Case Report

Gynecomastia: a rare adverse effect of isoniazid*

Ginecomastia: um efeito colateral raro da isoniazida

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Abstract

We report the case of a patient who twice developed gynecomastia following tuberculosis treatment. An 18-year-old male developed painful bilateral gynecomastia after three months of treatment with the isoniazid-rifampin-pyrazinamide regimen. Partial resolution of gynecomastia was achieved at the end of treatment. The patient was retreated with the same regimen eight years later, and gynecomastia recurred after six months of treatment. Hormone levels were normal, and a mammogram revealed bilateral gynecomastia. The isoniazid was discontinued, and the gynecomastia was partially resolved by the end of treatment. Four years later, gynecomastia was not detected. We conclude that isoniazid-related gynecomastia completely resolves when the medication is discontinued. Therefore, pharmacological and surgical treatment should be avoided.

Keywords: Isoniazid/adverse effects; Gynecomastia/chemically induced; Tuberculosis.

Resumo

Relata-se o caso de um paciente que desenvolveu ginecomastia duas vezes após tratamento para tuberculose. Homem de 18 anos de idade foi tratado com o esquema isoniazida-rifampicina-pirazinamida; no terceiro mês desenvolveu ginecomastia bilateral, dolorosa, com regressão parcial ao final do tratamento. Foi retratado oito anos após com o mesmo regime, e a ginecomastia recorreu após seis meses de tratamento. Dosagens hormonais foram normais, e a mamografia revelou ginecomastia bilateral. A isoniazida foi suspensa, tendo a ginecomastia regredido parcialmente no final do tratamento. Quatro anos após, não foi constatada ginecomastia. Conclui-se que a ginecomastia relacionada à isoniazida regride totalmente após a suspensão da droga e, portanto, o tratamento cirúrgico ou medicamentoso deve ser evitado.

Descritores: Isoniazida/efeitos adversos; Ginecomastia/induzido quimicamente; Tuberculose.

Introduction

Undesirable reactions to antituberculosis drugs are not uncommon, although rarely does any medication need to be discontinued.[1] Gastric intolerance, hepatitis, polyneuritis and allergic reactions are the most common undesirable effects of isoniazid (INH). Less frequently, other phenomena, such as convulsions, vivid or erotic dreams, rheumatism, lupus-like disease, mood swings, insomnia, excessive sleepiness, altered memory, tremors and impairment of intellectual activities, also occur.[2,3] Gynecomastia is one of the rarest side effects, albeit described in textbooks.[4,5] However, in the recent international literature (according to the Medline and Latin American and Caribbean Health Sciences Literature databases), only one case has been reported.[6]

Our objective was to report the case of a patient who twice developed gynecomastia after the initiation of INH therapy and presented complete resolution some months later.

Case report

A Caucasian male was first admitted to our facility in September of 1995, at the age of 18 years, after having been diagnosed with cavitary pulmonary tuberculosis, as diagnosed on the basis of a positive sputum smear microscopy result and positive culture for *Mycobacterium tuberculosis*. At the time, the patient complained of productive cough, weight loss (2 kg), asthenia and right-sided chest pain. A chest X-ray revealed an ulcerous and exudative process in the right upper lung lobe. The patient was a crack cocaine user, and the HIV serology was negative. He was treated with the regimen of INH, rifampin (RIF) and pyrazinamide (PZA). There was rapid clinical and radiological improvement, as well as sputum smear conversion. The PZA was discontinued two months later. Three months after the initiation of treatment, the patient complained of slight breast enlargement, accompanied by spontaneous pain and pain upon palpation, both of low intensity. Indomethacin

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was introduced, and the pain decreased. The tuberculosis treatment was continued for six months. At discharge, the chest X-ray was normal, and the sputum smear microscopy result was negative. There was no longer any breast pain, although the breasts remained slightly enlarged.

In March of 2003, the patient was readmitted. He reported having remained asymptomatic until 15 days before readmission, when he began to present mild hemoptysis, productive cough, weight loss (3 kg), left-sided chest pain, asthenia and anorexia. He reported no fever or night sweats. The patient was a smoker (12 pack-years), reported no history of alcoholism or any other risk factor for HIV and had not used crack cocaine since the previous treatment was initiated.

There were no other peculiarities. Physical examination revealed that the patient was in good general health (weight: 62 kg; height: 1.75 m) and presented normal respiration.

A chest X-ray revealed cavitation in the left upper lobe, the largest being 5 cm in diameter and thick-walled. In the right upper lobe, there was heterogeneous opacity, with small hypertransparent areas, but there was no lobe retraction. A sputum smear was positive for acid-fast bacilli, as was a culture, which confirmed it was an *M. tuberculosis* strain sensitive to INH, RIF, PZA, ethambutol and streptomycin. All routine tests (blood workup, glycemia, parasitological stool examination, liver function tests, determination of urea/creatinine levels and HIV testing) were normal.

Since the hospital facility did not begin to use computerized medical records until after the previous treatment, the fact that the patient developed gynecomastia during the first treatment was not noticed, and the usual doses of INH, RIF and PZA were prescribed (400 mg, 600 mg and 2,000 mg, respectively). The PZA was discontinued two months later, although the INH and RIF were continued. Six months after the initiation of treatment, the patient complained of enlargement of and mild pain in the right breast. He reported no changes in sexual activity. Examination revealed that the right breast was 5 cm in diameter, being slightly painful upon palpation, had an elastic consistency, and was nonadherent to the superficial and deep layers. The nipple of the right breast was normal, and no alteration was found in the left breast. The INH was discontinued.

Hormone levels were normal (Table 1). A mammogram revealed bilateral gynecomastia, more extensive on the right.

Two months after the INH was discontinued, the gynecomastia remained unaltered. One year after initiation, the treatment was discontinued, and the gynecomastia was partially resolved. Three months after discharge, the breasts were found to have normalized.

Four years later, the patient returned for follow-up evaluation. The chest X-ray was normal, as were the hormone levels (Table 1).

Discussion

The diagnosis of tuberculosis in the case reported is indisputable, since, at both time points, it was confirmed by direct examination and by culture. In addition, the clinical and radiological profile was consistent with the diagnosis. The patient received the usual treatment, and it should be emphasized that, in the retreatment, the same treatment regimen was used, since there was no evidence of

Table 1 - Hormone levels.

Hormone	At the time of gynecomastia	Four years later	Normal values for males
Free thyroxine, ng/dL	1.0	NP	0.8-1.9
TSH, µIU/mL	0.198	NP	0.4-4.0
Progesterone, ng/mL	0.42	0.4	≤ 0.75
Prolactin, ng/mL	8.7	4.6	2.5-17.0
FSH, mIU/mL	2.0	NP	0.7-11.1
Estradiol, pg/mL	34.3	33.9	≤ 206
Testosterone, ng/dL	1.368	574	286-1.511
LH, mIU/mL	4.6	NP	0.8-7.6

TSH: thyroid-stimulating hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; and NP: not performed.

bacterial resistance, which was confirmed by drug susceptibility tests.

In both treatment periods, gynecomastia was detected some months after the initiation of tuberculosis treatment (after three months in the first period and after six months in the second). Although physical examination is the principal element of the diagnostic process, a mammogram confirmed the hypothesis and revealed that the gynecomastia was bilateral, which was not apparent upon physical examination.

The differential diagnosis of gynecomastia should include other breast abnormalities, such as pseudogynecomastia and tumors. The presence of a firm and homogeneous breast structure is important for differentiating gynecomastia from pseudogynecomastia; gynecomastia of recent origin, as occurred in our patient, is usually accompanied by pain, which does not occur in gynecomastia of long duration or in pseudogynecomastia.[7]

A diagnosis of tumor can be easily ruled out by the absence of masses upon physical examination and on mammograms, as well as by the complete resolution of the gynecomastia after the INH is discontinued.

Gynecomastia due to primary or secondary hypogonadism can be ruled out by normal hormone levels and by the maintenance of sexual activity. Normal thyroid hormone levels rule out the possibility of hyperthyroidism.[4]

The pathological substrate for gynecomastia is ductal epithelial hyperplasia, periductal inflammatory infiltrate and an increase in fatty tissue in the subareolar area. Periductal fibrosis, stromal hyalinization and fat infiltration into the subareolar area characterize the chronic form.[7]

Although the physiopathology of gynecomastia has not been fully clarified, disruption of the estrogen/androgen balance seems to be fundamental. The relative increase in free estrogen would lead to gynecomastia. This event can have different mechanisms, such as decreased testosterone production or the stronger binding of testosterone to the transporter protein, with decreased free testosterone. Increased estrogen production, however, occurs in tumors, such as Leydig cell tumor, large cell carcinoma and adrenal tumor. Another known mechanism is increased aromatase activity, which degrades testosterone; this occurs, for example, in gynecomastia in the elderly.[4,7]

The relationship between gynecomastia and INH can be inferred by the absence of any other conditions that could cause it, such as use of medications (e.g., cimetidine, digitalis, anti-inflammatory drugs, phenytoin, spironolactone, alkylating agents, antiviral drugs, sex hormones or antihormones, benzodiazepines and use of medications in the form of herbs sold without a prescription), hyperthyroidism and congenital hormone deficiency. It should be added that the patient did not use any other medication, nor did he use illicit drugs, such as opioids or marijuana. Similarly, there was no evidence of hepatic, renal or neurological diseases, nor was there evidence of recovery from severe malnutrition.[4,7]

The relationship with use of antituberculosis drugs could be questioned, since, in 25% of the cases, the cause is not identified.[7] However, the reintroduction test occurred unknowingly, since the fact that this effect had occurred during the first treatment period went unnoticed. This test should be interpreted as definitive in characterizing the cause.[7]

The relationship between INH and gynecomastia is rarely reported in the literature, although it was recognized many years ago. A study carried out in 1973 reported the case of a 52-year-old patient with alcoholism who developed gynecomastia four months after the initiation of treatment. Hormone levels were normal, except for slightly decreased free testosterone levels. The patient received an excessive INH dose—600 mg/day (10 mg/kg)—and was a slow INH acetylator. Gynecomastia evolution was similar to that observed in our patient, with resolution some months after the medication was discontinued.[8]

More recently, the case of a 25-year-old patient who developed gynecomastia three months after the initiation of treatment, with resolution of the gynecomastia four months after the INH was discontinued, was reported.[6]

Predisposing factors for gynecomastia in males using INH have not been identified. However, it is important to point out that there is no impairment in sexual activity and there is complete resolution a few months after the medication is discontinued. Therefore, there is absolutely no justification for surgery or the use medications to correct the disorder. Determination of hormone levels is unnecessary, as is mammography.[7] It is advisable to

simply discontinue the medication and observe. An in-depth investigation should only be carried out in the event of the gynecomastia persisting after many months. It is possible, however, that some cases will not be detected in routine practice.

The phenotype of INH inactivation might contribute to the genesis of gynecomastia on a small scale, if at all. If the phenotype played an important role, the alteration would be much more common, since intermediate or slow acetylators make up half of he Brazilian population.[9,10]

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