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Case Report
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GYNECOMASTIA DURING THERAPY WITH NILOTINIB (AMN 107) FOR CHRONIC MYELOID LEUKEMIA – A RARE CASE REPORT.

[1*]Lalit Prashant Meena, [2]Jaya Chakravarty, [3]Saurabh Chopra, [4]Siddharth Samrat, [5]Madhukar Rai

[1]Assistant Professor, Department of Medicine,Institute of Medical Sciences, BHU, India.
[2]Associate Professor, Department of Medicine,Institute of Medical Sciences, BHU, India.
[3, 4]Jr, Department of Medicine, Institute of Medical Sciences, BHU, India.
[5]Professor, Department of Medicine, Institute of Medical Sciences, BHU, India.

***Correspondence for Author: Dr. Lalit Prashant Meena**
Assistant Professor, Department of Medicine, Institute of Medical Sciences, BHU, India.

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ABSTRACT

Nilotinib (AMN107) exhibits superior potency to imatinib as an inhibitor of wild-type BCR-ABL in a wide range of CML-derived and transfected cell lines. gynecomastia in male patients treated with imatinib and dasatinib has been reported in few cases.But gyenecomastia due to Nilotinib is never reported.Here we report the first case of Nilotinib induced gyenecomastia. 40 years old male patient was diagnosed as CML with chronic phase . Initially for two years he took Imatinib mesylate, but later on he was shifted on Nilotinib due to development of resistant to Imatinib. After six to seven month of treatment with nilotinib, he developed gynecomastia.

KEYWORDS:

INTRODUCTION

The BCR-ABL oncogene, which results from a reciprocal t(9;22) chromosomal translocation, encodes a chimeric BCR-ABL protein having constitutively activated Abl tyrosine kinase activity, and is the underlying cause of CML.[1,2,3] AMN107 exhibits superior potency to imatinib as an inhibitor of wild-type BCR-ABL in a wide range of CML-derived and transfected cell lines.[4,5,6,7] AMN107 maintains activity against imatinib-resistant BCR-ABL mutants, but has no significant activity against the T315I mutant.[8] Few authors reported several cases of gynecomastia in male patients treated with imatinib and dasatinib hypothesize a mechanism by which the drug reduces testosterone production through the block of PDGFR and c-kit in the testis.[9,10,11] Here we reporting the first case who developed gyenecomastia after treatment with Nilotinib.

CASE REPORT

Buchan Sharma 40 years old male presented with chief complain of heaviness in left upper abdomen 36 month back.There was no history of tuberculosis, hypertension and diabetes in past. He is married and have two children. On examination his vitals were within normal limit. Mild pallor was present. Per abdomen examination showed Massive splenomegaly (13 cm) and mild hepatomegaly (3 cm). All the other systemic examination were normal. Blood investigation reports showed; Hb 10.0 g/dl, TLC 210 $\times 10^3/\mu L$(N56 %, L 4%, E 2%, B 6%, Blast 4%, Metamyelocytes 18%, myelocytes 20 %), Pletelet counts 560 $\times 10^3/\mu L$, MCV 86.Other routine biochemical investigation (ranal, liver function, urine) were within normal limit. Peripheral general blood picture showed Marked leucocytosis,raised metamyelocytes and myelocytes, Normocytic normochromic anemia and with mildly raised platelet counts. A bone marrow aspirate was hypercellular, consistent with chronic phase CML.

Cytogenetic analysis of the bone marrow showed 100% Philadelphia chromosome positivity along with BCR/ABL gene rearrangement (93%) by RT-PCR .On the basis of these investigation diagnosis of CML in chronic was made and imatinib mesylate 400 mg was started. He showed very good response and within three month of treatment his spleen became non palpable, total leucocyte count came with in normal limit and remain asymptomatic for 28 months. After 28 month with continuing of treatment with Imatinib he became non responsive (total leucocyte count was raised and spleen became palpable). Again bone marrow was done which showed features of CML in accelareted phase .BCR-ABL Kinase domain mutation study was done which was negative for mutation study.Then the patient was shifted to Nilotinib 400mg twice a day.After starting of Nilotinib patient develop very good hematological response, but after few months of taking this drug patient developed bilateral gynecomastia**.** The patient had not taken any other medication potentially capable of influencing hormone levels. In laboratory reports the level of serum free testosterone, serum estradiol and level of βHCG was found within normal range.

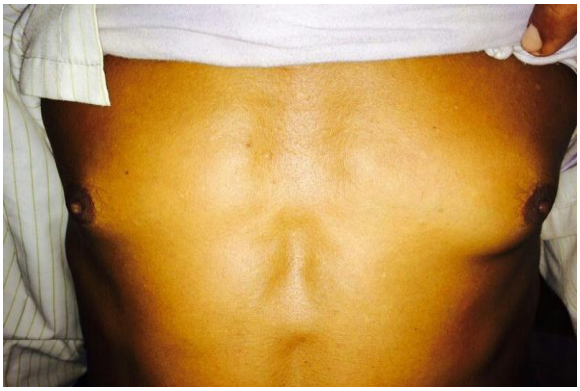

Image: Gynecomastia After Taking Nilotinib

DISCUSSION

Gynecomastia is enlargement of the glandular tissue in the male breast. It is some time found incidentally. The lesion is usually bilateral, but may also present with unilateral mass.The pathophysiology in development of gynecomastia includes imbalance between androgens and free estrogen that may accur due to multiple mechanisms.[12] In one study by Gambacorti-Passerini et al in which they measured hormone level in 38 men receiving imatinib for chronic leukemia and they found seven cases (18%) of gyenecomastia.[9] Some animal studies had been showed that Platelet-derived growth-factor (PDGF) signaling may constitute a common mechanism in the control of multiple steroidogenic lineages, and the c-Kit gene plays a role during the establishment, the maintenance and the function of germ cells.[13] Platelet-derived growth-factor receptors alpha (PDGFRa) and Receptor tyrosine kinases c-Kit are expressed in the testis. It is believed that they are to be involved in the bio-synthesys of testosterone. Imatinib mesylate and Second-generation tyrosine kinase inhibitors such dasatinib and nilotinib, are multi-target inhibitor, including receptor tyrosine kinases c-Kit and PDGFRa, and thus the production of testosterone may be decreased during its administration.[11] In our case we foun the normal level of serum free testosterone, serum estradiol and level of βHCG which is different finding than the other previous case reports.The patient is 40 years male with two children and he never gave history of any sexual problem. These finding suggest that might be there some other mechanism which causes gyenecomastia in these patients.

CONCLUSION

So far there has not been a single publication regarding gynecomastia in the toxicity profile studies of Nilotinib . Un like the other case reports (imatinib and dasatinib induced gyenecomastia) the hormonal profile of our patient remained normal .The purpose of the present report is to call for attention to this uncommon adverse event, further study is needed.

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