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Detection of c-kit and PDGFRA mutation for disease diagnosis and management of gastrointestinal stromal tumor

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Abstract

In contrast to epithelial tumors, gastrointestinal stromal tumor (GIST) is a tumor that originates from mesenchymal cells in the gastrointestinal tract. Although this tumor is a special entity and is the most common type of mesenchymal tumor amongst other types, GIST share similar clinical features with other types of mesenchymal tumors in the gastrointestinal tract. The tumors have similar clinical symptoms, like abdominal pain, bleeding, and mass or obstruction in larger tumor sizes. These similar clinical symptoms are one of the complicating factors in establishing the diagnosis of GIST, which differentiates it from other mesenchymal tumors of the digestive tract. Because GIST are known to not respond to chemotherapy used in the management of most malignancies, there is a need to differentiate between GIST and other mesenchymal tumors in the gastrointestinal tract. This review discusses the utilization of gene mutations known to be present only in GISTs, namely the c-kit and PDGFRA genes, through the detection of CD117 and DOG-1 proteins that are expressed due to the presence of these GIST-specific gene mutations, using the immunohistochemical examination. The prevalence of positive expression on immunohistochemical examination of CD117 and DOG-1 in GIST makes immunohistochemical examination the gold standard of GIST diagnosis. The diagnosis of GIST using CD117 and DOG-1 immunohistochemistry, as well as knowledge about GIST-specific gene mutations, is very useful for determining effective and efficient therapy.

Keywords: Gastrointestinal cancer; Gastrointestinal stromal tumor; CD117; DOG-1

1. Introduction

Gastrointestinal stromal tumor (GIST) is a type of gastrointestinal mesenchymal tumor that differs from epithelial tumors in that it has a specific histogenesis, with GISTs developing from mesenchymal cells, which are part of the muscle in the gastrointestinal tract (Kjetil et al., 2016). GISTs tend to have clinical symptoms that are difficult to distinguish from other types of gastrointestinal tract mesenchymal tumors, such as leiomyoma, leiomyosarcoma, lymphoma, lymphosarcoma or schwannoma. Patients with GIST or other GI mesenchymal tumors mostly present with complaints of abdominal pain, bloody or black stools, palpable lumps on the abdominal surface or obstruction in the GI tract (Mangla et al., 2012; Miettinen et al., 2013). In addition to the patient's complaints, GISTs and leiomyoma of the gastrointestinal tract, for example, both grow and appear as masses attached to and in the smooth muscle of the gastrointestinal tract. Both GISTs and leiomyomas appear as submucosal protrusions with a smooth surface and overlying mucosa, which can be seen by endoscopic examination (Ramai, D. et al., 2018; Marcella, C. et al., 2018). Although, GISTs and other mesenchymal tumors can be differentiated by the prevalence of each tumor site, both GISTs and other gastrointestinal mesenchymal tumors can grow along the gastrointestinal tract.

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The similar clinical symptoms and tumor location between GISTs and other GI mesenchymal tumors generally cause difficulties and confusion in the diagnosis process if only relying on endoscopic examination. GISTs are tumors that proliferate and differentiate into a specialized cell called the Interstitial Cell of Cajal (ICC) which is a smaller part of the gastrointestinal smooth muscle structure and acts as a pace maker for gastrointestinal muscle motility in the process of digesting food (Akahoshi et al., 2018; Barcelos et al., 2018). The different entity of GIST from other gastrointestinal mesenchymal tumors has implications for the therapy required by GIST. It is known that GIST does not respond to commonly used malignancy therapy, namely chemotherapy. Instead, GIST shows a high response to therapies that directly target the tyrosine kinase (cell growth factor) that is mutated in GIST cases resulting in cell proliferation and differentiation into tumor cells, a therapy called imatinib. Imatinib utilizes the GIST-specific c-kit and Platelet-Derived Growth Factor Receptor Alpha (PDGFRA) gene mutations as direct treatment targets. As many as 70-80% of GIST cases have mutations in the c-kit gene and the majority have deletions in exon 11 followed by deletions in exons 9, 13, and 17. Meanwhile, 5-10% of other GIST cases have mutations in the PDGFRA gene (Barcelos et al., 2018). And the rarest prevalence of GIST is GIST with Succinate Dehydrogenase (SDH) deficiency which is specific to GISTs that do not have mutations in the c-kit or PDGFRA genes (Gheorghe M et al., 2014). The knowledge of specific gene mutations in GISTs not only helps the management of GISTs, but also encourages the development of diagnosis using immunohistochemistry that uses the principle of antibody-antigen binding, where c-kit and PDGFRA gene mutations in GISTs will produce KIT and PDGFR proteins that become antigens in immunohistochemical examinations. GISTs that have mutations in the c-kit and PDGFRA genes will be positively expressed in the examination of CD117 and Discovered on Gist 1 (DOG-1), which are known as antibodies that can detect the presence of KIT and PDGFR proteins that are expressed due to gene mutations in GIST (Ríos-Moreno et al. 2012).

While GISTs are the most common type of mesenchymal tumor in the gastrointestinal tract, they are still relatively rare when compared to common malignancies such as breast cancer or lung cancer. (Kjetil et al., 2016). GIST cases in the UK range from 1.32-1.50 per 100,000 population, as well as in other countries where the number of GIST cases per 100,000 people is still below 2 (Starczewska A et al., 2014). Its small prevalence is in line with the need for further research on GIST, especially to determine its prevalence per population. The obstacle to determining the prevalence of GIST is due to the need for diagnostic criteria that are still difficult to differentiate from other mesenchymal tumors of the gastrointestinal tract. As a result, epidemiological evaluation is hampered, and global estimates of disease incidence and patterns are not yet available. Therefore, this review will discuss immunohistochemical techniques that are known to detect specific gene mutations in GIST with CD117 and DOG-1 antibodies to differentiate it from other gastrointestinal mesenchymal tumors easily.

2. Review Content

2.1. Gastrointestinal Stromal Tumor

It is known that Gastrointestinal stromal tumors (GIST) became a focal tumor entity in the literature after the year 2000. GISTs were previously classified under the diagnosis of mesenchymal tumors located in the smooth muscle of the gastrointestinal tract, namely leiomyoma, leiomyosarcoma, lymphoma, lymphosarcoma, or schwannoma (Joensuu, 2006). GISTs and other gastrointestinal mesenchymal tumors can grow along the gastrointestinal tract, specifically growing in the wall muscles of the gastrointestinal tract. However, researchers found that some of the tumors thought to originate from smooth muscle in the wall of the gastrointestinal tract were not characterized by microscopic structures of smooth muscle or schwann tissue. These entities, now known as GISTs, showed tumor features with a unique network of cells that did not resemble smooth muscle, cellular structures that resembled neural or embryonic tissue more than smooth muscle, and the presence of large compartments in the cytoplasm of tumor cells that suggested neural or neuroectodermal origins. Based on these findings, researchers concluded that GIST entities are different from other GI mesenchymal tumors because they originate from the myenteric nervous system, the nerve that controls GI motility called the Interstitial cell of Cajal (ICC) (Schaefer et al., 2017).

Clinically, GIST patients have the same features as other gastrointestinal mesenchymal tumors. In Indonesia, GIST and other gastrointestinal mesenchymal tumor patients most commonly present with complaints of bleeding in the gastrointestinal tract (Mangla et al., 2012; Miettinen et al., 2013). This is due to the growth of the tumor, which can damage the blood vessels and walls of the digestive tract, causing bleeding. Bleeding that occurs in GIST, leiomyoma, or leiomyosarcoma also has the potential to erode the lumen of the digestive tract wall, resulting in complications of abdominal pain or discomfort and even severe anemia if bleeding occurs continuously (Joensuu, 2006). However, overseas, many cases of GIST or leiomyoma are asymptomatic, as colorectal cancer screening programmed abroad through endoscopic examinations can identify GIST or leiomyoma at an earlier stage and without symptoms (Ang Supono et al., 2023). The main endoscopic findings in GISTs are, on average, similar to other gastrointestinal tract mesenchymal tumors, with a nonspecific smooth bulge covered by normal mucosa. This suggests that even radiological

examination (endoscopy), which is the primary examination for colorectal malignancies, does not provide sufficient information for the differential diagnosis of GIST and other mesenchymal tumors of the gastrointestinal tract, let alone as a determinant of therapy, which is known that the therapy that should be given to GIST patients must be different from the therapy applied to other mesenchymal tumors in the gastrointestinal tract (Schaefer et al., 2017).

The only aspect that distinguishes GIST from other mesenchymal tumors of the gastrointestinal tract is the presence of GIST-specific gene mutations, namely the c-kit and PDGFRA genes, which specifically characterize mutations in ICC cells (Joensuu, 2006). Meanwhile, mesenchymal tumors of the gastrointestinal tract that originate and grow from smooth muscle will yield positive results in immunohistochemical examinations that characterize the intermediate filaments of smooth muscle, such as desmin and S-100. The specific expression of antibodies in the immunohistochemical examination of each type of mesenchymal tumor has been utilized by researchers to develop diagnostic tools that exclude GIST from other mesenchymal tumors of the gastrointestinal tract. This has also served as the basis for the development of the most effective targeted therapy for GIST, namely the use of tyrosine kinase inhibitors (TKIs).

2.2. Molecular Testing for Gastrointestinal Stromal Tumor

Mutations of c-kit play an important role in the development and progression of gastrointestinal stromal tumors. About 60-70% of c-kit gene mutations activate a receptor tyrosine kinase called KIT, also known as CD117, which is located on the cell surface and homologous to stem cell factor. Click or tap here to enter text. Thus, mutations in the c-kit gene result in continuous activation of the KIT receptor, resulting in uncontrolled cell growth and the onset of tumor growth.

KIT is a receptor tyrosine kinase that is physiologically activated by the cytokine stem cell factor (SCF) (Joensuu, 2006). When KIT is activated through the process of KIT binding by SCF on the cell surface, a dimmer is formed that triggers autophosphorylation of KIT on tyrosine residues located in the intracellular tyrosine kinase domain. The activation of the signaling pathway will initiate the growth of cell differentiation and proliferation through the MAP kinase signal transduction pathway as a regulator of division, growth, and differentiation and the JAK/STAT pathway as a controller of growth, proliferation, and immune response (Hirano et al., 2008).

Most cases of GIST are found to have c-kit gene mutations located in axons 11 (90%), 9 (8%), 13 (1%), and 17 (1%) (Joensuu, 2006). The mutation in axon 11 is a missense mutation that substitutes valine for alanine at position 599 (A559V) and tryptophan for arginine at position 557 (W557R in the juxta-membrane domain. Both have a causal relationship in the constitutive activation of KIT in the process of tumor growth (Postow & Robson., 2012). Postow also mentioned that in addition to axon 11, GIST also has c-kit gene mutations located in axons 11 and 13, both of which encode tyrosine kinase II and I domains and are associated with familial or inherited GIST syndromes and are also associated with findings of resistance to GIST therapy. Thus, c-kit gene mutations in exons 9, 11, and 13 above play a role in the pathogenicity of gastrointestinal stromal tumors (GIST), which will lead to the malignant transformation of ICC cells. Ongoing signaling of the resulting KIT proteins promotes survival, proliferation, and drug resistance.

In some cases of GIST in a 2003 study, mutations in platelet-derived growth factor receptor-α (PDGFRA) were also detected. Similar to KIT, PDGFRA is also a tyrosine kinase from the type III receptor family (Joensuu, 2006). GIST cases with PDGFRA mutation are known to be less than GIST with c-kit mutation, which is 10%-20% of the total cases (Kiśluk et al., 2016). Mutations in the PDFRA gene also promote oncogenicity of GIST through continuous receptor activation. Similarly, in c-kit mutations, dimers will be formed through the binding of receptor tyrosine kinase and ligand (platelet-derived growth factor/PDGF), which will then trigger autophosphorylation leading to the activation of PI3K and RAS signaling pathways as cell survival and proliferation factors (Postow & Robson., 2012).

The majority of PDGFRA gene mutations in GIST occur in axon 18 in the form of tyrosine substitution with aspartate at codon 842 (D842V), which affects the abnormal activation loop of the PDGFRA gene, resulting in cell proliferation and resistance to apoptosis, which is transmitted continuously (Postow & Robson., 2012). GIST with this D846V mutation is known to be poorly responsive to tyrosine kinase inhibitors (imatinib), so the FDA approved avapritinib as a potent and selective treatment for GIST with axon 18 PDFRA gene mutations (Kelly et al., 2021; Mocellin et al., 2018). There is also a PDGFRA gene mutation present in axon 12 that is more commonly identified in young female patients and is associated with the incidence of GIST that is predominantly located in the stomach (Postow & Robson., 2012).

Knowledge of gene mutations specific to GIST is important in the diagnosis process because this is how GIST can be differentiated from other gastrointestinal mesenchymal tumors. DNA analysis techniques in GIST as a diagnostic tool can use single mutation approaches, namely PCR, qPCR, BEAMing, ddPCR or use a more unbiased approach for multiple targets, namely Next-Generation Sequencing (NGS) (Rassner et al., 2023). PCR and NGS not only serve as diagnostic tools that differentiate GIST from other gastrointestinal mesenchymal tumors, but moreover, the PCR and NGS imaging

results of c-kit and PDGFRA mutations provide a specific picture of axon deletions that occur differently in each individual with GIST. These detected axon deletions are very useful for determining the most effective tyrosine kinase inhibitor therapy for each GIST case (Koay et al, 2005).

2.3. Diagnosis of Gastrointestinal Stromal Tumor with Immunohistochemistry

In addition to PCR and NGS, it is known that specific gene mutations (c-kit and PDGFRA) in GIST can also be detected through immunohistochemical examination. This is in line with the need for a cheaper and less time-consuming diagnosis because the examination of c-kit and PDGFRA gene mutations in GIST performed using PCR and NGS in several countries including Indonesia is not covered by government health insurance (Rassner et al., 2023). Therefore, Baskin, Y et al. (2016) stated that immunohistochemical examination is the gold standard examination for the diagnosis of mesenchymal tumor types because the method is quite accurate, fast, and simple compared to other examinations.

The strong expression of KIT protein derived from the c-kit gene mutation is what underlies the positive CD117 immunohistochemical examination in most GIST cases. It was found that 95% of CD117 staining results were positively expressed in GIST cases (Von Mehren & Joensuu., 2017). In addition, it is known that there is an association between PDGFRA gene mutations and DOG-1 (Discovered on GIST-1), also known as ANO-1 (anoctamin 1). ANO1 is a transmembrane calcium-activated chloride channel protein that is highly expressed in GIST (Hirota et al. 2018). Its relationship with the KIT and PDGFRA genes was unclear in the study by Ríos-Moreno et al (2012), but the high positive result of DOG-1 staining in GIST in this study and previous studies, suggests the involvement of DOG-1 in the activation of KIT and PDGFRA receptors (Ríos-Moreno et al. 2012). Similar to CD117, DOG-1 is also identified and considered as a major factor initiating carcinogenicity in ICC, although DOG-1 can be expressed in KIT and PDGFRA gene mutations, DOG-1 is specifically helpful in many GIST diagnoses that do not have mutations in the c-kit gene (Kiśluk et al., 2016). Therefore, DOG-1 CPI is also recommended for the diagnosis of GIST because the specificity and sensitivity of DOG-1 CPI for GIST is quite high, which is more than 80%. Conversely, DOG-1 negative GIST cases cannot completely rule out the diagnosis of GIST, especially for PDGFRA mutant cases. Additional markers (e.g. CD117 or molecular testing for PDGFRA mutations) are required for testing the diagnosis of GIST. The negativity of DOG-1 in GIST makes the combination of immunohistochemical markers and molecular testing essential for an accurate diagnosis.

Immunohistochemical examination as the gold standard is usually combined with histologic examination results for the diagnosis of GIST. The histopathological picture of GIST also shows its characteristic, which is firmly circumscribed and surrounded by pseudo capsule, which microscopically are most commonly spindle-shaped (70%) and there is also a small portion that is epithelioid-shaped (20%), but can also be a mixed formation of spindle and epithelioid or even pleomorphic (Joensuu, 2006). Unfortunately, the histopathological examination of GISTs is often colocalized with other GI mesenchymal tumors, so that CD117 and DOG-1 expression that is positive on immunohistochemical examination in GISTs, but negative in other GI mesenchymal tumors (leiomyoma, leiomyosarcoma, lipoma, and schwannoma) becomes a diagnostic barrier between GISTs and other GI mesenchymal tumors.

The process of diagnosing GIST is carried out through systematic stages to ensure certainty of diagnosis and support the determination of appropriate therapy. It begins with the collection of tumor tissue samples via biopsy, either by endoscopic, percutaneous or surgical resection methods, for further analysis. These samples are then examined histopathological to evaluate tumor cell morphology and mitotic rate, which helps assess the nature and aggressiveness of the tumor. Furthermore, immunohistochemical (IHC) analysis is performed using specific markers such as CD117 (KIT) and DOG-1, which are typically positive in GISTs. If the IHC results do not provide reassurance, molecular tests are performed to detect mutations in the c-KIT or PDGFRA genes, which not only confirm the diagnosis but also guide targeted therapy with tyrosine kinase inhibitor (TKI). The combination of these steps ensures a high-precision diagnosis of GIST and supports optimal therapy planning.

2.4. Mutation Detection in Gastrointestinal Stromal Tumor Management

The common treatment for malignancy is chemotherapy, but in fact, chemotherapy in GIST did not provide significant therapeutic results, and it was known that GIST is generally resistant to chemotherapy (Von Mehren et al., 2022). GISTs are also known to be refractory to all conventional systemic therapies (Schaefer et al. (2017). After 2001, knowledge of the c-KIT and PDGFRA gene mutations in GIST became an aspect that led to the development of a specific therapy that directly inhibits the mutant receptor tyrosine kinase in GIST, known as imatinib mesylate therapy (Joensuu, 2006). Imatinib is a tyrosine kinase inhibitor that inhibits the expression of the mutant thyroxine kinase gene in GIST. Imatinib therapy, of course, begins with the detection that the patient is a GIST patient, whose tumor development originated from ICC. Diagnosis of GIST using immunohistochemistry is done to confirm a mesenchymal tumor that has mutations in the c-kit or PDGFRA gene. Furthermore, this knowledge directly plays a role in predicting the sensitivity of a particular treatment (Gheorghe M et al., 2014). In addition, histopathological criteria that accompany immunohistochemical

results in the diagnosis of GIST, such as size, mitotic rate, and location, are helpful in analyzing the aggressiveness of GIST, which is a criterion for the application of surgery or tyrosine kinase therapy in GIST patients. The histopathological criteria that have been established to assess the prognostic risk of GIST are not sufficient to define a GIST as having low or high aggressiveness. Case findings in the Fletcher et al (2002) study found cases with very small lesions (<2 cm) and very low mitotic rate (<5/50 hpf) incidentally metastasized. This phenomenon of uncertainty in GIST corroborates that the potential for malignancy is uncertain in GIST patients (Fletcher et al. 2002). This uncertainty has implications for the management applied to GIST patients, which can be the same or different and depends on the response to therapy in each patient.

Imatinib is the first line of treatment for GISTs and is clinically active against many GISTs. Still, not all GISTs are responsive to imatinib, as a therapeutic response can be measured by tumor mutation status. The presence of tumor mutation status, which includes mutations in the c-kit and PDGFRA genes, is associated with response to specific tyrosine kinase inhibitor therapy. Randomized trials evaluating imatinib as a therapy in GIST explained that the presence of c-kit exon 11 mutation had a better response compared to GIST with c-kit exon 9 mutation. In addition, studies involving GIST without a c-kit or PDGFRA gene mutation had 0% sensitivity to imatinib therapy. At the same time, GIST with PDGFRA mutation (D842V) was also found not to respond to imatinib therapy. There was even a survey conducted on 31 GIST patients, which found that 21 patients (68%) actually experienced disease progression with imatinib therapy. This suggests that the type of gene mutation involved in a GIST is instrumental in determining tyrosine kinase therapy in a case (von Mehren et al., 2022).

GIST patients with exon 9 mutant of the c-kit gene had longer progression-free survival when receiving double dose imatinib therapy (400mg, twice daily), where this double dose specifically produced a higher response in exon 9 mutants and a lower response in exon 11 mutants. In addition to the double dose, another tyrosine kinase inhibitor, sumatinib, was able to produce a good response for exon 9 mutant GIST. Sumatinib targets KIT/PDGFRA, CSF1R, and FLT3 to inhibit the proliferation, differentiation, and communication of tumor cells with their immune microenvironment and inhibits vascular endothelial growth factor receptors (VEBFR1-3) so that angiogenesis in tumor development does not occur (Kelly, Gutierrez Sainz, & Chi, 2021). Another tyrosine kinase inhibitor that targets VEGFR -1-3 is regorafenib. Regorafenib also targets oncogenicity factors (KIT, RET, RAF-1, BRAF and BRAFV600E), and the tumor microenvironment (PDGFR and fibroblast growth factor receptor (FGFR)) and is thus considered an oral multi-target tyrosine kinase inhibitor. The FDA approved regorafenib as advanced management for patients with GIST refractory to imatinib and sumatinib as it was shown to have a higher rate of disease control in trials. Therefore, it is reiterated that GIST treatment may be the same or different in each case.

Another tyrosine kinase inhibitor, avapritinib, is a potent inhibitor for GISTs with mutations in PPDGFRA D842V that have no response to imatinib therapy, which accounts for about 24% of GISTs with KIT and PDGFRA mutations. The benefit of avapritinib is known to reach 98% in PDGFRA D842V mutants, but its effectiveness is directly proportional to the side effect which is also specifically cognitive effects, namely memory impairment. Generally, this interesting side effect can be managed with dose modification, which is recommended at 300mg once daily (Kelly et al., 2021).

3. Conclusion

Gastrointestinal stromal tumors (GISTs) are one of the most common types of mesenchymal tumors, but their prevalence is much lower than other malignancies. GISTs develop from Interstitial Cajal Cells (ICC) that are specific to the gastrointestinal tract. These ICC cells are specific to GISTs that have ICC cell mutations in the c-kit and PDGFRA genes. Mutations in the c-kit and PDGFRA genes lead to the activation of receptor tyrosine kinases on the cell membrane that activates cell growth signaling pathways to become constitutively active and lead to uncontrolled cell proliferation and survival. Understanding the molecular basis of GIST (c-kit and PDGFRA mutations) led to immunohistochemical examination (CD117 and DOG-1) as the primary diagnosis of GIST, which can differentiate it from other groups of gastrointestinal mesenchymal tumors. Positive expression of CD117 and DOG-1 markers is also used as a basis for the development of therapy using a tyrosine kinase inhibitor called imatinib. Imatinib works by inhibiting several tumor cell growth, differentiation and proliferation factors associated with c-kit and PDGFRA mutations. However, not all GISTs respond well to imatinib therapy, as there are specific gene mutations in certain axons that are resistant to imatinib. This makes DNA analysis also important in the diagnostic work-up of GIST to determine the specific mutant genes in addition to the application of immunohistochemistry, especially to determine effective therapy for each individual with GIST.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest related to this publication

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