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

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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)

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**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.

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 polyph 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.
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.

### References:

1. Weisberg E, Manley PW, Breitenstein W et al: Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell, 2005; 7: 129–41
2. Druker BJ, Guilhot F, O’Brien SG et al: Five-year follow-up for patients receiving imatinib for chronic myeloid leukemia. N Engl J Med, 2006; 355: 2408–17
3. Caldemeyer L, Dugan M, Edwards J, Akard L: Long-term side effects of tyrosine kinase inhibitors in chronic myeloid leukemia. Curr Hematol Malig Rep, 2016; 11(2): 71–79
4. Baccarani M, Cortes J, Pane F et al: Chronic myeloid leukemia: An update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol, 2009; 27(35): 6041–51
5. Park DY, Lauwers GY: Gastric polyps classification and management. Arch Pathol Lab Med, 2008; 132: 633–40
6. Dirschmid K, Platz-Baudin C, Stolte M: Why is the hyperplastic polyp a marker for the precancerous condition of the gastric mucosa? Virchows Arch, 2006; 448: 80–84
7. Dijkstra SM, Entius MM, Clement MJ et al: Multiple hyperplastic polyps in the stomach: Evidence for clonality and neoplastic potential. Gastroenterology, 1997; 112(2): 561–66
8. Daibo M, Itabashi M, Hirota T: Malignant transformation of gastric hyperplastic polyps. Am J Gastroenterol, 1987; 82(10): 1016–25
9. Orlowska J, Jarosz D, Pachtewski J, Butruk E: Malignant transformation of benign epithelial gastric polyps. Am J Gastroenterol, 1995; 90(12): 2152–59
10. Zea-Iriarte WL, Sekine I, Itsuno M et al: Carcinoma in gastric hyperplastic polyps. A phenotypic study. Dig Dis Sci, 1996; 41(2): 377–86
11. Jalving M, Koornstra JJ, Wesseling J et al: Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Aliment Pharmacol Ther, 2006; 24(9): 1341–48
12. Zieltz A, Fernandez JL, Bilder C et al: Fundic gland polyposis and association with proton pump inhibitor intake: A prospective study in 1,780 endoscopies. Dig Dis Sci, 2011; 56(6): 1743–48
13. Freeman HJ: Proton pump inhibitors and an emerging epidemic of gastric fundic gland polyposis. World J Gastroenterol, 2008; 14(9): 1318–20
14. El-Zimaity HM, Jackson FW, Graham DY: Fundic gland polyps developing during omeprazole therapy. Am J Gastroenterol, 1997; 92(10): 1858–60
15. Declich P, Ferrara A, Galati F et al: Do fundic gland polyps develop under long term omeprazole therapy? Am J Gastroenterol, 1998; 93: 1393
16. Declich P, Ambrosiani A, Bellone S et al: Fundic gland polyps under omeprazole treatment. Am J Clin Pathol, 1999; 112: 576–78
17. Vieth M, Stolte M: Fundic gland polyps are not induced by proton pump inhibitor therapy. Am J Clin Pathol, 1999; 112: 716–20
18. Klinkenberg-Knol E, Nels F, Dent J et al: Long term omeprazole treatment in resistant gastroesophageal reflux disease: Efficacy, safety and influence on gastric mucosa. Gastroenterology, 2000; 118: 661–69
19. Pilot PR, Sablinska K, Owen S, Hatfield A: Epidemiological analysis of second primary malignancies in more than 9500 patients treated with imatinib. Leukemia, 2006; 20: 148–49
20. Voglova J, Muzik I, Faber E et al: Incidence of second malignancies during treatment of chronic myeloid leukemia with tyrosine kinase inhibitors in the Czech Republic and Slovakia. Neoplasma, 2011; 58: 256–62
21. Roy L, Guilhot J, Martineau G et al: Unexpected occurrence of second malignancies in patients treated with interferon followed by imatinib mesylate for chronic myelogenous leukemia. Leukemia, 2005; 19: 1689–92
22. Verma D, Kantarjian H, Strom SS et al: Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies. Blood, 2011; 118: 4353–58
23. Gambacorti-Passerini C, Antolini L, Mahon FX et al: Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. J Natl Cancer Inst, 2011; 103: 553–61
24. Duman BB, Paydas S, Disel U et al: Secondary malignancy after imatinib therapy: Eight cases and review of the literature. Leuk Lymphoma, 2012; 53: 1706–8
25. Stein BL: Chronic myeloid leukemia and risk of second malignancy in two eras of treatment. Leuk Lymphoma, 2012; 53: 1651–53
26. Novartis Pharmaceuticals Japan [Internet]. Prescribing Information. Tokyo, Tasigna [updated June 2013; cited 1 January 2017]. Available from; http://product.novartis.co.jp/tas/ts/pms_tas_shibo_20130628.pdf [in Japanese]
27. Kantarjian HM, Hochhaus A, Saglio G et al: Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol, 2011; 12: 841–51
28. Novartis Pharmaceuticals US [Internet]. Prescribing Information. US, Gleevec [updated January 2015; cited 20 December 2016] Available from; http://pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf
29. Kantarjian HM, Giles FJ, Bhatia KN et al: Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood, 2011; 117: 1141–45
30. Sekiguchi Y, Shimada A, Matsuzawa M et al: Occurrence of carcinoma of the pancreas following nilotinib therapy for chronic myeloid leukemia: Report of a case with review of the literature. Turk J Haematol, 2015; 32(3): 257–62
31. Shugo H, Hodo Y, Watanabe T et al: Multiple gastrointestinal stromal tumors during nilotinib treatment for chronic myelogenous leukemia in a patient with neurofibromatosis type 1. Nihon Shokakibyo Gakkai Zasshi, 2014; 111(8): 1579–86
32. Naranjo CA, Busto U, Sellers EM et al: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther, 1981; 30: 239–45