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GYNAECOMASTIA REVEALING AMIODARONE-INDUCED HYPERGONADOTROPIC HYPOGONADISM: AN OVERLOOKED COMPLICATION?

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ABSTRACT

We report a case of primary hypogonadism induced by amiodarone and review the relevant literature. Amiodarone has a well-established and extensive profile of side effects including thyroid toxicity, corneal deposits and skin discoloration. In rare cases, epididymitis or orchitis may occur. This inflammation can lead to testicular atrophy, inducing primary hypogonadism. We present the case of a 57-year-old patient, treated with amiodarone for several years, initially presenting with testicular pain followed by gynaecomastia, and finally loss of libido indicative of hypergonadotropic hypogonadism. Imaging confirmed bilateral testicular atrophy. Amiodarone was discontinued, and androgen replacement therapy was initiated. This case, combined with data from the literature, highlights the importance of careful monitoring of patients on amiodarone to identify symptoms or clinical signs suggesting testicular dysfunction, to diagnose and treat consequent hypogonadism.

KEYWORDS

Amiodarone, hypergonadotropic hypogonadism, gynaecomastia, testicular dysfunction, epididymitis

LEARNING POINTS

- This case highlights the causal relationship between prolonged amiodarone use and the development of hypogonadism.
- The underlying mechanism involves the destructive effect of amiodarone on testicular tissue, leading to primary hypogonadism through testicular atrophy.
- It is crucial to monitor patients for clinical signs of hypogonadism after prescribing amiodarone to ensure timely diagnosis and treatment of any resulting hypogonadism.

INTRODUCTION

Amiodarone, an anti-arrhythmic drug widely used in the treatment of atrial fibrillation (AF), is associated with numerous side effects. These are partly explained by its long half-life and requirement for frequent multi-systemic monitoring.

Thyroid dysfunction is the most studied endocrine abnormality associated with amiodarone. However, other

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endocrine abnormalities have also been reported with prolonged use, notably primary hypogonadism, characterised by decreased testosterone levels with elevated serum follicle stimulating hormone (FSH) and luteinising hormone (LH) concentrations. The testicular dysfunction is associated with the urological toxicity of amiodarone, leading to orchiepididymitis, which may or may not be complicated by testicular atrophy.

We report the case of a 57-year-old patient, intermittently treated with amiodarone for 16 years, who experienced testicular pain, gynaecomastia and loss of libido, which were corrected after analgesic use, hormone replacement therapy and discontinuation of amiodarone.

The interest in this case is threefold: to raise awareness among clinicians of the existence of this testicular and endocrine toxicity to facilitate its identification in routine practice; to provide practical guidelines based on literature data for monitoring and treatment; and, finally, to highlight the importance of monitoring the young male population, given the impact of such gonadal dysfunction on fertility.

CASE DESCRIPTION

At the age of 43, the patient developed AF. Treatment with amiodarone at a dosage of 400 mg/day was initiated, resulting in sustained sinus rhythm restoration. At the age of 45, amiodarone was discontinued due to corneal deposits, only to be reinstated one year later upon AF recurrence. Between the ages of 52 and 56, the patient experienced varying levels of testicular pain. An ultrasound revealed swelling of the epididymis head, and despite antibiotic therapy the pain was not relieved. At the age of 56, he underwent a cardiac intervention (pulmonary vein isolation) that successfully restored sinus rhythm, thereby facilitating the discontinuation of amiodarone. This led to a significant alleviation of testicular pain.

At the age of 57, he presented a right-sided unilateral gynaecomastia, with preserved libido. Laboratory investigations revealed mildly decreased morning total testosterone levels (272 ng/dl), elevated FSH (47.4 U/l; reference range: 1.55–9.74 U/l), and LH (21.3 U/l). The thyroid function remained normal; prolactin levels were normal. Testicular ultrasound confirmed testicular atrophy, with a right testicular axis of 3.5 cm and left testicular axis of 2.3 cm, alongside calcifications within the left testicle. Spontaneous resolution of gynaecomastia occurred. A conservative approach was chosen, with testosterone levels to be re-evaluated after one year. Approximately two years earlier, the patient had resumed amiodarone therapy at 400 mg/day for around 8 weeks due to AF recurrence, and experienced transient testicular pain resurgence. He was now reporting decreased libido; morning testosterone levels were low at 184 ng/dl which led to initiation of androgen replacement therapy *(Fig. 1)*.

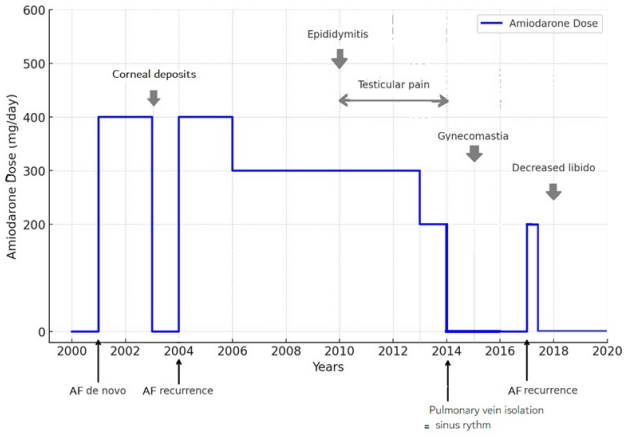


Figure 1. Amiodarone use over time correlated with urological, endocrine and cardiac events. Abbreviation: AF, atrial fibrillation.

DISCUSSION

One of the most common side effects of amiodarone is hyperthyroidism, which can lead to gynaecomastia through the stimulation of sex hormone-binding globulin synthesis by thyroid hormones in the liver, as well as increased aromatisation of androgens to oestrogens. In our case, amiodarone-induced gynaecomastia occurred not due to hyperthyroidism, but rather due to testicular insufficiency or peripheral hypogonadism. Primary hypogonadism is more likely to be associated with gynaecomastia than secondary hypogonadism, probably due to the stimulatory effect of LH and FSH on aromatase activity, resulting in a more increased oestrogen-to-androgen ratio. Typically, there are also signs of gonadal insufficiency, and palpation of the testes reveals a decrease in gonadal volume. Sometimes, gynaecomastia is the first sign of peripheral hypogonadism, not yet accompanied by sexual dysfunction or a decrease in testosterone concentration; in such cases, the diagnosis relies solely on elevated gonadotropins. This was the scenario in our clinical observation. There are relatively few identified causes of acquired primary hypogonadism, mainly including infections (such as mumps), radiation, alkylating agents, trauma and testicular damage. All these were excluded in our patient.

Since 1984, several cases have described a link between amiodarone and genito-urinary manifestations such as epididymitis and erectile dysfunction (incidence < 1%)[1]. Risk factors for genito-urinary complications include the duration of administration (> 7 to 15 months) and the dose (generally > 700 mg/day)[2]. Our patient had been taking amiodarone for over 10 years, with a maximum dosage of 400 mg/day. Orchiepididimytis is usually diagnosed using doppler ultrasound, there is no bacteriological evidence of an infectious process and an improvement in symptoms is observed after discontinuation of amiodarone[2]. This was the case in our observation. A Naranjo score of 9 was calculated for this case[3], indicating a definite correlation between amiodarone use and the observed adverse effect. This score reflects that the adverse effect followed a reasonable temporal sequence post-drug administration, which improved upon drug withdrawal and reappeared upon re-exposure.

The mechanism of amiodarone-induced testicular damage is not fully understood. It may be due to a direct toxicity of microdeposits of amiodarone metabolites[4] or rather to an autoimmune response to anti-amiodarone antibodies. Due to its high lipophilicity and long elimination half-life, the drug and its major metabolite desethylamiodarone can accumulate extensively in adipose tissue and in organs such as the testis where concentrations can increase 25 to 3,000 times higher than those in plasma.

In our case, testicular pain seemed to be directly related to amiodarone consumption while testicular damage leading to atrophy, and hypogonadism appeared to be a progressive long-standing effect persisting after amiodarone withdrawal. The only prospective study on testicular dysfunction associated with amiodarone was conducted in 1991[5]. A group of seven amiodarone-treated men underwent evaluation for sexual dysfunction. An elevation in serum gonadotropin concentration was detected, suggesting testicular dysfunction. Because of this finding, gonadal function was prospectively evaluated in 44 men (18 treated with amiodarone and 26 treated with anti-arrhythmic drugs other than amiodarone). Amiodarone-treated men had higher serum FSH and LH concentrations compared with control subjects, and atrophic testes were more commonly observed in amiodarone-treated men. Following this study, no further significant investigations have been conducted in this field. In terms of treatment, the literature overwhelmingly supports that discontinuation of the drug typically leads to symptom relief, with symptom recurrence upon drug resumption aiding in clinical diagnosis. Consensus dictates withdrawing or reducing the dose promptly upon signs and symptoms of epididymitis. When withdrawal is unfeasible, doses of 200 mg per day or below seldom induce epididymitis symptoms. Bilateral epididymectomy should be considered only as a last resort; urinary tract analgesics are effective for pain relief, and testosterone replacement is necessary in cases of symptomatic primary hypogonadism.

CONCLUSION

Among the numerous adverse effects of amiodarone, we aim to highlight testicular dysfunction, which may result from orchiepididymitis causing testicular atrophy, thereby resulting in hypergonadotropic hypogonadism. Further research is needed to determine whether the drug exerts a direct chemical impact on the testis or triggers an autoimmune response. In terms of future perspectives, it is crucial to acknowledge that to date, only one prospective study conducted in the 1990s has established a correlation between amiodarone and primary hypogonadism. Our observation could serve as a catalyst for new investigations aimed at assessing the occurrence of hypergonadotropic hypogonadism during amiodarone treatment. Meanwhile, we suggest identifying specific symptoms of hypogonadism such as reduced libido, decreased spontaneous erections or erectile dysfunction in patients under amiodarone treatment to identify hypogonadism[6].

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