignant potential of 20-30%.[5,6] The prediction of the behavior of GIST still remains controversial after all these years and in many cases, inconclusive. Though GIST cases have been reported in all age groups including children, most GISTs occur in adults over 40 years of age, the median age being 63 years. No clear sex predilection has been noted nor any association with geographic location, race or occupation.

GISTs can be found throughout the GIT, but the commonest location is stomach(60%),and small intestine i.e jejunum and ileum (30%). Colon and rectum account for approximately 5% of cases with esophagus and appendix constituting <1%. Other less common locations are the mesentery, retroperitoneum, omentum, gall bladder, pancreas and even a primary GIST arising from the pleura.[7]

GISTs can vary greatly in size from few mm to >30 cms, however the median size observed is 5-8 cms. Grossly GISTs usually appear as exophytic growths projecting into the abdominal cavity. Mucosal ulceration is seen only in 50%.

Most of the patients' with GIST(70%) present with non-specific clinical symptoms which are variable depending on the site of involvement. Common symptoms include bleeding, perforation and rarely obstruction. Rest of the tumors remain asymptomatic or are discovered as an incidental finding on autopsy.

Pediatric GISTs

Pediatric GISTs represent 1-2% of all GISTs and occur in the 2nd decade of life with a predilection for females. Pediatric GISTs arise mainly in the stomach and frequently metastasize to lymph nodes. Unlike adults, only 10-15% of pediatric GISTs harbor c-kit or PDGFRα mutation.[8] Thus they fall in the category known as " wild type" GIST. Recent studies have uncovered germline mutations in succinate dehydrogenase (SDH) resulting in complete loss or reduction in SDH protein.[8]

Diagnosis

Although diagnostic procedures include several examinations like barium examination, CT and angiography, the useful role of endoscopic ultrasound guided fine needle aspiration(EUS FNA) has been pointed out in several studies with a reported accuracy of 80-85%.[9] A French study assessed EUS criteria of surgically resected upper gastrointestinal lesions and found that tumours of irregular extraluminal borders, cystic spaces and malignant appearing lymph nodes were predictive of borderline stromal cell tumours.

[10] The sensitivity and diagnostic yield of EUS-FNA compare favourably with other well accepted indications such as sampling pancreatic lesions and lymph nodes, and at present should be considered the procedure of choice for a tissue diagnosis of GIST, since EUS guided trucut biopsy has given inconsistent results in its ability to provide adequate tissue yield.

Pathology

GISTs are smooth, well circumscribed tumours and have a fleshy pink or tan-white cut section with foci of hemorrhage, cystic degeneration or necrosis.

GISTs can be divided into 3 major subtypes depending on their histopathological features. The majority are composed of spindle cells arranged in short fascicles or whorls with pale eosinophillic fibrillary cytoplasm, ovoid nuclei and synctial cell borders. (Fig. 1).Paranuclear vacuolization is usually present. Extracellular deposits of dense collagen (skenoid fibres) may also be seen. About 20% of GISTs are composed of epithelioid cells with pale eosinophillic to clear cytoplasm and round nuclei . Tumor cells are arranged in nests, sheets and cords and this morphology is commonly seen in pediatric GISTs.[11]The remaining 10% tumors exhibit both spindle and epithelioid cell morphology. GISTs may also show sclerotic, collagenous or myxoid stromal changes.

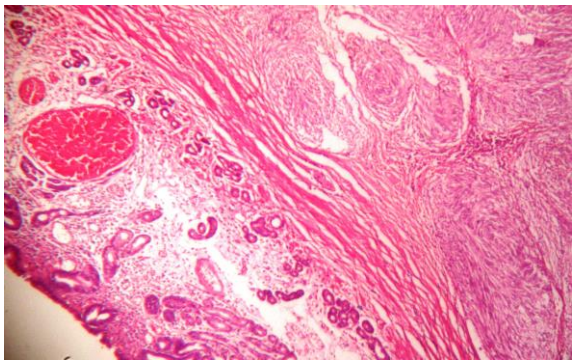

Figure 1. H & E image showing tumour in submucosa composed of spindle cells arranged in short fascicles or whorls with pale eosinophillic fibrillary cytoplasm, ovoid nuclei and synctial cell borders.(400x)

Oncogenic c-kit and PDGFRA mutations

c-kit and PDGFRA genes encode for structurally similar tyrosine kinase receptors. In GISTs mutations in c-kit and PDGFRA result in expression of protein with constitutive oncogenic signaling in absence of their ligands. The vast majority of c-kit mutations are juxtamembrane and found in exon 11 and exon 9.[12] Whereas exon 11 mutations can be found anywhere in the GIT, exon 9 mutations are found exclusively in the small bowel. PDGFRA mutations represent a minority (<10%) of GISTs and are primarily in exon 18 or exon 14. These mutations are limited to the stomach, are predominantly epithelioid in morphology and clinically less aggressive. [13]

Immunohistochemistry

c kit expression is a specific and sensitive marker for GIST and over 90% of GISTs are immunoreactive for c-kit.[14] (Fig.2)

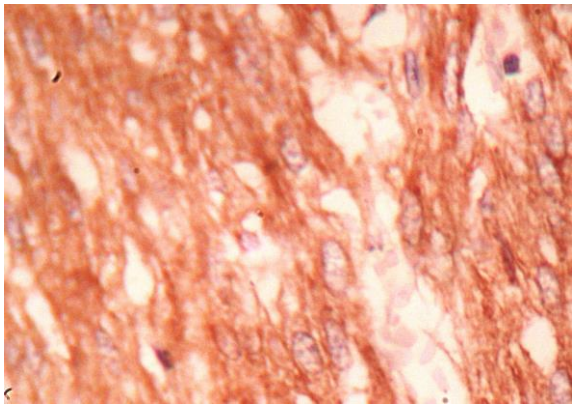

Figure 2. GIST with a strong and diffuse cytoplasmic positivity for c-kit.(400x)

Most GISTs show a strong and diffuse cytoplasmic staining for c-kit , and a minority may show a dot like or membranous staining pattern.[15] Another promising marker which appears to be sensitive and specific for GIST is DOG1. It is positive in pediatric GISTs and DOG1 stains about 33% of c-kit negative GISTs.[16] Antibodies to PDGFRA, a tyrosine kinase receptor closely related to c-kit can be employed in cases of c-kit negative GISTs harboring a mutation in PDGFRA. Strong immunoreactivity can be found in epithelioid GISTs. Other markers like nestin (90-100%)

and CD34 (70%), smooth muscle actin (20-30%) and heavy caldesmon (80%) are often expressed. Keratin and and S-100 protein can be variably immunoreactive whereas desmin is usually negative. GIST needs to be differentiated from other spindle cell neoplasms eg Inflammatory myofibroblastic tumour, Schwannomas, MPNST, smooth muscle neoplasms, intraabdominal desmoids fibromatosis, an appropriate panel of immunohistochemical stains will avoid diagnostic errors.[15]

Treatment

Surgical resection with negative gross margins remains the mainstay of therapy for primary GISTs. Regional lymph node resection is not of much value since GIST rarely gives rise to lymph node metastasis.Tumour size or its location may determine the exact extent of resection.En block resection of the local disease is recommended when GISTs adheres to a contiguous organ . However recurrence is common and 5 year survival rate after complete resection ranges from 40-65%.[17,18] A recent study of a retrospective review of 127 patients' over a 10 year period who underwent surgical resection for GIST revealed primary disease without metastasis in 64%, metastatic lesions at presentation in 9% and recurrent disease in 27%.Patients' with primary disease underwent complete resection of gross disease. The 5 year disease free survival (DFS) was 46.5% and overall survival (OS) was 53.4%.[19] Partial resection must only be performed in case of large tumours, for palliative purposes or the control of symptoms or its complications.

Though clinical history. light microscopy and immunohistochemistry are sufficient to establish the diagnosis of GIST, however in those tumours where the diagnosis is uncertain, RT-PCR testing for c-kit or PDGFRA gene mutations may be useful.

Molecular Testing

The role of conventional chemotherapy is limited in the management of GIST as these tumours show a poor response(<10%) and radiotherapy has a role only in palliation.The advent of imatinib mesylate in control of of advanced and metastatic GIST has revolutinised the management of these tumours. Imatinib is a powerful selective tyrosine kinase inhibitor (TKI) of PDGFR and c-kit receptor.The use of imatinib mesylate in recurrent or metastatic GIST has shown a response in 50% of the patients'. The 2 year survival after imatinib therapy is 70% and 50% of the patients' showed no progression of the disease.[4]The treatment is usually well tolerated but includes side effects such as periorbital edema,nausea, muscle cramps, diarrhea, headache, fatigue and abdominal pain. Other side effects include neutropenia, leucopenia and abnormal liver function. The ideal dose of imatinib is not determined, but the current data suggest that doses of 400 mg-800mg are safe and well tolerated.[20]

.Knowledge of mutations in particular exons helps predict the response rate to imatinib.

In c-kit mutant GISTs, a mutation in exon 11 was associated with a higher response rate to imatinib (67-83%) than mutation in exon 9 (35-48%). Conversely primary resistance to imatinib was associated with specific c-kit mutations especially point mutations in exon 13 and 17.GISTs with neither c-kit nor PDGFRA mutations showed the least treatment response (0-39%) and the highest primary resistance to imatinib.[21] Whereas the great majority of GISTs are often highly responsive with tyrosine kinase inhibitors, acquired resistance is a problem affecting the majority of patients. Mechanisms of resistance most commonly include secondary (acquired) mutations in the c-kit kinase domain and rarely c-kit / PDGFRA genomic amplification or activation of alternate oncogenes. [22] Secondary c-kit mutations are most likely single nucleotide substitutions and can be detected in 83% of patients'.

Liegl et al have demonstrated substantial inter and intralesional heterogeneity with TKI resistant mutations in patients' treated with imatinib alone or both imatinib and sunitinib.[22] Currently there are no established guidelines for

routine c-kit or PDGFRA mutational testing .Irrespective of their mutational status, most GISTs are treated with imatinib as first line therapy which may however change in the future.

The National Comprehensive Cancer Network (NCCN) and European Organisation for Research and treatment of Cancer (EORTC) suggest obtaining mutational testing in GISTs that are unresectable or metastatic at presentation, are in young patients, have an epithelioid morphology and have primary resistance to imatinib.

The poor response of patients' to 400 mg imatinib orally in patients' with exon 9 mutations than those with exon 11 mutations argues for the relevance of genotyping. Increasing the dose to 800 mg in patients' with exon 9 mutations improves the response, however no benefit is seen at higher dosage for exon 11 patients.

As our understanding of the relationship between genotype and response to various TKI increase genotyping will become increasingly relevant for therapeutic selection.

Recently, a study by Belev V and co workers [(23)] evaluated the role of ki-67 as a prognostic factor for the relapse of initially localized disease ($p < 0.0001$) inspite of whichever way the patients' were treated. The cut off value of ki-67 used in the above study was 6% .ki-67 could thus possibly be used as a parameter predicting tumour recurrence and suggest adjuvant treatment after surgery of localized disease

The use of Imatinib as an adjuvant therapy after complete primary resection of GIST is under evaluation. The American College of Surgeons Oncology Group(ACOSOC)[(24)] has conducted a prospective trial to patients' after complete resection of the tumour.The results from this study appear encouraging since Imatinib is well tolerated in the neoadjuvant setting. However other trials administering imatinib and placebo as adjuvant therapy, showed no difference in the overall survival between the two groups.[(4)]

Before the introduction of imatinib for GIST therapy, the 5 year survival rate after surgical resection was 40-75% and the median survival of recurrent GIST was 15 months.[(25)] The prognosis of low risk GIST after complete resection was excellent but the prognosis of high risk GIST was poor and the rate of recurrence with 5 year survival ranged from 0-30%. However, after the introduction of imatinib, there has been a major improvement in survival. GISTs have an unpredictable behavior and long term followup is required for all patients' especially within the first -5 years as the majority of tumours recur within this period.

Conclusion

GISTs are the most common mesenchymal tumours of the GI system. Improved knowledge of the oncogenic mutations and the operational resistant mechanisms will help in personalizing treatments tailoring to achieve optimum therapeutic response.

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