

Imatinib-induced gynecomastia: A case report

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Abstract. Chronic myeloid leukemia is a myeloproliferative neoplasm characterized by the unregulated and abnormal proliferation of both mature and immature granulocytes, which results in the proliferation of peripheral blood leukocytes. Imatinib, a tyrosine kinase inhibitor, is the first-line treatment for patients diagnosed with chronic myeloid leukemia. However, despite its favorable safety profile, imatinib use is associated with a number of side effects. Gynecomastia is a rare adverse effect of imatinib treatment and may be associated with an imbalance in sex hormones. The present study reports the case of a patient with chronic myeloid leukemia diagnosed with gynecomastia after imatinib treatment. The aim of the present report was to highlight to clinicians this adverse reaction to imatinib treatment and investigate a treatment strategy with fewer side effects.

Introduction

Chronic myeloid leukemia (CML) is a type of malignant tumor formed by the clonal proliferation of bone marrow hematopoietic stem cells (1). A majority of patients with CML exhibit slow disease progression and remain asymptomatic in the early stages of disease (2). The pathogenesis of CML is attributed to ectopic rearrangement of chromosomes 9 and 22, which produce an abnormal BCR activator of RhoGEF and GTPase-ABL proto-oncogene (BCR-ABL) fusion gene (3). This fusion gene can produce an abnormal protein with tyrosine kinase activity, which prompts increased cell proliferation and may lead to CML pathogenesis (4). Therefore, tyrosine kinase inhibitors (TKIs) targeting BCR-ABL have exhibited high efficacy in CML treatment. Imatinib (IM) is the first-line treatment for CML (4,5). The use of IM and second-generation TKIs, such as nilotinib and dasatinib, has considerably prolonged disease-free

survival in patients with CML (4,5). However, despite its excellent safety profile, IM can cause certain adverse reactions, including edema, nausea, vomiting, joint and muscle pain, rash, fatigue, abdominal distension, diarrhea, muscle spasms, liver and kidney dysfunction, bleeding, ascites and exfoliative dermatitis (6). Rare, but potentially adverse reactions with a risk of morbidity, have also been reported. These rare adverse effects include splenic rupture, severe rash, hair repigmentation, bone marrow necrosis, acute fulminant hepatitis, breast carcinoma and male gynecomastia (7-9). The present study reports a case of IM-induced gynecomastia and aims to discuss the therapeutic considerations in this unique population.

Case report

A 48-year-old male patient was admitted to the Department of Gastroenterology of The First Affiliated Hospital of Jishou University (Jishou, China) in March 2016 with a complaint of abdominal distension persisting for over 2 months. Physical examinations showed splenomegaly with three transverse fingers under the splenic ribs. Routine blood tests showed a white blood cell count of $342.48 \times 10^9/l$ (normal range, $\sim 4.00-10.00 \times 10^9/l$), a hemoglobin count of 82 g/l (normal range, 110-150 g/l), a platelet count of $242 \times 10^9/l$ (normal range, $\sim 100-400 \times 10^9/l$) and a mean corpuscular volume size of 104.90 fl (normal range, 80.00-100.00 fl). Abdominal color ultrasound results demonstrated an enlarged spleen measuring ~ 164 mm in length and ~ 52 mm in thickness (Fig. 1). The patient was advised to undergo treatment at the Department of Hematology of The First Affiliated Hospital of Jishou University.

The patient had a history of hepatitis B and hepatitis E infection, and took entecavir capsule to control the proliferation of HBV, but their liver function (Hitachi 7060 automatic biochemical analyzer; Shanghai Kehua Bio-Engineering Co., Ltd.) and liver color ultrasound were normal, and the nucleic results of hepatitis B virus were < 2.00 IU/ml (normal range, < 2.00 IU/ml). The patient had no history of alcohol consumption. Bone marrow testing (10) was performed after admission to hospital. Hyperactive bone marrow proliferation was shown, with the proliferation of various stages of the neutral myelocytes (5% acidophils and 3% alkalophils; 200 cells were manually counted under a microscope, and the specific values are the ratio of acidophils and alkalophils

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in 200 cells multiplied by 100%) (Fig. 2). These findings were consistent with the symptoms of CML. The results of a bone marrow biopsy (fixed with Bouin fluid; thickness, 3 μ m; lined separately for hepatocyte growth factor, H&E and Gomori staining) (11-13) demonstrated active bone marrow hyperplasia with an increased granulocyte/erythrocyte ratio and granular hyperplasia, containing mature cells and acidophilic granulocytes (Fig. 3). The bone marrow chromosome test results (GTG banding; ISCN 2009) (14,15) demonstrated the presence of the Philadelphia chromosome (Fig. 4). The results of bone marrow fluorescence *in situ* hybridization experiment to detect BCR/ABL fusion were positive (Fig. 5). Quantification of the BCR/ABL fusion gene P210 was performed using a two-color dual-fusion DNA probe (Beijing Jinpujia Medical Technology Co., Ltd.) and imaged using an OLYMPUS-BX51 fluorescence microscope (Olympus Corporation) (16). The quantification of the BCR/ABL fusion gene (BCR-ABL copy number/ABL copy number \times 100%) was demonstrated to be 251.9126% (17). Considering the patient's symptoms and the results of blood and bone marrow-related tests, a diagnosis of CML-chronic phase with a Sokal score of 1.2 (18) was suggested. After admission, the patient was treated with hydroxyurea (1.0 g orally three times a day) for 2 weeks in March 2016 and then with 400 mg of IM/day since the CML diagnosis in March 2016 (400 mg/day from March 2016; 300 mg/day from April 2017; 400 mg/day from January 2018). Routine treatment with 400 mg of IM/day was continued after hospital discharge. In July 2016, October 2016, January 2017 and April 2017, the peripheral blood BCR/ABL fusion gene P210 quantification was 3.20, 0.16, 0.05 and 0.125%.

In January 2017, the patient visited the breast and thyroid clinic at the aforementioned hospital with a complaint of double breast pain. Color ultrasound of breast tissues demonstrated that the size of the left breast was \sim 14 \times 13 \times 6 mm and the size of the right breast was \sim 27 \times 29 \times 8 mm. Right breast enlargement was observed (Fig. 6). The patient was then advised to undergo breast surgery, but refused. A color ultrasound performed in April 2017 to determine whether the mammary gland exhibited an enlargement trend showed that the right breast gland had a size of 34 \times 27 \times 11 mm (Fig. 7). A sex hormone test of a peripheral blood sample demonstrated a marginal increase in progesterone levels (Table I). After follow-up, the potential adverse effects caused by IM were considered. As the androgen level was not decreased, testosterone undecanoic acid was not administered. A reduction of the IM dose to 300 mg/day was recommended to the patient to reduce the adverse side effects. After this change in the treatment plan, the severity of the patient's symptoms and the size of both breasts decreased, and the patient reported no breast pain. Quantification of peripheral BCR/ABL fusion gene expression was reported to be 0.067, 0.122 and 0.454% in July 2017, December 2017 and January 2018, respectively. Subsequently, the IM dose was increased to 400 mg/day. Owing to the side effects of IM and poor treatment efficacy, the patient underwent dasatinib (orally; 100 mg/day) treatment since March 2018. A subsequent BCR/ABL quantification test showed negative results and the patient reported no abnormal breast development. Whilst undergoing dasatinib treatment, a color ultrasound showed normal liver, gallbladder and splenic function (Fig. 8). Peripheral blood liver and renal

Table I. Sex hormone test results.

Sex hormone	Patient result	Normal laboratory reference value
Serum prolactin, ng/ml	7.66	4.79-23.30
Folkopietin, mIU/ml	12.26 ^a	25.80-134.80
Luteinizing hormone, mIU/ml	4.89 ^a	7.70-58.50
Estradiol, pg/ml	28.00 ^b	<5.00
Progesterone, ng/ml	0.98 ^b	0.10-0.80
Testosterone, ng/ml	9.28 ^b	0.08-0.48

^aDecreased or ^belevated compared with normal laboratory reference values.

Table II. Laboratory test results of the patient.

Variable	Patient result	Normal laboratory reference value
Alanine aminotransferase, U/l	12.00	0.00-40.00
Aspartate aminotransferase, U/l	17.00	0.00-40.00
Total bilirubin, μ mol/l	8.80	3.40-20.50
Direct bilirubin, μ mol/l	2.00	0.00-6.84
Indirect bilirubin, μ mol/l	6.80	0.00-18.00
Cholinesterase, U/l	8,516.00	4,000.00-11,000.00
Total bile acid, mmol/l	2.00	0.00-12.00
Carbamide, μ mol/l	4.50	2.50-7.14
Creatinine, μ mol/l	68.60	40.00-120.00
Hepatitis B virus DNA IU/ml	<2.00	<2.00

function and HBV-DNA results were normal (Table II). In May 2024, the patient underwent follow-up in the outpatient clinic. No specific symptoms were observed during the last follow-up appointment. The patients will be followed up in the outpatient clinic every 1-2 months.

Discussion

Gynecomastia is highly prevalent in the elderly and may affect up to 24-65% of men among those aged 50-80 years (19). Unlike in children and young adults, gynecomastia in older adults is more likely to be associated with certain pathological factors. Pathological gynecomastia is associated with several factors, including liver cirrhosis, drug therapy, hypogonadism, malnutrition, hyperthyroidism, testicular tumors and chronic kidney disease (20). IM is an antitumor-targeted chemotherapeutic agent that inhibits tyrosine kinase receptors, including



Figure 1. Abdominal color ultrasound performed in March 2016. The ultrasound demonstrated an enlarged spleen measuring ~164 mm in length and ~52 mm in thickness. Left panel, liver; right panel, spleen.

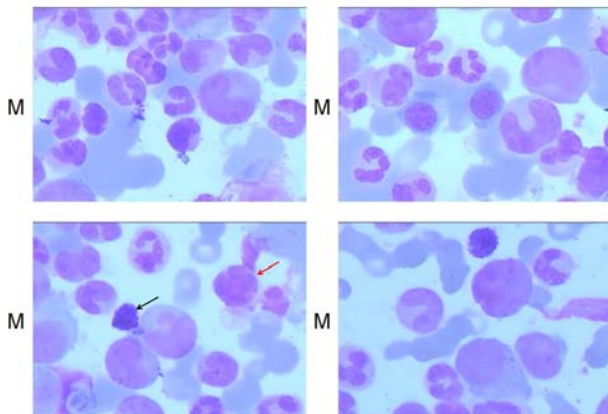


Figure 2. Bone marrow smear results indicating hyperactive bone marrow hyperplasia. Neutrophilic myelocytes exhibited hyperplasia, with 5% acidophils (red arrow) and 3% alkalophils (black arrow). Magnification, x100.

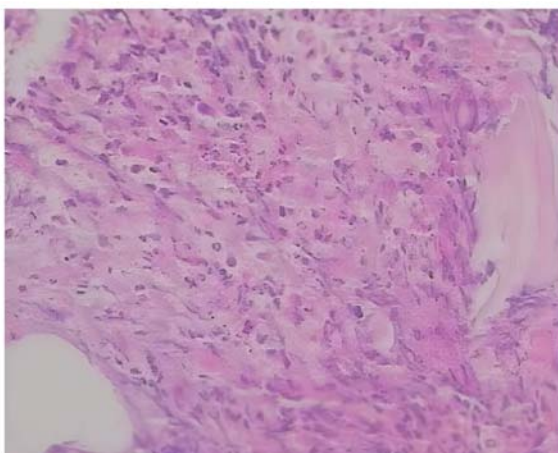


Figure 3. Bone marrow biopsy showing active bone marrow hyperplasia, increased proportion of erythroid lines, granular hyperplasia, predominance of mature cells and acidophilic granulocytes. Magnification, x40.

c-Kit, BCR-ABL and platelet-derived growth factor receptors (PDGFRs). These receptors regulate a number of cellular processes, including cell proliferation, differentiation and

survival (21). Despite its excellent safety profile, IM can cause distinct side effects, such as edema, nausea, vomiting, fatigue, splenic rupture, severe rash, breast cancer and gynecomastia (8,22). The present study reported a rare case of IM-induced gynecomastia in a patient with CML.

A limited number of studies have reported findings on gynecomastia occurring in response to IM treatment (9,23-29). The patient in the present study developed gynecomastia ~10 months after starting treatment with IM. During IM administration, the patient took the 'entecavir capsule' to control HBV replication and without any solid tumors. Therefore, it was hypothesized that gynecomastia was an adverse reaction caused by IM. However, owing to the small number of cases currently published, the relationship between IM and gynecomastia remains unclear. Therefore, the relevant literature was reviewed using PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=imatinib+and+gynecomastia&size=50>; key words, imatinib and gynecomastia) and discussed.

The literature suggested that free testosterone levels decrease and estrogen levels increase in response to IM administration, thus indicating that an imbalance in sex hormone levels may lead to gynecomastia (26-29). IM, as a TKI, can selectively block the c-Kit receptor and PDGFR via the same mechanism (30), both of which are expressed in both male and female gonads. By binding with its ligands, IM can promote the proliferation and development of primordial germ cells, thus maintaining their normal physiological function and survival. In addition, IM also promotes the secretion of testosterone by testicular stromal cells and ovarian endometrial cells (31,32). A number of clinical trials conducted on animals and patients have reported that the serum levels of testosterone, follicular hormone and luteinizing hormone increase significantly in response to IM use (33). Hormone tests conducted on patients treated with IM in China showed that the triiodothyronine levels of some patients decreased and their thyroid-stimulating hormone levels increased, whilst the testosterone levels of some male patients decreased (34). These changes in hormone levels were related to a number of corresponding clinical symptoms, such as body temperature drop, cold hands and feet, loss of appetite, fatigue, dizziness, memory loss, and edema for low



Figure 4. Bone marrow cell chromosome analysis demonstrating the presence of the Philadelphia chromosome (arrow).

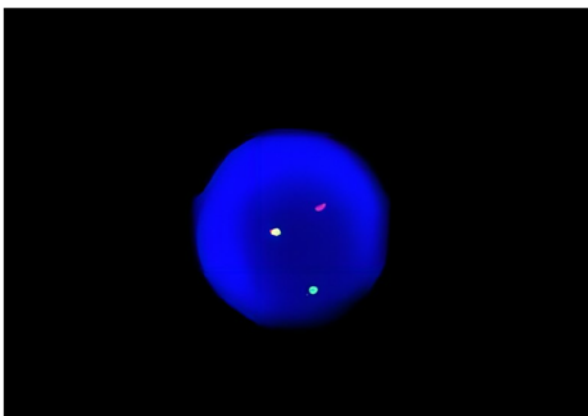


Figure 5. Fluorescence *in situ* hybridization of bone marrow samples showing positive expression of the BCR activator of RhoGEF and GTPase-ABL proto-oncogene fusion gene. Magnification, x1,000.

triiodothyronine levels, fear, myxoedema, weight gain and increased heart rate for high thyroid-stimulating hormone levels, and decreased sexual desire, lack of energy, mood

abnormalities and osteoporosis for low testosterone levels. These effects were also related to the duration of drug administration; testosterone decreased with administration time and was negatively associated with administration time (34). Among second-generation TKIs, dasatinib and nilotinib are also multitarget inhibitors of target receptors such as c-Kit, tyrosine kinases and PDGFR (35). Caocci *et al* (36) reported a case of gynecomastia in a patient with CML receiving dasatinib. Therefore, the aforementioned studies indicated that IM may affect the function of certain receptors, such as c-Kit and PDGFR, which causes an imbalance in physiological sex hormone levels and can lead to the abnormal development of breasts in male patients.

It has also been reported that gynecomastia caused by IM may be dose-dependent. Gambacorti-Passerini *et al* (27) reported a significant association between the therapeutic dose of IM and gynecomastia, with IM doses of 600-800 mg/day reducing testosterone levels more than 400 mg/day IM. Zhao *et al* (29) achieved satisfactory treatment efficacy by subsequently reducing the IM dose from 400 to 300 mg in patients with CML. In the present case, the IM dose was reduced from 400 to 300 mg/day, which improved the symptoms reported by

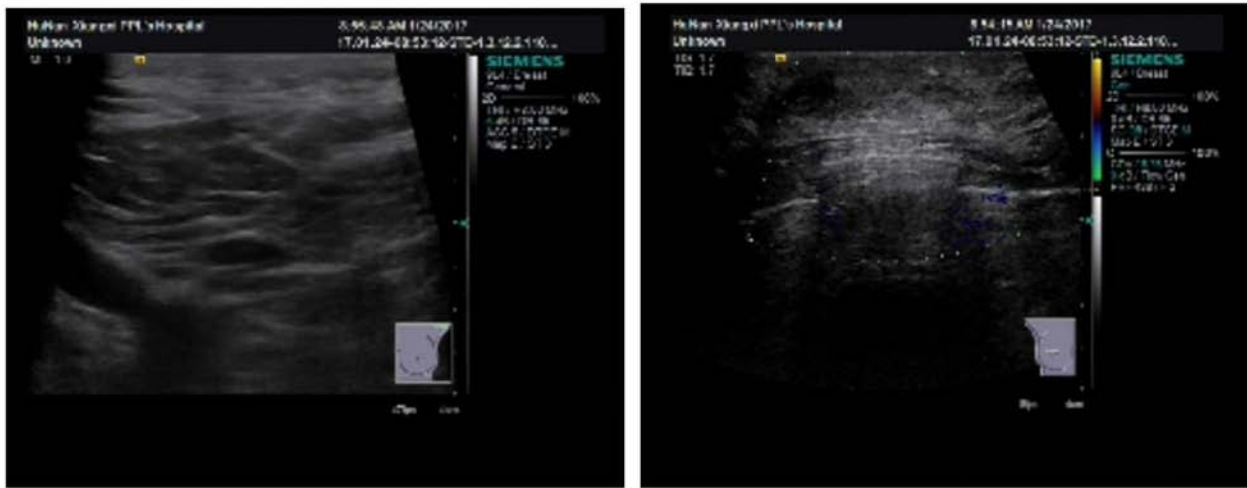


Figure 6. Color ultrasound of breast tissue performed in January 2017. The right breast tissue had a size of 27x29x8 mm. The hierarchy of the right breast was clear, the skin surface was smooth and the echo of the gland layer was uniform. The left mammary gland had a discoid echo and was ~14x13x6 mm in size. Left panel, left breast; right panel, right breast.

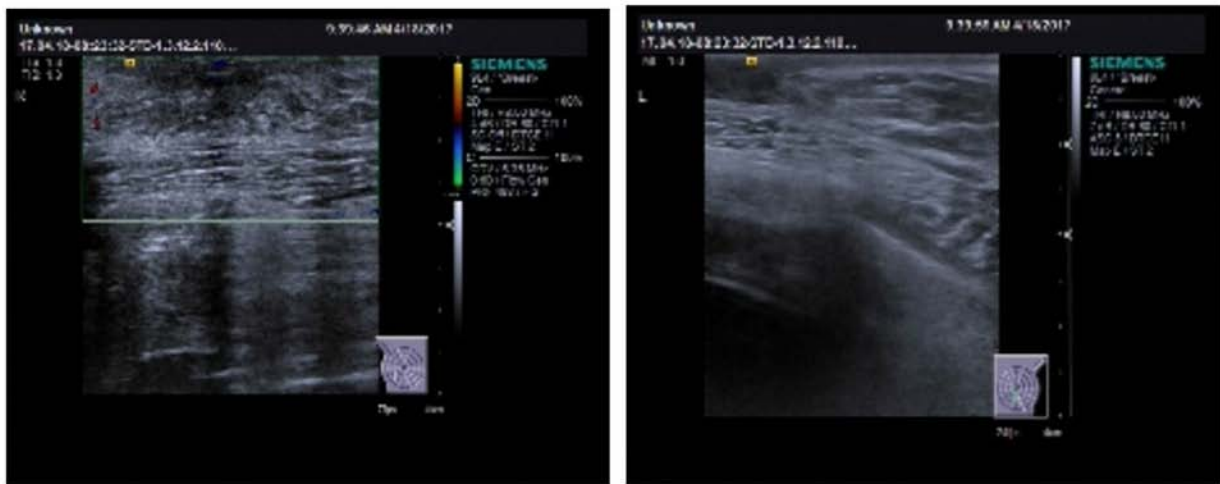


Figure 7. Color ultrasound of breast tissue performed in April 2017. The right breast tissue had a size of 34x27x11 mm. The right breast had clear layers and low echogenicity. The left gland layer was uniform, with no obvious dilated ductal echo. The left mammary gland had a discoid echo and was ~14x13x6 mm in size. Left panel, right breast; right panel, left breast.



Figure 8. Abdominal color ultrasound performed in April 2024 showing normal liver, gallbladder and splenic function. Left panel, portal vein blood flow chart; middle panel, right kidney exhibited hydronephrosis; right panel, the right ureter was dilated, and stones can be seen in the upper section.

the patient. Subsequently, the patient was recommended an alternative treatment, dasatinib, owing to the poor efficacy and side effects of IM. Upon dasatinib treatment, the patient did

not show further signs of gynecomastia. This suggested that gynecomastia in the patient in the present report was likely a side effect of IM treatment.

Gynecomastia can be treated using radiotherapy, surgery and medication. Drugs such as androgens, antiestrogens, aromatase inhibitors, tamoxifen and danazol are reported to be effective for the treatment gynecomastia (25,32,37,38).

With the continuous use of new and increasingly effective TKIs, published reports on IM-induced male breast development have decreased. However, clinicians should be aware of such adverse reactions. Based on the results of the present case report, it could be recommended that clinicians assess the hormonal status of each patient before and during treatment and take timely measures to compensate for the adverse consequences of sex hormone imbalance.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XLL, ML and ZWS were responsible for collecting clinical, imaging and pathological data of the patient and drafting the manuscript. HJF, SKT and LZW analyzed the data. KS designed the study. JT participated in making the pathological diagnosis and was involved in data collection and analysis. XLL and KS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent for publication of the case report and any accompanying images, without any potentially identifying information, was provided by the patient.

Competing interests

The authors declare that they have no competing interests.

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