Posaconazole-induced gynaecomastia in a patient with COVID-19–associated mucormycosis: a case report

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Case presentation

A 49-year-old man with a history of poorly controlled diabetes for over 10 years was hospitalised 6 months earlier, on 2 April 2023, for severe COVID-19 infection. He was discharged after 3 weeks but later developed right-sided facial pain and diplopia. He was diagnosed with sino-orbital mucormycosis based on the clinical symptoms and imaging features (Fig a). Histopathological examination of a sinus biopsy revealed invasive ribbon-like hyphae, confirming the diagnosis. The patient underwent sinus and surgical debridement of the orbit and was prescribed antifungal treatment. After two surgical debridements of necrotic tissue and 6 weeks of combination antifungal treatment with liposomal amphotericin B (400 mg daily via infusion) plus posaconazole (300 mg twice daily on the first day and 300 mg daily intravenously thereafter), the patient was discharged in good general health but with right eye blindness. He was advised to continue treatment with oral posaconazole (300 mg twice daily on the first day, then 300 mg daily thereafter) for a duration of 12 weeks and to control his blood sugar with insulin.

In September 2023, 2 months after discharge, the patient presented to the hospital for follow-up, complaining of increased bilateral breast volume, particularly in the right breast (Fig b and c). He had first noticed this increase in volume approximately 1 month after hospitalisation, and it had gradually intensified.

Clinical examination revealed bilateral breast swelling with increased breast adipose tissue volume, more pronounced on the right side. No tenderness or palpable mass was detected. Ultrasound findings were consistent with gynaecomastia. Hormone testing showed a normal prolactin level and pituitary axes but markedly decreased testosterone and elevated oestrogen levels (Table).

In view of these results and the possible association of gynaecomastia with azole use, posaconazole was discontinued. The patient was prescribed liposomal amphotericin B 400 mg daily and monitored daily to ensure compliance with medication and to evaluate any possible side-effects. He exhibited minor hypokalaemia while receiving amphotericin B, which resolved with the administration of potassium supplements. There was

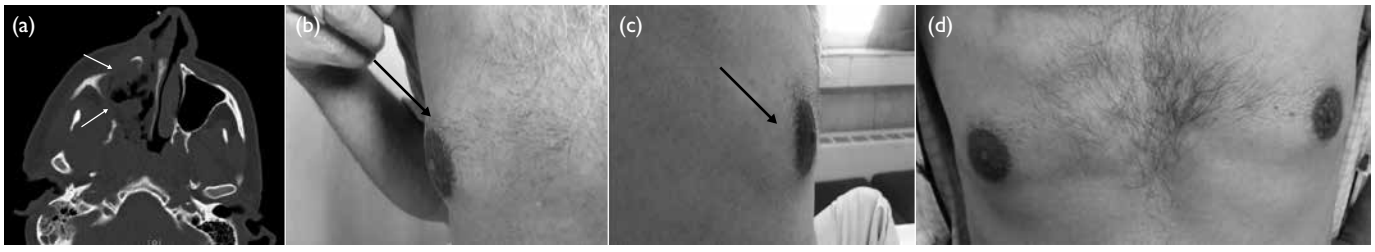

FIG. (a) Axial paranasal computed tomography image revealed right maxillary sinus involvement with bone destruction (arrows). Clinical photographs demonstrating (b) right-sided and (c) left-sided gynaecomastia (arrows). (d) Resolution of bilateral breast enlargement 4 weeks after discontinuation of posaconazole

TABLE. Laboratory results of the patient

	Value	Reference range
Prolactin, ng/mL	20	15-25
Luteinising hormone, IU/mL	2.6	1.24-7.8
Follicle-stimulating hormone, mIU/mL	3.5	1.4-15.4
Testosterone, ng/dL	50	300-1000
Estradiol, pg/mL	300	10-50
Thyroid-stimulating hormone, mIU/L	2.5	0.5-5.0

no evidence of hyperaldosteronism during treatment with posaconazole. Following the discontinuation of posaconazole, the patient's gynaecomastia improved significantly over 4 weeks (Fig d).

Discussion

At the time of writing, this report represents the second documented case of posaconazole-induced gynaecomastia. Information on this adverse effect is limited, despite its recognised association with azole use. Given the common use of posaconazole for the prevention and treatment of mucormycosis, other patients may be at risk of similar complications. Disseminating this information is essential for clinical pharmacists to manage such cases effectively.

Our case was a middle-aged man with a history of diabetes and COVID-19, who developed gynaecomastia following the prescription of posaconazole for mucormycosis. Gynaecomastia is a benign enlargement of the breast tissue that may occur in many adult men.[1] Physiological gynaecomastia in infants, adolescents, and older adult men is usually unilateral. Non-physiological gynaecomastia may arise in patients with chronic diseases such as hypogonadism, cirrhosis, neoplasms or uraemia, or as a consequence of drug use. Additionally, non-physiological gynaecomastia may cause localised pain.[2] In our patient, bilateral and painless non-physiological gynaecomastia developed as a consequence of azole use.

Azole antifungals are the mainstay of prevention and treatment for invasive fungal infections such as mucormycosis.[3] Most reported cases of azole-induced gynaecomastia have involved patients taking ketoconazole and, to a lesser extent, itraconazole. Both inhibit cytochrome P450 enzymes involved in steroidogenesis.[4] In-vitro evidence suggests that posaconazole can inhibit cytochrome P450 17A1, an enzyme involved in the lyase reaction required for androgen production. In addition, posaconazole, similar to ketoconazole, may inhibit hepatic oestrogen metabolism.[5] Accordingly, our patient's serum testosterone level was lower than normal, while the oestradiol level was significantly elevated. This is comparable to the first reported case of posaconazole-induced gynaecomastia by Thompson et al.[6] In that patient, who was prescribed long-term posaconazole for coccidioidomycosis (300 mg/day slow-release formulation), the oestradiol level was raised despite a normal testosterone level. Notably, gynaecomastia did not improve following a switch from posaconazole to voriconazole. In contrast, our patient showed improvement after the complete discontinuation of azole agents.

The main limitation of this report is the absence of a serum posaconazole level, as testing was unavailable due to economic constraints affecting resource availability. This limits the ability to draw a definitive conclusion regarding the association of posaconazole with the development of gynaecomastia, or the observed improvement following its discontinuation.

Author contributions

Concept or design: M Salehi, H Khalili.
Acquisition of data: A Kazemzadeh, M Alaei.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: M Salehi, A Tabari.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This study was approved of by the institutional review board of Tehran University of Medical Sciences, Iran (Ref No.: IR.TUMS.IKHC.REC.1403.165). Written consent was obtained from the patient for publication of this case report.

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