Gynecomastia is clinically defined as benign breast enlargement in male patients because of the proliferation of glandular component with deposition of fat. It usually occurs due to an imbalance between the actions of estrogen and androgen on the breast tissue. However, gynecomastia can be induced by some pathological conditions, including adverse effect of drug, endocrine disorder, liver cirrhosis and renal failure etc. Drug related gynecomastia accounts for approximately 20-25% of all cases.[1] For instance, some cardiovascular medicine can cause gynecomastia including digoxin, spironolactone, amlodipine, nifedipine, verapamil, captopril, enalapril, amiodarone.[2]

Eplerenone is one selective MRA in which is recommended as the guideline-directed medical treatment of heart failure. Due to the high selectivity of eplerenone to the aldosterone receptor, eplerenone is known to cause less gynecomastia in male patients than spironolactone so eplerenone induced gynecomastia has been rarely reported.[3] Herein, we report one male patient with heart failure suffering bilateral gynecomastia after eplerenone use.

**Case Report**

This 88-year-old man presented with clinical symptoms of acute decompensated heart failure. Echocardiography showed the ejection fraction about 35%. We prescribed the guideline-recommended treatment for reduced ejection fraction heart failure, including loop diuretics (furosemide 40mg daily), MRA (eplerenone 25mg daily), angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan 50mg twice daily) and beta-blocker (bisoprolol 2.5mg daily). About one month after the treatment, he complained of breast pain and enlargement (Fig. 1). Physical examination revealed grade II gynecomastia with tenderness. The liver function and renal function were within normal limit. He also denied to receive
any additional medicine regarding the hormone changes. We reviewed his drug list and found that MRA may cause gynecomastia due to blockage of androgen receptor and decreased testosterone production. According to the selectivity of eplerenone for the aldosterone receptor, eplerenone is known to cause less gynecomastia in male patients than spironolactone. However, this side effect of spironolactone, gynecomastia may also be observed in patients with eplerenone use. Eventually, we discontinued the use of eplerenone. Bilateral gynecomastia resolved within 3 weeks.

**Discussion**

Both eplerenone and spironolactone are effective and safe in the treatment of hypertension and heart failure. However, spironolactone has been reported to have some antiandrogen effects which may cause some sexual and endocrine disorders. The antiandrogen action of spironolactone responsible for the development of gynecomastia depends on the dose and duration of treatment and the gynecomastia is usually bilateral.

In contrast to spironolactone, eplerenone is one selective MRA with greater selectivity for mineralocorticoid receptors. Its potency is about 370 times less than spironolactone in blocking dihydrotestosterone-activating androgen receptors, thus resulting lesser incidence of gynecomastia. EPHESUS and RALES were two important trials of MRA for the treatment of heart failure. Eplerenone and spironolactone were found to be effective in heart failure populations. However, in EPHESUS trial, the incidence of hyperkalemia in the eplerenone group was higher, compared with placebo group. There was no significant difference of hyperkalemia in RALES trial. Moreover, the incidence of gynecomastia in men was significantly lower in the patients with eplerenone use in EPHESUS trial, compared with spironolactone use in RALES trial. According to rare and limited sexual and endocrine adverse effects of eplerenone, eplerenone was ever reported to be a safe and effective alternative therapy for reversing spironolactone induced gynecomastia in cirrhotic patients.

In conclusion, although Eplerenone is a spironolactone derivative designed to enhance selective binding to mineralocorticoid receptor while minimizing blockage of androgen receptors, gynecomastia can still occur as described in our case. In general, discontinuation of the drug may be necessary and the gynecomastia can be resolved within several weeks.

**Disclosures**

**Informed Consent:** Written informed consent was obtained from the patients’ family for the publication of the case report and the accompanying images.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.


**References**