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A RARE CASE REPORT OF ISONIAZID INDUCED UNILATERAL GYNECOMASTIA DURING ANTITUBERCULAR THERAPY

Respiratory Medicine

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ABSTRACT

Introduction: Gynecomastia is a rare but recognized adverse effect of isoniazid, which is a key component of anti-tubercular therapy (ATT). While bilateral gynecomastia is more commonly reported, unilateral presentation is exceedingly uncommon. **Case Report:** A 47-year-old male presented with a complaint of painful swelling over the right side of the chest for three weeks. Patient was on first line ATT for 2 months for treatment of microbiologically confirmed pulmonary TB. Local examination revealed a firm, tender, mobile, subareolar swelling approximately 3 cm in diameter over the right breast. Investigations were normal except for mildly elevated prolactin and glandular tissue hypertrophy in breast ultrasonography. Diagnosis of isoniazid induced gynecomastia was made, patient was reassured and pyridoxine dose was increased from 10mg/day to 40mg/day. At six-week follow-up, tenderness was resolved and swelling size reduced. **Conclusion :** Isoniazid-induced gynecomastia is a rarely reported adverse effect of a widely used drug in India. This case report serves to highlight the need for increased awareness.

KEYWORDS

INTRODUCTION:

Gynecomastia is enlargement of breast tissue in males. Physiologically, gynecomastia is seen in new-borns, elderly and during puberty.[1] Excessive estrogen leading to increased estrogen/androgen ratio causes gynaecomastia. 25% gynaecomastia cases are due to persistent pubertal gynecomastia, 10%-25% are drug-induced and 25% are idiopathic.[2] Common drugs causing gynecomastia include cimetidine, digitalis, phenytoin, spironolactone, protease inhibitors, and antiandrogens.[1]

Isoniazid is a first-line antitubercular agent which acts by mycolic acid synthesis inhibition. It is bactericidal to Intracellular and extracellular bacteria. Common and well known side effects of this drug are peripheral neuropathy, hepatitis, gastric intolerance, depression, encephalopathy, skin rashes etc.[3] Isoniazid is rarely associated with gynecomastia, and even more uncommonly presents unilaterally. The exact mechanism is not fully understood but may involve interference with steroid metabolism or hormonal imbalance. Here, we report a rare case of unilateral gynecomastia in a patient receiving isoniazid as part of antitubercular therapy.

Case Report:

A 47-year-old male auto-rickshaw driver from rural Kerala presented with a complaint of painful swelling over the right side of the chest for three weeks. The swelling had a gradual onset and was associated with mild tenderness. There was no nipple discharge, fever, or visible skin changes. The patient had been diagnosed with sputum-positive pulmonary tuberculosis two months earlier and was initiated on first-line antitubercular therapy (Category I HRZE regimen: isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1500 mg, and ethambutol 1200 mg) as per NTEP guidelines. Pyridoxine 10 mg daily was also co-prescribed. The patient reported noticing right breast enlargement approximately five weeks after starting therapy. There was no history of trauma, supplement or drug use beyond prescribed ATT, or symptoms suggestive of hepatic or endocrine dysfunction. He denied smoking, alcohol use, and any similar illness in the family. There was no past history of testicular disorders or malignancy.

On examination, the patient's vitals were stable. Local examination revealed a firm, mobile, subareolar swelling approximately 3 cm in diameter over the right breast, with mild tenderness. There was no skin discoloration, nipple discharge, or axillary lymphadenopathy. The breast was normal. Systemic examination was unremarkable.

Laboratory investigations, including complete blood count, renal and liver function tests, were within normal limits. Chest X-ray findings were consistent with pulmonary tuberculosis, showing upper lobe infiltrates. Hormonal evaluation showed normal serum estradiol, testosterone, LH, and FSH levels, with mildly elevated prolactin. Breast ultrasonography revealed glandular tissue hypertrophy without any cyst, abscess, or suspicious mass.

Given the timing of symptom onset following isoniazid initiation, absence of other causative factors, and supportive hormonal and imaging findings, a diagnosis of isoniazid-induced gynecomastia was made. Causality assessment using the WHO-UMC scale classified the reaction as “probable,” and the Naranjo score was 6, indicating a probable adverse drug reaction.

The patient was reassured about the benign nature of the condition. As the symptoms were mild and non-progressive, isoniazid was not substituted. Pyridoxine dose was increased to 40 mg/day, and symptomatic relief for breast pain was provided using analgesics. He was advised to report any worsening or persistence of the swelling.

At six-week follow-up, the patient reported complete resolution of breast tenderness and gradual regression of the swelling. There were no new complaints. Pulmonary symptoms had improved significantly, and the sputum smear had converted to negative at the two-month mark.

This case highlights a rare, mild, and reversible instance of unilateral gynecomastia associated with isoniazid therapy, managed conservatively without discontinuation of the offending agent.

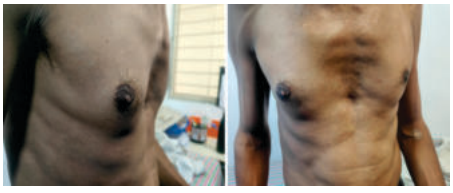

Figure 1. Unilateral enlargement of right breast in lateral and frontal view

DISCUSSION:

Gynecomastia is defined as the benign proliferation of glandular breast tissue in males and is one of the most common breast-related conditions affecting men. The term is formed from the Greek words gyne(females) and mastos(breasts). Gynaecomastia should be clearly differentiated from pseudogynaecomastia, which is an accumulation of excess fat in a male breast.[4] Gynaecomastia has a wide range of etiologies, including developmental causes, congenital disorders such as Klinefelter syndrome, hermaphroditism, and enzymatic defects in testosterone biosynthesis. Acquired factors include trauma, infection, testicular torsion, radiation exposure, mumps, chemotherapy, and certain cancers such as bronchogenic carcinoma. Systemic illnesses like congenital adrenal hyperplasia, cirrhosis, renal failure, and thyrotoxicosis also contribute. Alcohol use and medications are significant contributors, with drug-induced gynecomastia accounting for approximately 10–25% of all cases.[5] Increase in plasma oestrogen activity or inhibition of testosterone synthesis or action are some of the

explained reasons for drug related gynaecomastia. For many drugs exact mechanism is not known.[6]

Isoniazid inhibits pyridoxal phosphokinase and binds with pyridoxine to form Isonicotinyl hydrazide leading to pyridoxin (vitamin B6) deficiency. It also alters oestrogen- androgen metabolism. Pyridoxal 5-phosphate (PLP), the physiologically active form of Vitamin B6, acts as a modulator of steroid hormone receptor mediated gene expression. Increased levels of intracellular PLP leads to decreased transcriptional response to glucocorticoid hormones, progesterone, androgens and estrogen, while vitamin B-6 deficient cells exhibit enhanced responsiveness to steroid hormone.[7] Another possible explanation is the "refeeding gynecomastia" phenomenon, which results from nutritional recovery, weight gain, and restoration of normal gonadotropin and gonadal function during treatment.[8] Thiacetazone and ethionamide are the other antituberculosis drugs reported to cause gynecomastia.[9] Predisposing factors for INH related gynaecomastia have not been identified. Previous case reports have mentioned complete resolution after stopping medication for few months, hence there is no justification for surgery or the use of medications to correct the disorder.[10]

CONCLUSION

Despite its long-standing use, very few cases of isoniazid-induced gynecomastia have been reported in India, highlighting the need for increased awareness. Recognizing this potential side effect is important for clinicians, as it can improve patient management and guide appropriate therapeutic decisions.

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