
Isoniazid related gynecomastia: Description of a case and systematic review of literature

Sir,

Glandular enlargement of the breast in males is known as gynecomastia. Normally, gynecomastia occurs in the neonates, during puberty, and with aging, as a physiological phenomenon.^[1] Imbalance in androgen or estrogen action in the breast tissue through a variety of mechanisms leads to pathological gynecomastia. Drug-induced gynecomastia is one such mechanism seen commonly in day-to-day practice. Common drugs incriminated in the causation of gynecomastia are cimetidine, digitalis, phenytoin, spironolactone, protease

inhibitors, and antiandrogens.^[1-3] Although the incidence of drug-induced gynecomastia varies from 20 to 25%, only occasionally the antituberculous therapy (ATT) is incriminated in the causation of gynecomastia^[4] Among them, only isoniazid, and rarely thiacetazone, is reported to be associated with gynecomastia.^[5-16] Herein, we describe a case of isoniazid-induced gynecomastia during the treatment of tuberculous lymphadenitis.

A 45-year old male presented to the chest clinic with bilateral cervical lymphadenopathy associated with evening

rise of temperature and constitutional symptoms in the form of malaise, loss of appetite, and weight loss. General physical examination was unremarkable. Fine-needle aspiration from the lymph node revealed granulomatous inflammation and stain for acid-fast bacilli was positive. Chest X-ray was normal and he denied treatment with antituberculous therapy (ATT) or other drugs causing gynecomastia in the past. Tuberculin skin test was strongly positive while human immunodeficiency virus (HIV) serology was non-reactive. He was started on category III ATT (Rifampicin 600 mg, isoniazid 600 mg, pyrazinamide 1.5 g thrice a week) under directly observed treatment short course (DOTS) as per the Revised National Tuberculosis Control Programme (RNTCP) protocol. At the end of intensive phase of ATT, he showed symptomatic improvement with decrease in lymph node size. After 3 months of ATT, he visited the chest clinic with painful progressively enlarging swelling of breast on the left side [Figure 1]. On examination, a firm mound of tissue measuring approximately 4 cm around the nipple-areola complex was present, suggesting gynecomastia. No other obvious cause on detailed evaluation (normal genital and thyroid examination with normal secondary sexual characteristics) led to a presumptive diagnosis of isoniazid-induced gynecomastia due to the temporal association with ATT. This diagnosis was based on probable (WHO-UMC causality categories) role of isoniazid in causing gynecomastia. The patient was reassured and was shifted to rifampicin and ethambutol-based therapy for the next 3 months. After 1 month of stopping isoniazid, the pain subsided, and at the end of 3 months, the swelling had decreased by 25%. The patient was eventually lost to follow-up.

This case highlights the importance of recognizing the temporal association of this benign side effect of isoniazid therapy during the course of ATT that can be managed simply with reassurance and withdrawing the culprit drug, thus avoiding the need for unnecessary diagnostic evaluation. Withdrawing the offending drug, isoniazid as in this case, is both diagnostic and therapeutic, and should be

done irrespective of presence or absence of painful reaction. True gynecomastia is defined as glandular enlargement of breast tissue of more than 4 cm in men. It should always be differentiated from the pseudogynecomastia by demonstrating firm, fibrous cord-like tissue that is concentric with nipple-areola complex in true gynecomastia by approximating thumb and forefinger together from either side of the breast during clinical examination.^[1]

Pathological gynecomastia most commonly occurs due to imbalance between androgen and estrogen or because of increased aromatase activity in the adipose tissue leading to excess estrogen. Prolactin at times may be involved in the genesis of gynecomastia through negative feedback on gonadotropin hormone release.^[17] When the cause for gynecomastia cannot be determined, it is termed as idiopathic. By decreasing androgen or increasing estrogen, drugs are an important and common cause of gynecomastia and should always be included in the evaluation as the possible causal agent.

Our patients received 600 mg of isoniazid as part of thrice weekly regimen of RNTCP, similar to reported by Dixit *et al.*, but other reported instances of gynecomastia occurred with lesser doses of isoniazid.^[10-13,15,16] Gynecomastia related to the use of isoniazid was first recognized in 1953 with subsequent four more reports in French and Italian literature,^[5-9] However, a systematic review of the database PubMed using text terms like: Drug-induced gynecomastia, isoniazid-induced gynecomastia, ATT-induced gynecomastia, and search of our personal files revealed only five cases of gynecomastia related to isoniazid [Table 1].^[10-13,15] In all the reported cases, gynecomastia was noted after at least 3 months of isoniazid therapy, and in all cases, withdrawal of isoniazid led to its resolution, which is consistent with findings in our patient. The demonstration of temporal association of gynecomastia twice with isoniazid therapy in the same patient by Morrone *et al.* and resolution following its withdrawal strongly supports its causal relationship



Figure 1: Unilateral enlargement of left breast in frontal and lateral view

Table 1: Details of all the cases of isoniazid-related gynecomastia reported in the English literature

Author (yr)	Age (yrs)	Diagnosis	Treatment and regimen of ATT used	Onset of gynecomastia after ATT (months)	Signs	Outcome
Khanna <i>et al.</i> (2003) ^[10]	25	Tubercular pleural effusion	H 300 mg, R 450 mg, Z 1500 mg, E 800 mg, non-DOTS daily therapy	4	B/L Soft tender lump of 5×4 cm	Resolution after stopping isoniazid
Dixit <i>et al.</i> (2008) ^[11]	42	Tubercular lymphadenitis	H 600 mg, R 450 mg, Z 1500 mg, Thrice weekly, category III ATT under RNTCP	4	B/L Tender lump of 6×8 cm	Resolution after stopping isoniazid
Morrone <i>et al.</i> (2008) ^[12]	18	Sputum positive cavitory pulmonary tuberculosis	H 400 mg, R 600 mg, Z 2000 mg, daily therapy	First episode 3 Second episode 6	Tender lump of 5×5 cm	Resolution after stopping isoniazid in both episodes
Garg <i>et al.</i> (2009) ^[13]	60	Sputum positive pulmonary tuberculosis	H 300 mg, R 450 mg, Z 1000 mg, E 800 mg, non-DOTS daily therapy	5	B/L soft tender lump of 5×6 cm	Resolution after stopping isoniazid
Mansoor <i>et al.</i> (2009) ^[15]	50	Tubercular epididymo-orchitis	NA	4	B/L non-tender soft lump	Resolution after stopping isoniazid
Lee <i>et al.</i> (2009) ^[16]	72	Sputum negative pulmonary tuberculosis	H 300 mg, R 450 mg, Z 1500 mg, E 800 mg, non-DOTS daily therapy	4	B/L rubbery tender lump of 4×4 cm	Resolution after stopping isoniazid

H: Isoniazid; R: Rifampicin; Z: Pyrazinamide; E: Ethambutol; B/L: Bilateral; DOTS: Directly observed treatment short course; RNTCP: Revised National Tuberculosis Control Programme

rather.^[12] The exact mechanism of isoniazid causing gynecomastia remains unknown; plausible proposed mechanisms are altered androgen–estrogen due to disturbance in pyridoxine metabolism as well as refeeding syndrome during recovery from chronic illness, which needs further clarification.^[11]

In conclusion, the importance of this entity lies in the fact that simple recognition and withdrawal of the offending drug can lead to resolution of this problem.

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