

Ethionamide-induced gynecomastia

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ABSTRACT

Gynecomastia is very rare during antituberculosis chemotherapy. We describe a 38-year-old male patient who developed a painful gynecomastia following second-line drug therapy for multidrug-resistant pulmonary tuberculosis. Gynecomastia disappeared after stopping the ethionamide. A published literature on antituberculosis-induced gynecomastia is also briefly discussed.

Key words: Antituberculosis therapy, drug-induced gynecomastia, ethionamide

INTRODUCTION

Gynecomastia is defined as unilateral or bilateral enlargement of male breast due to benign enlargement of the duct tissue and periductal stroma in the male breast.^[1] This is seen in a variety of clinical conditions such as during puberty and old age, after exposure to several drugs, during refeeding after starvation, at the beginning of hemodialysis treatment and in alcoholic cirrhosis, endocrine disorders, and neoplastic disorders.^[2]

The drugs commonly implicated with drug-induced gynecomastia are calcium-channel blockers (verapamil, nifedipine, and diltiazem), ACE inhibitors (captopril, enalapril), digoxin, β -blockers, amiodarone, methyldopa, nitrates, neuroleptics, diazepam, phenytoin, tricyclic antidepressants, indinavir, griseofulvin, amphetamines, theophylline, cimetidine, omeprazole, spironolactone, testosterone, domperidone, heparin, antiandrogens, environmental estrogens, ketoconazole, metronidazole, methotrexate, alkylating agents,

etc. Apart from these, among the antituberculosis drugs isoniazid, thioacetazone, and ethionamide are included in the causative list of gynecomastia.^[3] Gynecomastia caused by isoniazid was first reported by Guinet *et al.*^[4] in 1953. Although rare, isoniazid-induced gynecomastia has been reported since then in few reports in French and Indian literature.^[5-8] The literature on Medline search on ethionamide-induced gynecomastia is silent. This communication describes a patient who develops gynecomastia following ethionamide therapy in view of lack of the published report due to its rare occurrence.

CASE REPORT

A 38-year-old, non-smoker, non-alcoholic, asthenic male patient (BMI 16) was referred to us with persistent fever and cough for 2 years. He was previously diagnosed as sputum positive pulmonary tuberculosis (TB) and had already received two courses of anti-TB treatment under the revised national tuberculosis control program (RNTCP) of India. His sputum smear examination for acid-fast bacilli (AFB) was still positive. In view of positive sputum at the end of retreatment regimen, a possibility of drug-resistant TB was considered and his sputum was sent for mycobacterial culture and drug sensitivity test.

He was started empirically on second-line anti-TB drugs, according to the body weight of 49 kg, consisting of kanamycin (0.75 g intramuscular), ofloxacin (800 mg),

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ethionamide (750 mg), cycloserine (750 mg), ethambutol (800 mg), and pyrazinamide (1.5 gm) daily. Subsequently, the sputum culture report revealed the growth of *Mycobacterium tuberculosis*-resistant to isoniazid, rifampicin, ethambutol, and streptomycin. A final diagnosis of multidrug-resistant tuberculosis (MDR TB) was made and a revised treatment was initiated, substituting *para*-amino salicylic acid (12 gm) for ethambutol. There was symptomatic relief after this treatment.

Two months later, the patient presented with painful enlargement of the right nipple area. On examination, there was a soft tissue swelling at the nipple areola complex measuring $2 \times 3 \text{ cm}^2$. It was soft, not fixed to underlying structures, but tender. There was no nipple retraction, skin dimpling, nipple discharge, or bleeding was noted. Ultrasonography of the breast showed glandular tissue hyperplasia. On detailed examination of the patient, there was a normal secondary sexual characters and external genitalia. He also denied the use of over the counter drugs, herbal products, or any other medications apart from prescribed regimen recently. An endocrinologist opinion and subsequent hormonal investigations reveal nothing abnormal. His routine investigations of blood, renal, and liver function tests were normal. His serum was nonreactive of HIV-1 and HIV-2. Ultrasound examination of abdomen was also normal.

In view of negative workup for any pathological causes of gynecomastia and a temporal association with anti-TB treatment led to a differential diagnosis of refeeding gynecomastia *versus* ethionamide induced gynecomastia, as this drug is also mentioned to cause gynecomastia in a standard text book of pharmacology.^[9] As the patient was anxious and gynecomastia was painful, ethionamide was stopped, the patient was reassured and rest anti-TB drugs were continued. The gynecomastia reduced subsequently and totally disappeared over next two months.

On follow-up, the symptoms of the patient improved and he also gained 2.5 kg weight during treatment. For a definitive diagnosis, we decided to rechallenge the patient with ethionamide, and hence the drug was re-introduced at a dose of 750 g per day. Three weeks later, the patient returned to us complaining of tenderness and swelling on both nipple areas. Clinical examination revealed a recurrence of gynecomastia on the right side, while the left nipple and areola were slightly enlarged and tender to touch [Figure 1]. His renal and liver function tests were repeated, and found to be normal. A clinical diagnosis of ethionamide-induced gynecomastia was thus made, and the drug was discontinued. A casualty assessment of definite was made according to the Naranjo's ADR probability scale as in Table 1.^[10] The patient was motivated to continue on the other drugs throughout the treatment course.

The patient improved with the above therapy and sputum also converted to negative after 6 months of second-line therapy. Kanamycin and pyrazinamide were stopped after



Figure 1: Patient showing recurrence of gynecomastia

Table 1: Naranjo's ADR probability scale and its score in the present case

Question	Yes	No	Do not know	Score in our case
Are there previous conclusive reports on this reaction?	+1		0	+1 ^a
Did the adverse event appear after the suspected drug was administered?	+2	0	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+2
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	+1
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total score				9

^aAlthough there is no published report, this adverse reaction is well mentioned in standard text books of pharmacology and tuberculosis

sputum conversion and the rest of the drugs were continued. Gynecomastia did not appear after stoppage of ethionamide. The patient was declared cured based on sputum culture and serial chest X-ray examination after 18 months of therapy.

DISCUSSION

Gynecomastia is defined as enlargement of male breast due to benign enlargement of the duct tissue and periductal stroma in the male breast. Although seen bilaterally and symmetrical, gynecomastia may also be unilateral or asymmetric. For reasons that are not clear, unilateral gynecomastia seems to be more common on the left side.^[11] Gynecomastia is often asymptomatic and detected incidentally during routine examination. Pain or tenderness may be present if the onset of the condition is recent.^[12]

Occurrence of gynecomastia during anti-TB therapy is very rare despite the use of these drugs for so many decades. Among the drugs used to treat TB, only isoniazid and thiacetazone have been reported as cause for gynecomastia.^[5-8,13] Although implicated as a cause of gynecomastia,^[9,14] the descriptions of ethionamide-induced gynecomastia remains a grey area in the medical literature. A MEDLINE search on ethionamide-induced gynecomastia did not reveal any published report in the English literature. Lack of published reports on painful gynecomastia induced by ethionamide prompted us to report this case.

Ethionamide is a nicotinamide derivative (thiimide) having a narrow spectrum of activity—chiefly against *M. tuberculosis* and *M. leprae*, used as a second-line anti-TB drug.^[9] Most common untoward effects to ethionamide are anorexia, nausea and vomiting, gastric irritation, and a variety of neurologic symptoms. Severe postural hypotension, mental depression, drowsiness, and asthenia are not uncommon. Convulsions and peripheral neuropathy are rare adverse effects. Other rare untoward effects are severe allergic skin rashes, purpura, gynecomastia, impotence, menorrhagia, and alopecia. About 5% of cases, treated with ethionamide, are also associated with hepatitis.^[9]

Gynecomastia caused by drugs may be due to a direct action of estrogen and estrogen-like substances, enhanced production of estrogen from testes, testosterone receptor antagonism, or inhibition of synthesis of testosterone or a rise in the prolactin level.^[15] Some drugs like spironolactone is proposed to act *via* multiple mechanisms *viz.* androgen receptor antagonism and also interfering with testosterone biosynthesis.^[16] However, how the majority of drugs cause gynecomastia remains unknown.^[12]

Refeeding gynecomastia was first reported during World War II, when prisoners liberated from prison camps developed

gynecomastia on resuming a normal diet. The condition usually persists for one to two years and regressed spontaneously. Significant malnutrition and weight loss are often associated with hypogonadism due to a decreased secretion of gonadotropin. When the gonadotropin secretion and gonadal function returns to normal on weight gain, a puberty like state (second puberty) is attained and this may be the cause of gynecomastia.^[17]

The mechanism of anti-TB treatment induced gynecomastia is not clearly known. The rarity of the clinical condition may be a reason why it is still a poorly understood phenomenon. It has been hypothesized that isoniazid induces gynecomastia by an alteration in estrogen–androgen metabolism, especially in slow acetylators.^[5] A refeeding mechanism in patients on isoniazid has also been suggested by Carlson *et al.*^[17] In our case, the patient responded very well to a revised treatment regimen, and gained weight. Since all the endocrinological and biochemical investigations were within the normal limits, a possibility of refeeding gynecomastia was also considered along with ethionamide-induced gynecomastia. The gynecomastia disappeared on stopping ethionamide, and reappeared again when ethionamide was reintroduced. The liver function tests and thyroid function tests were also within normal limits throughout the therapy. Further this case recorded a score of 9 on the Naranjo ADR Probability scale^[10] incriminating the drug as a definite cause for the reaction. However, the exact mechanism by which ethionamide causes gynecomastia is unknown.

Our case appears to be first one of this kind and highlights that clinically significant gynecomastia may occur during treatment with ethionamide and treating physicians should be aware of this phenomenon.

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