ISONIAZID INDUCED GYNAECOMASTIA: A CASE REPORT
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Summary: Gynaecomastia due to anti-tubercular chemotherapy is a rare side effect. Isoniazid causing breast tissue enlargement has been very rarely reported. We report a 60-year-old male patient of Pulmonary Tuberculosis who was started on anti-tuberculous treatment (ATT) with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z) together for initial two months and R, H & E thereon. After five months of initiation of treatment, while receiving RHE, he developed painful bilateral gynaecomastia. Isoniazid was stopped and patient was continued on R & E till completion of the treatment up to nine months. After stopping isoniazid, his breast swelling subsided to some extent and became non-tender. Follow up, at six months, after stopping the course of treatment, patient was asymptomatic except for slight bilateral non-tender breast enlargement. [Indian J Tuberc 2009; 56:51-54]

Key Words: Isoniazid, Gynaecomastia

INTRODUCTION
Side-effects to anti-tubercular drugs are fairly common but there are a few side effects that belong to the rare category. Isoniazid is one of the most effective and cheapest among anti-tuberculous drugs. It is bactericidal against metabolically active bacilli and bacteriostatic against resting bacilli. Isoniazid is well tolerated at recommended dose. It is rarely associated with serious adverse effects that include hepatitis, peripheral neuropathy, cutaneous reactions and mental changes. Gynaecomastia i.e. enlargement of breast tissue as opposed to adipose tissue due to isoniazid is one of the rare but non-serious side-effects of it. Though this has also been implicated as a cause of gynaecomastia but the description in literature is very sparse. Online search on Pub Med revealed only one case report from India, two reports from France and one from Italy. The first report from France was published in 1953 and the second report on it was from Italy in 1957. In the literature, only one case report from India is available in English and elsewhere this finds mention in the long list of drugs causing gynecomastia. The rarity of such an extent prompted us to report this case.

CASE REPORT
SN, a 60-year-old male smoker, non-alcoholic patient presented to Department of Pulmonary Medicine, King George’s Medical University, Lucknow with complaints of cough, expectoration, low grade fever, decreased appetite and streaking. On further evaluation, he was diagnosed as a case of sputum positive pulmonary tuberculosis. Patient was put on isoniazid 300 mg, rifampicin 450 mg, ethambutol 800 mg and pyrazinamide 1000mg once daily. Pyrazinamide was stopped after two months. Patient responded well to the treatment and gained 5-kilogram weight during the initial intensive phase of treatment. Under treatment follow up at 5th month while continuing with rifampicin, isoniazid and ethambutol patient complained of pain and swelling in both breasts. On examination, patient had bilateral tender mobile breast lump (Figs. 1, 2), about 5x6 cm in diameter. Suspecting it to be drug induced gynaecomastia, isoniazid which appeared to be most obvious cause of it was withdrawn immediately from the treatment and rest were continued with further investigation of the patient to know the cause of gynaecomastia. On examination, secondary sexual characters and

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external genitalia were found normal, his mammogram showed features suggestive of, bilateral benign mammary tissue hyperplasia (Fig. 3). His ultrasonogram showed it to be glandular tissue hyperplasia. Patient’s thyroid stimulating hormone level was 0.77uIU/mL (0.3-6.0),

Leutinizing hormone was 6m IU/ml [0.7-7.4], follicle stimulating hormone 6.8 mIU/ml [1.0-14.0], prolactin 11.0 ng/mL [1.8-17 ng/mL], testosterone 4.0 ng/mL [3-20 ng/mL] and estradiol was 54.9 pg/mL [21-79 pg/mL]. His hepatic and renal functions were within normal limits. Ultrasonogram of external

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**Fig. 1:** Frontal view of the patient showing Gynaecomastia developed during isoniazid based anti-tuberculosis treatment.

**Fig. 2:** Lateral view of the patient showing Gynaecomastia.

**Fig. 3:** Mammogram of the patient showing glandular hypertrophy indicating true gynaecomastia.

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genitalia revealed no abnormality. He recuperated well after stopping isoniazid, pain from the breast subsided within a month. Follow-up at six months after the prescribed nine months of treatment revealed an asymptomatic patient with non-tender slightly enlarged breast.

DISCUSSION

Gynaecomastia is one of the most common breast problems in men and was first described by Paulus Aegineta (AD 625-690), who thought it was due to formation of fat. It can occur due to numerous causes which include developmental gynaecomastia, congenital causes like Klinefelter syndrome, hermaphroditism, enzyme defects of testosterone production, acquired causes like trauma, infection, torsion (twisted testicles), radiation, mumps, chemotherapy, malignancies like bronchogenic carcinoma, alcoholism, systemic causes like congenital Adrenal hyperplasia, cirrhosis, renal failure, thyrotoxicosis and drugs.

Drugs are a very common cause of gynaecomastia and should always be entertained as the possible causal agent of such a condition. Most of the drugs causing gynaecomastia have been reported by means of case reports, which document temporal association of the offending drug. Clinically significant gynaecomastia caused by drugs may be due to an impaired balance in the serum estrogen to androgen ratio or a rise in prolactin level. In case of isoniazid induced gynaecomastia it has been hypothesized that disturbance in vitamin B₆ complex activation in liver leads to altered oestrogen-androgen metabolism. It has also been postulated that isoniazid probably acts by phenomenon called ‘Refeeding gynaecomastia’, which is supposed to be caused by restoration of weight, gonadotrophin secretion and gonadal functions.

Among anti-tubercular drugs, Isoniazid, Thioacetazone and Ethionamide have been implicated as causes of gynaecomastia. First report of isoniazid induced gynaecomastia came in 1952, then from Italy in 1957 and another French report came in 1976. The only Indian report was published in 2003. French report described painless, bilateral gynaecomastia in 52-year old man who was receiving 600 mg of isoniazid daily for four months along with rifampicin and ethambutol. On investigation, he was slow acetylator. Strikingly similar to the only other Indian case report, ours was also receiving isoniazid 300 mg daily and also had bilateral painful enlargement of breast in contrast to other foreign reports which had reported it with higher dose of isoniazid and painless enlargement of the breast. The acetylator status was not carried out in this case and the same is also not available in other Indian report. In contrast to other Indian report we stopped isoniazid only, rather than all the ATT after initiation of symptoms and were able to achieve good symptomatic relief. There appears to be temporal association with this offending drug as in all the reports it has occurred in later part (continuation phase) of the therapy.

It is difficult to distinguish true breast enlargement from increased adipose tissue (lipomastia). True glandular tissue is often palpable, especially around the areola, as it is firmer and contains cord like features distinct from the texture of adipose tissue. In difficult cases, true gynaecomastia can be identified by ultrasound, which is recommended as the first-line imaging investigation although mammography may be added to confirm the diagnosis. In this case both were done to confirm the true gynaecomastia which was not done in any of the previous reported cases.

Most patients with gynaecomastia require no treatment other than the removal of any inciting cause. Specific treatment of enlarged breast tissue is indicated if it is causing sufficient pain, embarrassment, or emotional discomfort to interfere with patient’s daily life.

The other anti-tuberculosis drugs which are implicated in the list of drugs causing gynaecomastia are thioacetazone and ethionamide only. As of now, there are no reports implicating...
rifampicin and ethambutol causing gynaecomastia which prompted us to attribute isoniazid as the inciting etiology.

Our case appears to be the first well worked up case after the similar case report in English literature and highlights the fact that isoniazid therapy can lead to development of painful gynaecomastia which may be very embarrassing to the patient, especially if the patient is elderly.

REFERENCES