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DETECTION OF JAK2 V617F MUTATION IN A PATIENT WITH C-KIT POSITIVE GASTROINTESTINAL STROMAL TUMOR: CASE REPORT

Sanja Trajkova [1], Svetlana Krstevska Balkanov[1], Aleksandra Pivkova Veljanovska [1], Fana Lichoska-Josifovikj [2], Marija Popova Labacevska [1], Nevenka Ridova[1], Simona Stojanovska Jakimovska[1], Milce Cvetanovski[1], Lazar Cadievski[1], Bozidar Kocoski [1], Martin Stojanovski [1], Andrea Paunovska[1], Merve Purde[1], Irina Panovska Stavridis[1]

[1]University Clinic for Hematology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia, [2]University Clinic of Gastroenterohepatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia

Abstract

C-Kit is receptor tyrosine kinase which is involved in various signaling pathways and has been recognized in pathogenesis of several types of cancers including gastrointestinal stromal tumor (GIST). More than 50 years, scientist have been studied GIST and made advances in treatment based on c-Kit inhibition.

One of the signaling pathway involving activation via c-Kit is the JAK/STAT pathway located on hematopoietic cells resulting activation of transcription of a variety of genes. Here, we provide a case report of patient with two malignancy c-Kit positive GIST and Essential Thrombocytemia (ET) positive for JAK2 V617F mutation.

Keywords*:* c-Kit, GIST, JAK2 V617F mutation, ET.

Introduction

Gastrointestinal stromal tumors (GISTs) are soft tissue sarcomas affecting the gastrointestinal tract. Most affected age is late sixth and early seventh decades of life, with male predominance.

The most commonly affected region of the digestive tract with GISTs is in the stomach in 55-60% and small intestine 20-30%, as well as in extra intestinal sites such as the gallbladder, omentum. Metastatic locations for GIST include the liver and omentum, less common in lungs, regional lymph nodes and bone [1].

GISTs share similar morphologic and immunophenotypic features with the interstitial cells of Cajal (ICC), pacemaker cells in the gut wall that regulate peristalsis. Like GISTs, ICCs have both smooth muscle and neural features and tend to express Kit (CD117) and CD34 [2].

In addition, Kit signaling is required for proper ICC development and differentiation but constitutive Kit activation by gain-of-function mutation is associated with GIST pathogenesis [2].

Thus, GISTs are proposed to originate from ICCs or stem cells that differentiate toward ICCs. It is now estimated that nearly 95% of GISTs stain positive for Kit [1].

Other known immunohistochemical markers for GISTs include CD34 with expression of 70%, smooth muscle actin expressed in 35% of cases and low expression of S-100 and desman (1). Kit presently remains the most sensitive immunohistochemical marker for GIST diagnosis [3].

GISTs exhibit three major histological subtypes: spindle cell subtype, epithelioid subtype and one rear subtype mixed subtype [4].

Malignant potential of primary GISTs have been defined by three most predictive factors: the site of primary tumor, the tumor size and the number of mitoses per high-powered field. Even though the true malignant activity of primary GISTs is unpredictable, as even small tumors less than 1 cm may recur 10 years or more after diagnosis.

The human race has 58 known receptor tyrosine kinases, categorized into 20 subfamilies. One of the prominent members of this family is c-Kit, also known as stem cell growth factor receptor [5].

It is one of the type III receptor tyrosine kinases and is known to play a critical role in the manifestation and proliferation of tumors [6]. Physiologically, the activation of c-Kit occurs via binding of

stem cell factor (SCF), leading to the homodimerization of the receptor, which results in a series of events involving transphosphorylation, auto-inhibitory interactions, and activation of multiple downstream effectors [7].

Though the overall outcome of c-Kit activation depends on the environment of the involved cell, several effector biomolecules have been reported to be activated, such as MAP kinases, Src family kinases, p85 subunit of PI3K, and phospholipase C-gamma [8].

Impaired function of of c-Kit, including overexpression and gain of function mutations, have been reported in different types of cancer, such as gastrointestinal stromal tumors (GISTs in 70–80% of the cases), small-cell lung carcinomas, and acute myeloid leukemia, presenting its clear oncogenic role [9]. Expectedly the use of c-Kit inhibitors has provided novel insights for cancer treatment (10). A promising cancer-targeting approach is inhibiting c-Kit via kinase inhibitors, such as imatinib and related analogs.

c-Kit is a noticeable component of cellular signaling in stem cells, where physiologically, it is involved in the crucial functions of cell maintenance and differentiation. Very high expression of c-Kit has been detected in stem cells, progenitor cells, and other cells with selfrenewal potency [5].

It has been shown that c-Kit is present in hematopoietic cells, a stem cell type that divides asymmetrically and differentiates into various kinds of hematopoietic cell lineages (e.g., macrophages, neutrophils, basophils, eosinophils, erythrocytes, T-cells, and B-cells).

The levels of c-Kit expression are significant in the original hematopoietic cells; it weakens after the process of differentiation. Studies have established the role of c-Kit in the development and function of interstitial cells of Cajal (ICC), as we previously mention that like GISTs, ICCs have both smooth muscle and neural features and tend to express Kit (CD117).

c-Kit participates in the signal transduction through different intracellular pathways including JAK/STAT pathway located on hematopoietic cells with function activation of transcription of a variety of genes. c-Kit results in the permanent phosphorylation of all three, STAT1, STAT3, and STAT5 proteins with transcriptional activity.

The phosphorylation could be either basic or by the receptor-associated JAK tyrosine kinase. The influence of c-Kit on the activation and molecular functions of the above- mentioned signaling pathways and cellular proteins varies considerably depending on the nature of the involved cells. Usually, c-Kit functions in close coordination with other growth factors and cytokines.

A separate entity are myeloproliferative diseases, which are characterized by the presence of V617F mutation in the Janus kinase 2 (JAK2) tyrosine kinase which leads to ooverstated erythropoiesis and megakaryocytopoiesis, which are hallmarks of Polycythemia Vera (PV) and essential thrombocythemia (ET).

The JAK2 V617F point mutation makes the normal hematopoietic progenitor cells hypersensitive to thrombopoietin, erythropoietin, and myeloid progenitor cells, leading to trilinear hematopoietic myeloproliferation. Essential thrombocythemia is a myeloproliferative disorder (MPD) with a relatively long median survival.

Though, the clinical course of the disease is complicated by a high incidence of thrombohemorrhagic episodes and arterial and venous thromboses significantly contribute to the morbidity and mortality of ET patients. Approximately 50% to 60% of patients with ET and PMF harbor the JAK2 V617F mutation.

Here, we provide a case report of patient with two malignancy c-Kit positive GIST and essential thrombocythemia (ET) positive for JAK2 V617F mutation.

Case report

A 74-years old patient (S.O) in December 2023 was addressed to university clinic for hematology because elevated platelet values were noted in laboratory blood test by the primary care doctor. Blood test presented normal value of Hemoglobin (Hgb) 135 gr/dl, White blood cells (WBC) 19,5 x 10^3 /uL and Platelets (Pl) 991x 10^3 /uL, normal findings of DDimers and biochemistry except elevated creatinine 123 μmol/L and LDH 672 U/L, peripheral blood smear was normal with platelet aggregates.

The patient listed several past illnesses such as cardiovascular disease treated with the placement of 6 stents and thrombotic manifestations in the toes of the left foot.The patient was referred for molecular analyses under suspicion of myeloproliferative diseases JAK2 mutation, MPL, CALR, Bcr-Abl.

The patient reported gastric pain and discomfort after meals, which led to a gastroscopy. Molecular tests showed the presence of a JAK2 V617F mutation and hematologist gave a recommendation for antiagregation therapy with Aspirin 100mg once daily and protection with low weight molecular heparin during the examination and surgery. The performed gastroscopy detected a stomach tumor measuring 28x24mm and under suspicion of malignant stomach disease, the patient was referred to a digestive surgeon.

In February 2024, a partial resection of the stomach was performed with subsequent pathohistological analysis of the surgical material. Microscopic analysis showed tumor involvement of the submucosa and mucosa of the stomach. Immunohistochemical analysis of tumor cells showed positivity for the following stains:CD117+(c-kit), CD34+, vimentin+, with low proliferative rate Ki-67 1-2%. Patohistology findings reveled the diagnosis of Gastrointestinal stromal tumor of stomach and according to UICC (VIII): pTNM=pT2, pL0, pV0, Stage IA.

Computer tomography of thorax and abdomen were with normal findings and oncologist proposed only regular controls without any chemotherapy.

In July 2024 patient came to regular hematology control and there was elevation of platelet values Pl 1101 x 10^3 /uL with platelets aggregates on peripheral blood smear. Due to comorbidities such as six stents placed, a previous myocardial infarction and malignant stomach disease, the patient was placed on therapy to reduce the number of platelets with capsules Hydrae (hydroxyurea) 500mg, therapy for essential thrombocytemia (ET) positive for JAK2 V617F mutation and prevention of thrombotic complications.

In November 2024 on last hematology control platelet values were normal Pl 238 x 10^3 /uL, but the patient complained of a cough and was referred for CT evaluation. CT evaluation of lungs reveled nodular findings with dimension of 13x11mm in medial segment of right lung with other 2 nodular findings in apical segment (suspicious about metastasis deposits). CT of stomach reveled hipodensal findings in liver with dimension of 17x13mm (suspicious about metastasis deposits).

A puncture of that liver lesion was performed under CT control. Analysis of the biopsy material confirmed the diagnosis of GIST. Patient consulted with the oncologist about starting imatinib therapy for GIST, and the hematologist would be discontinued the therapy with Hydrea (hydroxyurea) 500mg.

Discussion

There are a few small-molecule official by the FDA as c-Kit inhibitors for the management of different types of cancer, sharing similar structural features.

The list is presented with these c-Kit inhibitors: Sorafenib, Imatinib, Dasatinib, Sunitinib, Nilotinib, Amuvatinib, Regorafenib, Avapritinib, Ripretinib, Tivozanib [11]. c-Kit and its physiological functions were first clarified roughly two decades ago. Since then, there have been significant advances in the knowledge concerning its implications in both normal and pathology cellular functions.

As a type-III receptor tyrosine kinase, it is involved in several signaling pathways, including the PI3K pathway, MAPK pathway, responsible for cellular growth and proliferation. In medicinal chemistry and medication innovation, c-Kit is considered one of the key targets for the management of various types of cancer, including melanoma and GISTs.

Discovery of the role of Kit and PDGFRα in GIST pathogenesis and the ability of Imatinib to target the oncogenic activity of these kinases has resulted in improved survival and quality of life of patients with metastatic or inoperable GISTs. Imatinib has shown its greatest effects in the metastatic setting, but it may also prove to be beneficial in patients with locally inoperable disease [12].

A series of clinical studies have been presented where Imatinib has been prescribed as adjuvant and non-adjuvant therapy and at a dose of 400, 600 mg. Results show excellent overall and disease-free survival [12].

The development of alternative tyrosine kinase inhibitors and other drugs may benefit patients who have Imatinib-refractory disease or who may benefit from combination therapies to improve response rates.

We present a patient with two malignancies that have defined molecular causes that interfere with the pathogenesis of the diseases. GIST that are positive for c-kit with a good response to targeted therapy with Imatinib whose mechanism of action is inhibition of constitutive tyrosine kinase activity.

As we know, tyrosine kinases are proteins that cells use for signaling and cell growth. Imatinib binds to BCR-ABL kinase domain by preventing the transfer of a phosphate group to tyrosine on the protein substrate and the subsequent activation of phosphorylated protein. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor and stem cell factor c-Kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, Imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation.

ET as part of MPD with the JAK2 V617F mutation present the core feature of elevated platelets and is associated with thrombotic or hemorrhagic manifestations. The initiation of cytoreduction therapy was not conditioned by the platelet count but by the presence of thrombotic comorbidities of a cardiovascular nature, which are both a consequence of elevated platelets and the underlying ET disease. A therapeutic option for this patient is Imatinib, which will inhibit c-kit activity in GIST cells but will also allow control of myeloproliferation. Data from literature presented that Imatinib will lead to control of elevated platelet counts by reducing the possibility of thrombotic or hemorrhagic manifestations [13].

In the available literature on BCR ABL negative myeloproliferative diseases, there is no report of the coexistence of Essential Thrombocythemia and GIST with their molecular markers JAK2 and cKit. The current review of the literature presents a case report of MPN cases such as ET with the co-presence of two molecular pathways such as JAK2 and CALR (14), but there is no data available on the coexistence of JAK2+ ET with c-kit + GIST, which makes it a very rare and interesting case. Although the initial clinical presentation of GIST did not require therapy, it necessitated more frequent CT evaluations on for a 6 month period, which detected disease progression and the need for therapy with Imatinib.

Conclusion

A case of a patient with two malignancies is presented. Two malignancies have presence of signaling pathways characteristic of the entities and available therapy for their inhibition is presented. We presented a very rare case of a patient with two malignancies that have not been presented in the literature before, making it unique and rare. It imposes the need for future research with an emphasis on myeloproliferative diseases with GIST that have distinctive molecular mechanisms, clinical presentations, and common therapy based on tyrosine kinase inhibition. Patients with these malignancies with characteristic molecular pathways require intensive and careful monitoring of both ET with regular hemogram controls by a hematologist, and GIST with regular CT evaluations at a shorter time period of 3 to 6 months by a gastroenterohepatologist, demonstrating the multidisciplinary view of this issue.

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