Ethionamide-induced gynecomastia: A rare case report

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Gynecomastia is a rare side effect of antitubercular chemotherapy. A 22-year-old male patient was diagnosed as a multidrug-resistant tuberculosis case and was put on standard second-line antituberculosis drugs. Two months later, the patient developed painful enlarged left breast with size 2×3 cm^2, mobile, tender, and normal nipple-areola without any discharge. Common endocrinological and biochemical tests were normal. Ethionamide-induced gynecomastia was suspected. Ultrasonography of the breast showed hypoechoic shadow suggesting glandular tissue hyperplasia without any deeper tissue infiltration. On discontinuing ethionamide, gynecomastia reduced gradually. On reintroduction, gynecomastia reappeared and again disappeared within weeks after withdrawal. Thus, painful gynecomastia induced by ethionamide was concluded. We report this case of unilateral painful gynecomastia because of its rarity and for the purpose of documentation and awareness.

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Introduction

Gynecomastia refers to unilateral or bilateral enlargement of male breast due to benign enlargement of the duct tissue and periductal stroma [1]. A large number of drugs have been implicated in causing this embarassing situation [2], in addition to many other clinical conditions such as puberty, old age, alcoholic cirrhosis, endocrine disorders, poststarvation refeeding, neoplastic disorders, and hemodialysis treatment [3]. Among the anti-tuberculosis (anti-TB) drugs, isoniazid, thioacetazone and ethionamide can induce gynecomastia [2]. The prevalence of ethionamide-induced gynecomastia (EIG) is not known. EIG is now a growing concern during the treatment of multidrug-resistant tuberculosis (MDR-TB) cases. Because of its rarity and for the purpose of documentation, we report this case of unilateral painful gynecomastia, which was associated with the use of ethionamide.

Case report

A 22-year-old, nonsmoker, nonalcoholic, male patient (BMI=17.5) presented with persistent cough and fever for 2 months, disclosing his past treatment with antitubercular drugs (ATD) twice under the revised national tuberculosis control programme as a sputum positive pulmonary TB case. Therefore, a case of MDR-TB was suspected. His recent sputum smear for acid fast bacilli turned out positive. Sputum culture grew *Mycobacterium tuberculosis* complex, which were resistant to isoniazid and rifampicin under the programmatic MDR-TB (PMDT) control programme. A final diagnosis of MDR-TB was made. After admission into drug resistance (DR-TB) centre indoor ward, his pretreatment evaluation came out normal, except for low hemoglobin (9.2 g%). He was put on standard second-line anti-TB drugs at indoor, according to his body weight (42 kg), consisting of ethambutol (800 mg), pyrazinamide (1250 g), kanamycin (0.5 g intramuscular), levofloxacin (750 mg), ethionamide (500 mg), cycloserine (500 mg), and pyridoxine (100 mg) as daily therapy as per PMDT. These drugs were tolerated well and so the patient was discharged on the seventh day.

Two months later, the patient came back with painful enlargement of the left breast. On examination, the breast swelling around the nipple areola was soft but tender, measuring 2×3 cm^2, but not fixed to underlying structures. Any nipple retraction, skin dimpling, nipple discharge, or bleeding on pressure was absent (Fig. 1). Ultrasonography of the enlarged breast showed hypoechoic shadow suggesting glandular tissue hyperplasia without any deeper tissue infiltration (Fig. 2). On examination, there were normal secondary sexual characters and external genitalia. On enquiry, he denied any regular use of over-the-counter drugs, or herbal products, or any other medications apart from the prescribed regimen recently. An endocrinologist's opinion and subsequent hormonal investigations revealed nothing abnormal. His routine investigations of blood and renal and liver function tests were normal. His serum was nonreactive for HIV-1 and HIV-2. Here, gynecomastia due to ethionamide was

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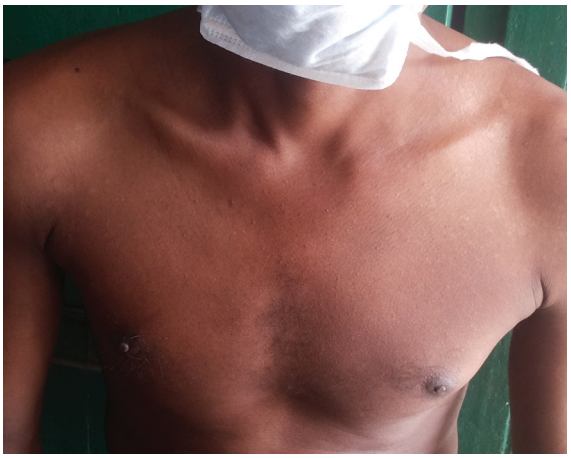
suspected among given ATDs, because this drug is implicated for gynecomastia [4]. Ethionamide was replaced with p-aminosalicylic acid because of his anxiety, embarrassment as well as pain. Ibuprofen 400 mg three times daily for 10 days controlled his breast pain gradually.

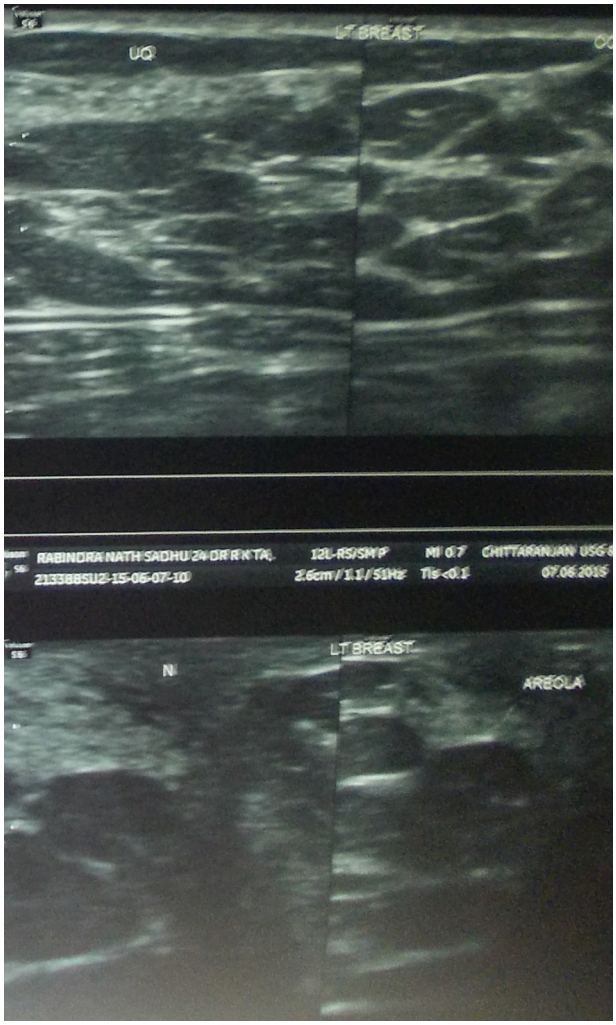
The patient was assured and other anti-TB drugs were continued. The gynecomastia reduced gradually and later disappeared over the next 1 month (Fig. 3). On follow-up at third month, he had gained 2.5 kg weight on treatment and chest symptoms were also improved. To affirm our suspicion of EIG, ethionamide (500 mg daily) was reintroduced. Three weeks later, the patient returned to us with similar swelling and tenderness on the same breast. Clinical examination showed a recurrence of gynecomastia on the same side (Fig. 4). Re-evaluations of renal and liver function tests were normal. A clinical diagnosis of EIG was thus made, and the drug was discontinued with readministration of p-aminosalicylic acid. The patient was motivated

Figure 1



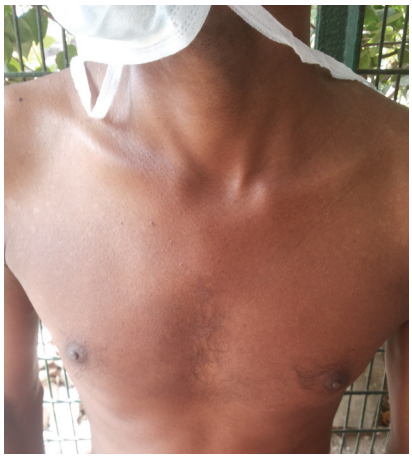
Appearance of enlarged breast tissue (left) with normal appearance of the nipple and areola.

Figure 2



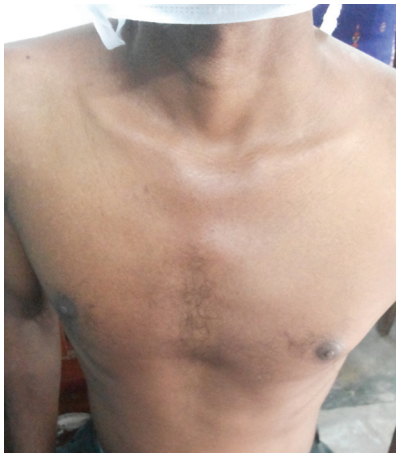
Ultrasonography of the enlarged breast (left) showing hypoechoic shadow of glandular tissue hyperplasia without any deeper tissue infiltration.

Figure 3



Near-normal breast tissue after ethionamide withdrawal.

Figure 4



Reappearance of gynecomastia.

to continue other ATDs throughout the treatment course without ethionamide. His breast tissue gradually became normal again within 2 weeks without any subsequent enlargement of the same during follow-up. He subsequently became negative for culture and smear for acid fast bacilli. His chest symptoms were also relieved and, currently, he is under follow-up.

Lack of published reports on painful gynecomastia induced by ethionamide prompted us to report this case. We are experiencing similar side effects among few other MDR-TB cases under PMDT in our DR-TB center. This embarrassing side effect needs to be validated with estimated frequency.

Discussion

Gynecomastia is often a clinical problem in men. The entity was first described by Paulus Aegineta (AD 625–690). The term comes from the Greek word 'gyné' (stem *gynaik*) meaning 'woman' and 'mastós' meaning 'breast'. The causes of gynecomastia remain often uncertain and generally been attributed to an imbalance of sex hormones or lack of tissue responsiveness to them. Further, a root cause is rarely determined for individual cases [5].

Lipomastia is a common differential diagnosis but sometimes difficult to differentiate from drug-induced gynecomastia. True glandular tissue (lipomastia) 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, ultrasound of the breast is recommended as the first-line imaging investigation, although mammography may be added to confirm the diagnosis.

Drug-induced gynecomastia is common and might account for up to a quarter of all cases [6]. Anti-TB therapy-induced gynecomastia is very rare despite their use throughout many decades. Its mechanism often remains unclear. The rarity of the clinical condition may be a reason. Among the anti-TB drugs, isoniazid was found first to cause gynecomastia. In 1953, a report from France implicated this drug as a cause of gynecomastia [7].

After isoniazid, thiacetazone was suggested as a cause of gynecomastia in a single report [8]. The authors hypothesized that a disturbance in vitamin B_6 complex activation in the liver could have caused an alteration in estrogen–androgen metabolism. It has also been postulated that isoniazid may act 'by means of a refeeding mechanism in men with tuberculosis'.

One of the rarest adverse effects of ethionamide is gynecomastia. Most standard text books and reference books of pharmacotherapeutics have not even mentioned about it [3]. Ethionamide is an important second-line anti-TB drug used for the treatment of MDR-TB. It is a structural analog of isoniazid (INH); both are prodrugs that need to be activated by mycobacterial enzymes to exert their antimicrobial activity. However, the exact mechanism by which ethionamide causes gynecomastia is unknown. The use of ethionamide is increasing with an increase in the prevalence of resistant TB. The most common adverse effects associated with this drug are anorexia, nausea and vomiting, gastric irritation, and a variety of neurologic symptoms. Severe postural hypotension, mental depression, drowsiness, and asthenia are common, but convulsions and peripheral neuropathy are rare [9].

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 [4]. Significant malnutrition and weight loss are often associated with hypogonadism due to a decreased secretion of gonadotropin. When the gonadotropin secretion and gonadal function return to normal on weight gain, a puberty-like state (second puberty) is attained, and this may be the cause of gynecomastia [10]. Our patient gained weight after ATDs. For unclear reasons, unilateral gynecomastia seems to be more common on the left side [11], as in our case. Pain or tenderness may be present if the onset of the condition is recent [6]. Our patient also experiencing pain and tenderness from beginning of the swelling.

The endocrinological and biochemical investigations, including liver function tests and thyroid function tests, were within the normal limits in our case. Thus, systemic cause was excluded. Serology for human immunodeficiency virus (HIV I and II) was nonreactive. Fine-needle aspiration cytology was usually not required in the absence of suspicious malignant growth in the breast or associated lymphadenopathy. Ultrasound of the enlarged breast tissue identified glandular hyperplasia without any features of adjacent tissue penetration. Mammogram could not be performed for technical reasons. The gynecomastia disappeared on stopping ethionamide, and reappeared again when ethionamide was reintroduced within 3 weeks and later it subsided again after withdrawal of the agent.

Treatment for gynecomastia is seldom required, unless it causes discomfort or embarrassment to the patient. If a trial of medical therapy fails, surgical resection of enlarged breast glandular tissue could be offered through a periareolar incision, with or without suction-assisted lipectomy to remove the subglandular adipose tissue [12]. Our patient needed simple withdrawal of ethionamide to reverse the gynecomastia, thereby establishing the cause–effect relationship. Similar case [13] reports are few.

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Conflicts of interest
There are no conflicts of interest.

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