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CASE REPORT

Gynecomastia in a Chronic Myeloid Leukemia Patient After Switching from Imatinib to Flumatinib

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Abstract: Gynecomastia refers to the abnormal enlargement of the male breast caused by the proliferation of the glandular component of the breast, typically due to sexual hormone disturbance. Multiple medications have been linked to the development of gynecomastia with varying incidences. This adverse event has also been associated with TKIs such as imatinib, dasatinib, and rarely nilotinib. However, it is poorly described and regarded as a rare event. Herein, we present the first case of a CML patient who developed gynecomastia after switching from imatinib to flumatinib. The patient is an 82-year-old male. He was diagnosed with CML and initially treated with imatinib. However, the treatment response milestone after three months of imatinib was not achieved. Hence, flumatinib was used to replace imatinib. Unexpectedly, two weeks later, he developed gynecomastia. Gynecomastia usually causes distress to patients, and there are currently no clear mechanisms or management strategies for this condition. Inspired by this case and through a review of the literature, we propose possible mechanisms and management strategies for this rare adverse event associated with TKIs, along with future perspectives. This may assist others in dealing with this issue and stimulate research on it.

Keywords: gynecomastia, chronic myeloid leukemia, flumatinib

Introduction

Tyrosine kinase inhibitors (TKIs) have changed the treatment landscape of chronic myeloid leukemia (CML), achieving impressive long-term outcomes compared to traditional therapies. Despite approval of the third generation, side effects, including myelosuppression, fluid retention, rash, myalgia/arthralgia, cardiovascular disease, hyperglycemia, pulmonary arterial hypertension, and liver toxicity, consistently trouble some patients, leading to dosage reduction and even discontinuation.[1] Gynecomastia is a relatively rare adverse event of TKIs, and has been associated with imatinib, dasatinib, and nilotinib.[2–4] Gynecomastia is an abnormal condition characterized by the enlargement of the male breast, which is caused by the proliferation of the glandular component of the breast, typically due to sexual hormone disturbance. Drugs, such as antiandrogens and 5 alpha-reductase inhibitors, have been estimated to cause about 10–25% of all cases of gynecomastia. Despite the widespread use of TKIs in CML, gynecomastia is regarded as a rare event associated with it and it is poorly described.[5,6] Flumatinib is a second-generation TKI and was approved for patients with Philadelphia chromosome-positive CML in China in 2019. Here, we present the case of a CML patient who developed gynecomastia after switching from imatinib to flumatinib. To the best of our knowledge, this is the first case report of gynecomastia associated with flumatinib. Currently, there are no well-defined mechanisms or established management strategies for this condition. Inspired by this case and through a comprehensive review of the literature, we put forward possible mechanisms and management strategies for this rare adverse event associated with TKIs, along with future perspectives. We suggest that gynecomastia may be a potential adverse event for all TKIs and should be given due attention, and this paper may help others address this issue and stimulate research on it.

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Case Presentation

An 82-year-old male of Han nationality was admitted to the endocrinology department of our hospital in August 2023 because of poor glucose control. Regular complete blood count (CBC) showed a significant white blood cell count of 78.18×10^9/L, with neutrophil dominance (70.25×10^9/L) and increased basophilic granulocytes (3.28×10^9/L), thrombocytosis (572 ×10^9/L), and HGB (118 g/L). Abdominal ultrasonography revealed slight splenic enlargement, with a maximum dimension of 12.1 cm. Bone marrow aspiration was performed for morphology, immunology, cytogenetics, and molecular (MICM) detection. The patient was diagnosed with chronic myeloid leukemia (CML). He was initially treated with hydroxyurea to reduce white blood cells as an inpatient, and then with imatinib as an outpatient. Three months later, a response evaluation showed BCR-ABL-210/ABL (56.58%). Imatinib was discontinued and the patient was subsequently started on flumatinib. Two weeks later, he experienced pain in both breasts, and ultrasonography on 2024.2.19 showed mammary gland hyperplasia, left 0.26 cm, right 0.3 cm (Figure 1a). Approximately one month later, the patient still complained of pain. Repeat breast ultrasonography revealed significant enlargement of the mammary glands, left 3.4×0.26 cm, right 4.3×0.3 cm, and gynecomastia was confirmed (Figure 1b). After reviewing his medical history carefully, no other medications or underlying medical conditions, apart from flumatinib, could have contributed to the development of gynecomastia. And the patient refused to check his hormonal status changes after initiating flumatinib treatment or at the time of gynecomastia occurrence.

Even so, flumatinib was the last resort in the TKI arsenal in our department, and he was deprived of nilotinib owing to diabetes mellitus. He continued with flumatinib and was advised to undergo bilateral subareolar mastectomy; however, he refused it and was under follow-up.

Discussion and Future Perspective

Although TKIs are classified as targeted drugs, they do not strictly act on a single target, leading to off-target effects. The first-generation TKI imatinib is a signal transduction inhibitor that inhibits BCR-ABL, c-KIT, and platelet-derived growth factor receptor (PDGFR).[7] Besides BCR-ABL, the second-generation TKI dasatinib can also inhibit Src, c-KIT,

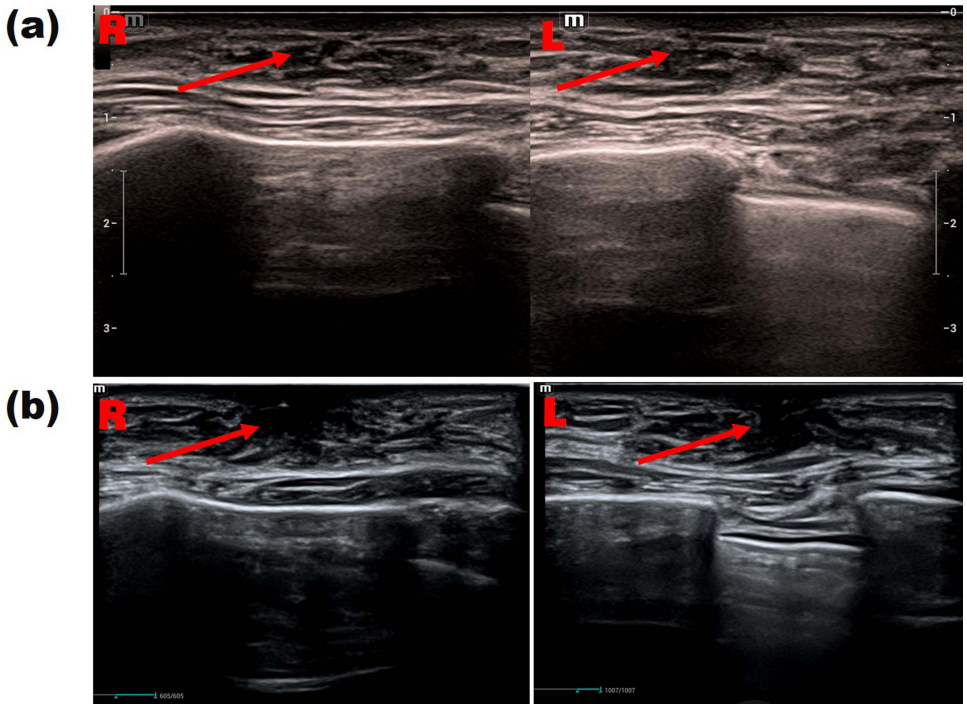

Figure 1 Ultrasonography images show developmental mammary glands. (**a**) Two weeks after flumatinib; (**b**) One and a half months after flumatinib. The red arrows indicate enlarged gland.
Abbreviations: R, right; L, left.

and PDGFR.[3] Gynecomastia is thought to be related to c-KIT and PDGFR because they are receptors expressed in the testis, and the inhibition by TKIs results in a reduction of testosterone production, thus contributing to gynecomastia. Imatinib is the most commonly reported TKIs that causes gynecomastia, with a frequency of 6–18%, followed by dasatinib.[2,3,8] Similarly, nilotinib can also exert antagonism against c-KIT and PDGFR, however, we only found a single case.[4] Flumatinib is a second-generation TKI and a selective inhibitor of BCR-ABL, PDGFR, and c-KIT, which have been increasingly used, especially in China.[9] To the best of our knowledge, this is the first report of gynecomastia associated with flumatinib therapy. Interestingly, gynecomastia occurred after the replacement of imatinib with flumatinib in our patient, indicating discrepant pharmacodynamics of different TKIs on the c-KIT/PDGFRA axis.[10] Similarly, Caocci et al reported a case of gynecomastia after the replacement of imatinib with dasatinib, and tamoxifen was prescribed, with a significant regression of gynecomastia within 1 month.[3] On the contrary, Natalie et al reported a patient with the disappearance of gynecomastia after changing dasatinib to imatinib.[11] In the aforementioned case, the patient developed gynecomastia after switching from imatinib to nilotinib, which resolved within 3 months after switching to dasatinib, and nilotinib was considered more effective than dasatinib on c-KIT.[4,12] The cases indicated that the second generation TKIs are more likely to cause gynecomastia because they cause a more potent inhibitory action on c-KIT and PDGFR, moreover, dose dependence.[3,7,9] This could also be explained by their molecular structure and pharmacokinetics and pharmacodynamics. Flumatinib is obtained by replacing the phenyl ring of imatinib with a pyridine group and introducing a trifluoromethyl group. These structural alterations enable flumatinib to attain higher potency. In comparison with other TKIs (imatinib, nilotinib, and dasatinib), the chemical structure of flumatinib is similar.[13] However, compared with imatinib, the second-generation TKIs have fewer total users and a later market entry time, which could potentially explain the lower number of cases of gynecomastia associated with them.

Inspired by the case and literature, we speculated that any TKIs targeting the c-KIT/PDGFRA axis has the potential to cause gynecomastia, which should be noted and informed to patients taking or changing TKIs. For patients who develop gynecomastia after TKIs treatment, individualized treatment should be arranged, such as close observation, symptomatic treatment, hormonal therapy, changes of TKIs, and subareolar mastectomy. However, the clear mechanism underlying it and the actual gynecomastia frequency of different TKIs should be further studied. This is the first report of gynecomastia associated with flumatinib, similar to other TKIs, flumatinib has the potential to cause gynecomastia and physicians should know this unusual adverse event.

Data Sharing Statement

The datasets are available from the corresponding author (Dr. Chengxin Luan, gejian52@163.com) upon request.

Statements of Ethics

Written informed consent was obtained from the patient for publication of this study. Ethical approval: Not required for this type of paper in accordance with the guideline of our hospital.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflicts of interest.

References

1. García-Gutiérrez V, Breccia M, Jabbour E, Mauro M, Cortes JE. A clinician perspective on the treatment of chronic myeloid leukemia in the chronic phase. *J Hematol Oncol*. 2022;15(1):90. doi:10.1186/s13045-022-01309-0
2. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia*. 2016;30(8):1648–1671. doi:10.1038/leu.2016.104
3. Caocci G, Atzeni S, Orrù N, et al. Gynecomastia in a male after dasatinib treatment for chronic myeloid leukemia. *Leukemia*. 2008;22 (11):2127–2128. doi:10.1038/leu.2008.106
4. Nilotinib. *Reactions Weekly*. 2012;1385:34. doi:10.2165/00128415-201213850-00126
5. Deepinder F, Braunstein GD. Drug-induced gynecomastia: an evidence-based review. *Expert Opin Drug Saf*. 2012;11(5):779–795. doi:10.1517/14740338.2012.712109
6. Trinchieri A, Perletti G, Magri V, Stamatiou K, Trinchieri M, Montanari E. Drug-induced gynecomastia: a systematic review and meta-analysis of randomized clinical trials. *Arch Ital Urol Androl*. 2021;93(4):489–496. doi:10.4081/aiua.2021.4.489
7. Gambacorti-Passerini C, Tornaghi L, Cavagnini F, et al. Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet*. 2003;361 (9373):1954–1956. doi:10.1016/S0140-6736(03)13554-4
8. Liu H, Liao G, Yan Z. Gynecomastia during imatinib mesylate treatment for gastrointestinal stromal tumor: a rare adverse event. *BMC Gastroenterol*. 2011;11:116. doi:10.1186/1471-230X-11-116
9. Zhao J, Quan H, Xu Y, Kong X, Jin L, Lou L. Flumatinib, a selective inhibitor of BCR-ABL/PDGFR/KIT, effectively overcomes drug resistance of certain KIT mutants. *Cancer Sci*. 2014;105(1):117–125. doi:10.1111/cas.12320
10. Shyam sunder S, Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Signal Transduc Targ Therap*. 2023;8(1):262. doi:10.1038/s41392-023-01469-6
11. Natalie Anne Torrente MK, Quan WJR. Gynecomastia with dasatinib use in chronic myeloid leukemia; 2022. Available from: https://sma.org/abstracts/gynecomastia/. Accessed September 17, 2024.
12. Blay JY, von Mehren M. Nilotinib: a novel, selective tyrosine kinase inhibitor. *Semin Oncol*. 2011;38:S3–9. doi:10.1053/j.seminoncol.2011.01.016
13. Jiang B, Qi J, Sun M, et al. Pharmacokinetics of single- and multiple-dose flumatinib in patients with chronic phase chronic myeloid leukemia. *Front Oncol*. 2023;13:1101738. doi:10.3389/fonc.2023.1101738