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Nilotinib Induced Recurrent Gastric Polyps: Case Report and Review of Literature

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 62
Final Diagnosis: Chronic myeloid leukemia
Symptoms: Gastric polyps
Medication: Nilotinib
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual or unexpected effect of treatment

Background: Tyrosine kinase inhibitors (TKIs) are currently an important targeted drug class in the treatment of chronic myeloid leukemia (CML). Imatinib was the first approved TKI for CML in 2001. Nilotinib is a second-generation TKI, approved in 2007; it inhibits BCR-ABL, PDGFR, and c-KIT, and is 30 times more potent than imatinib. Tyrosine kinase enzymes are expressed in multiple tissues and are involved in several signaling pathways; they have been shown to have several off-target side effects.

Case Report: We report a case of an elderly male with CML and no history of gastrointestinal diseases, treated with nilotinib, and developed recurrent gastric polyps after three years of treatment. We excluded common causes of gastric polyps and therefore considered nilotinib as a probable cause of recurrent gastric polyps.

Conclusions: Recurrent gastric polyps could be a potential side effect of nilotinib treatment. Careful long-term monitoring of patients on TKI therapy is necessary and further long-term studies of TKI side effects are needed.

MeSH Keywords: Adenomatous Polyps • BCR-ABL Positive • Chronic Myelogenous Leukemia • Drug-Related Side Effects and Adverse Reactions • Imatinib • Nilotinib • Tyrosine Kinase Inhibitors (TKI)

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903485

Background

Tyrosine kinase inhibitors (TKIs) are currently an important targeted drug class in the treatment of chronic myeloid leukemia (CML). Imatinib was the first approved TKI for CML, approved in 2001. Nilotinib is a second-generation TKI, which was approved in 2007; it inhibits BCR-ABL, PDGFR, and c-KIT, and is 30 times more potent than imatinib because of its increased ABL kinase selectivity and binding site affinity [1]. TKIs are expressed in multiple tissues and are involved in several signaling pathways, they were found to have several off-target side effects. The short-term side effects of TKIs are well known, but the long-term side effects, especially for the newer agents, have not yet been clearly identified [2,3].

We present a case of a patient with CML who developed recurrent gastric polyps after three years of nilotinib therapy as a second-line treatment. To the best of the authors' knowledge, this is the first case of nilotinib-associated gastric polyps.

Case Report

A 62-year-old male known to have hypertension treated with irbesartan and amlodipine, diabetes mellitus type II treated with sitagliptin and metformin, dyslipidemia treated with simvastatin, and chronic phase CML treat with imatinib 400 mg PO daily as upfront therapy. After five years of imatinib treatment, the patient lost his molecular remission and treatment was shifted to the second-line TKI nilotinib at 400 mg BID. During the first month of this treatment, he developed toxicity to nilotinib: facial edema, skin rash, severe myalgia. In addition, his diabetes became uncontrolled, and so he was referred to an endocrinologist for diabetes control.

After a few weeks, he improved spontaneously; CML monitoring showed major molecular response as per the European Leukemia Net (ELN) recommendations [4], and therefore treatment with nilotinib was continued.

After three years of nilotinib therapy, during his regular follow-up, the patient's CBC showed hemoglobin 10.1 g/dL (normal 13–17 g/dL) with MCV of 73.4 fL (normal 83–101 fL). Anemia workup revealed iron deficiency anemia. He was treated with oral iron for four months and showed clinical improvement.

As part of the anemia workup, his esophagogastroduodenoscopy (OGD) showed multiple gastric polyps that were removed; histopathology showed hyperplastic gastric polyps (Figure 1). A colonoscopy was performed and revealed normal results. The patient was started the proton pump inhibitor (PPI) rabeprazole.

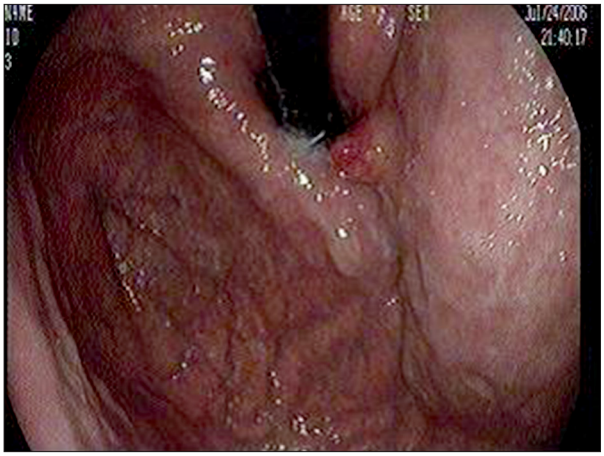

Figure 1. 2 cm stalked polyp in the greater curvature.

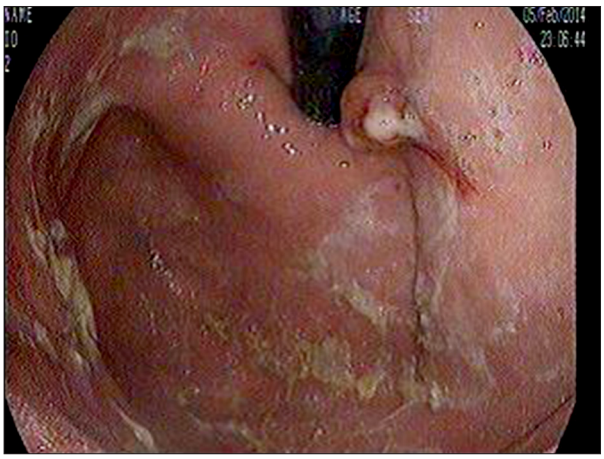

Figure 2. Stomach with small cardiac hyperplastic polyp (same size as previous endoscopy).

The first recurrences of gastric polyps after a two month follow-up, as shown by OGD (Figure 2), were removed; histopathology showed: 1) focal foveolar hyperplasia and features in keeping with reflux; and 2) focal intestinal metaplasia. Further investigations were requested: gastrin level showed 55.2 pg/mL (normal range up to 115 pg/mL) and vitamin B12 at 192 pmol/L (normal 133–675 pmol/L).

The second recurrence of gastric polyps one year after the first recurrence were removed by OGD; histopathology showed: 1) fragmented gastric mucosa with lymphoplasmacytic infiltrate and large number of eosinophils; 2) ulceration and granulation tissue formation with attached acute inflammatory exudates noted; 3) negative for *Helicobacter pylori*; and 4) no intestinal metaplasia, dysplasia, or malignancy.

The third recurrence of gastric polyps, eight months from the second recurrence, OGD showed stomach cardiac hyperplastic polyps. A biopsy was taken, and histopathology showed diffuse intestinal metaplasia negative for *H. pylori* organisms or malignancy.

The typical differential diagnosis of gastric polyps includes familial adenomatous polyposis, Zollinger-Ellison syndrome, *H. pylori*, and pernicious anemia. In this case, an unrevealing family history, absence of previous gastrointestinal disease, normal gastrin, negative *H. pylori*, and normal vitamin B12 level made these differential diagnoses highly unlikely.

The patient's gastric polyps were removed and the patient's treatment with nilotinib has continued at the dosage in which the patient remained stable and in complete molecular remission. The treatment plan includes follow-up by a gastroenterologist and OGD every six to 12 months.

Discussion

Gastric polyps can be defined as luminal lesions that originate in the gastric epithelium or submucosa and protrude into the stomach lumen. Several subtypes of gastric polyps are recognized; fundic gland polyps (FGP), hyperplastic polyps, and adenomas are the most common benign polyps. However, some of these subtypes are considered to have malignant potential and to be precursors of early gastric cancer [5].

The malignant potential of gastric polyps has been correlated to their pathologic features. It has been reported in the literature that there is an association between gastric carcinomas and the presence of hyperplastic polyps. Around 1–20% of hyperplastic polyps have been reported to harbor foci of dysplasia [6–10].

Several TKIs are approved for the treatment of CML; however, the safety of these drugs remains an important concern as they have several off-target side effects.

In our case, since differential diagnoses were excluded, and in the absence of a previous history of gastrointestinal disease, the possibility of drug-induced polyposis was raised and subsequently the patient's medications were reviewed. He was receiving irbesartan and amlodipine for hypertension, sitagliptin and metformin for diabetes, simvastatin for dyslipidemia, nilotinib for CML, and rabeprazole then esomeprazole for gastritis.

A literature review was conducted using PubMed and Medline from 2001 to 2016 using key words "Irbesartan, Amlodipine, Sitagliptin, Metformin, Simvastatin, Nilotinib, Imatinib, Tyrosine kinase inhibitor, Proton pump inhibitor, gastric polyp, hyperplastic polyp" to review the correlation between these medications and recurrence of gastric polyps. No reports for gastric polyps were found for irbesartan, amlodipine, sitagliptin, metformin, or simvastatin.

Several reports and retrospective studies reported an association between PPIs and the development of FGP, with a mean interval of 32.5 months for polyp development [11–14]. In an observational study that included 599 patients undergoing endoscopy, long-term PPI use (defined as ≥ 5 years) was associated with an up to fourfold increase in the risk of FGP, while risk was not increased with short-term PPI therapy [11]. Other studies have not demonstrate a definitive link between long-term PPI and FGP [15–18]

No reported cases of nilotinib-associated gastric polyps were found in our literature review; however, there have been reports of secondary neoplasms associated with nilotinib and imatinib therapies. These secondary neoplasms included papilloma, gastric cancer, fibroma, thyroid neoplasms, pancreatic cancer, and gastrointestinal stromal tumors [19–31].

Two cases of gastric cancer were reported with nilotinib therapy in a post-marketing clinical use survey in Japan [26] and one case was reported in a global phase III multicenter trial [27].

Nilotinib was given as an upfront treatment (first-line treatment) in some cases and as a second-line treatment in other cases; the impact of the line of therapy on the occurrence of secondary neoplasms was not raised in literature and therefore remains uncertain.

Based on the aforementioned literature review, the possibility of PPI-induced gastric polyps in our patient case was highly unlikely since our patient started PPI after the occurrence of gastric polyps, the first recurrence of polyps occurred after less than two months of PPI treatment; the second and third recurrences occurred after less than two years of therapy, which was not considered long-term therapy as suggested by the reviewed reports. Moreover, in the reported cases in the literature, PPI-induced polyps were mainly FGP; whereas in our case the polyps were hyperplastic.

Despite the absence of reports supporting the association of nilotinib with gastric polyps, the possibility could not be excluded, as nilotinib is a relatively new drug and long-term side effects have not yet been extensively studied. In contrast, irbesartan, amlodipine, sitagliptin, metformin, and simvastatin are older drugs that have been studied in larger population and for a longer duration. Therefore, the absence of reports of this adverse event in the literature could exclude them from being the cause of gastric polyps, however, this does not rule out the possibility of occurrence of this condition as a result of simultaneous use of these drugs or PPI with nilotinib.

Furthermore, reports of nilotinib-associated secondary neoplasm, especially gastric cancer, and the fact that hyperplastic polyps have malignant potential and are precursors of early gastric cancer [6–10] further supports the association of nilotinib with hyperplastic polyps.

Table 1. Naranjo Adverse Drug Reaction Probability Scale: Items and score.

	Question	Yes	No	Don't know	Patient's Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	**0**
2.	Did the adverse event appear after the suspected drug was administered?	+2	– 1	0	**+2**
3.	Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	**0**
4.	Did the adverse reaction reappear when the drug was re-administered?	+2	– 1	0	**0**
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	– 1	+2	0	**+2**
6.	Did the reaction reappear when a placebo was given?	– 1	+1	0	**0**
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**0**
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	**0**
9.	Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	**0**
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	**+1**

Scoring • >9 = definite ADR • 5–8 = probable ADR • 1–4 = possible ADR • 0 = doubtful ADR.
Naranjo et. al. Clin Pharmacol Ther, 1981; 30(2): 239–45.

To assess the probability of this adverse drug reaction, we used the Naranjo Adverse Drug Reaction Probability Scale (Table 1) [32]; the calculated score of 5 indicated that nilotinib was the probable cause for the development of recurrent gastric polyps in our patient.

Conclusions

Gastric polyps could be a probable side effect of nilotinib therapy. Considering the malignant potential of hyperplastic polyps and polyposis, in the era of TKIs, gastric polyps should be thought of as a potential premalignant condition. Careful long-term monitoring of patients on TKI therapy is necessary, and further long-term studies of side effects of TKIs are needed.

Conflict of interest

None declared.

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