

## CLINICAL VIGNETTE

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# Amiodarone Induced Thyroid Dysfunction

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### *Introduction*

The antiarrhythmic medication, amiodarone is often associated with thyroid dysregulation. This is due to both the intrinsic toxic effect of amiodarone on the thyroid gland and the high iodine content of the medication.<sup>1,2</sup> This can result in hypothyroid or hyperthyroid conditions. When thyroid abnormalities occur, it is important to manage both the arrhythmia and abnormal thyroid effects on the patient. The following cases are examples of amiodarone effects, on a euthyroid patient and a patient with existing hypothyroidism.

### *Case 1*

A 60-year-old male with CLL, malignant meningioma, atrial fibrillation, mitral regurgitation status post repair, hypertension, hyperlipidemia presented with 2 weeks of increased hand tremor, pruritus, and weight loss despite good appetite. Patient denied history of thyroid disease. His CLL and malignant meningioma have been stable. He was previously on amiodarone for atrial fibrillation until 1 year ago when it was discontinued. However, 6 weeks prior to presentation he self-resumed it at 100mg daily due to increased palpitations which he attributed to atrial fibrillation.

Vitals: T 97.9, BP 113/69, P 66, O2 97%.

Physical exam was significant for rate controlled irregular heart rhythm, intermittent fine tremor of bilateral hands and otherwise normal neurologic exam. There was no rash and the thyroid was without tenderness, enlargement or nodules.

Significant labs: TSH < 0.02.

Free T4= 3.1, Free T3= 606, TPO <9.0, TR Ab = < 1, Thyroglobulin 22.8, Thyroglobulin Ab < 0.9. His prior TSH was normal at 4.5, five months prior.

The patient was diagnosed with Type II Amiodarone induced thyrotoxicosis (AIT). Endocrinology recommended symptomatic treatment and stopping amiodarone. Cardiology concurred, and amiodarone was stopped. Five months later, labs showed subclinical hypothyroidism with TSH of 16 and Free T4 of 1.3. Repeat TSH was 12.7, FT4 1.2, FT3 299. He was started on levothyroxine 25 mcg daily. Repeat labs after 6 weeks of treatment showed TSH 1.8, FT4 1.10.

### *Case 2*

An 82-year-old female with CLL, atrial fibrillation status pacemaker placement, hypothyroidism on low dose levothyroxine, hypertension, and aortic stenosis presented for follow-up.

Five months prior she was started on amiodarone 200 mg daily for uncontrolled atrial fibrillation. Labs at the current visit were notable for TSH 28.7 and FT4 at 1.1. Thyroglobulin Ab < 0.9, TPO < 9.0. Patient denies any symptoms of hypothyroidism.

Given the need for amiodarone for her atrial fibrillation, her levothyroxine was increased to 50 mcg daily with improvement in TSH to 22 after 6 weeks. It was increased to 75 mcg daily, however TSH remained elevated at 18. Additional adjustments increased Sunday dose to 150 mcg. Eventually, amiodarone was discontinued by cardiology as it was not effective. After 8 weeks, her TSH normalized but FT4 was elevated at 2. Her levothyroxine was then decreased down to 75 mcg per day with eventual normalization of her thyroid function tests.

### *Discussion*

Amiodarone can affect thyroid hormone production through increasing iodine content and/or direct intrinsic effect on the thyroid gland.<sup>1,2</sup> It has long half-life of 100 days, thus the toxicity can occur well after drug withdrawal.<sup>1</sup> Thyroid hormone synthesis requires organified iodine in tyrosyl residues in thyroglobulin. Amiodarone contains two iodine atoms, therefore, every 100mg of metabolized amiodarone will release 3 mg of inorganic iodine into the body. This significantly increases the daily iodine load in patients as the typical diet contains only 0.3 mg /day.<sup>2</sup> When the iodine concentration is elevated, the body autoregulates by inhibiting iodine transport and thyroid synthesis temporarily until the level normalizes. This mechanism is known as Wolff-Chikoff effect.<sup>3</sup> This mechanism is defective in patients with underlying thyroid conditions such that additional iodine substrate can result in excessive thyroid hormone synthesis and thyrotoxicosis.<sup>3</sup> With amiodarone therapy, patients will have 3-6 mg of iodine/day making them susceptible to hyperthyroidism. Additionally, amiodarone can have a direct toxic effect on thyroid hormone production. It can inhibit T4 causing decreased T3 production and block T3 receptor binding to nuclear receptors and decrease expression of thyroid hormone related genes.<sup>4</sup> Amiodarone may also have direct toxic effect on thyroid follicular cells leading to a destructive thyroiditis.<sup>5</sup>

The type of amiodarone-induced thyroid dysfunction may depend on the patient's underlying thyroid condition and iodine intake.<sup>2,6,7</sup> In patients without underlying thyroid issues, there may be an increase in T4, FT4 concentration by 20-40% and reverse T3 concentration by 20% within a few weeks after initiation of amiodarone.<sup>2,7,8</sup> In these patients, a euthyroid state may be possible after 3 to 6 months of the therapy.<sup>8</sup> Some euthyroid patients may experience destructive thyroiditis leading to a hyperthyroid state when taking amiodarone.<sup>5</sup> Patients with existing autoimmune thyroid disease have higher chance of developing amiodarone induced hypothyroidism due to failed autoregulation, while patient with multinodular goiter or latent Grave's disease will have hyperthyroidism due to increased iodine thus enhancing thyroid hormone production.<sup>9</sup> Interestingly, dietary iodine will affect type of amiodarone induced thyroid dysfunction. In iodine-sufficient areas, 20 percent of patients developed amiodarone-induced hypothyroidism.<sup>6</sup> In contrast, hyperthyroidism is more common than hypothyroidism in iodine deficient regions.<sup>7</sup>

Most patients remain euthyroid with amiodarone treatment with one meta-analysis showing only 14 percent of those receiving amiodarone became hypothyroid.<sup>10</sup> Hypothyroid symptoms may develop as early as 2 weeks or up to 39 months after start of the amiodarone therapy.<sup>11</sup> This can be a transient state for those who were euthyroid prior to the treatment.<sup>8</sup> Patients with existing Hashimoto's thyroiditis or anti-thyroid antibodies are more likely to have persistent hypothyroidism with a higher prevalence amongst females.<sup>7</sup> It is important to assess thyroid function after initiation of amiodarone with follow up tests every few months for surveillance especially in those with underlying autoimmune thyroid conditions.<sup>12</sup> Patients with amiodarone-induced hypothyroidism should receive levothyroxine with the goal to normalize the thyroid level. A larger dose may be required as amiodarone can effect multiple areas of the thyroid gland.<sup>6</sup> Amiodarone does not need to be discontinued unless it is not controlling the arrhythmia. It is important to continue to monitor thyroid function after discontinuing amiodarone. Hypothyroidism may resolve in patients without underlying thyroid conditions but may persist for those with chronic autoimmune thyroiditis with high TPO antibodies and goiter, necessitating permanent thyroid supplementation.<sup>2,6,7,12</sup>

Diagnosis and management are more complicated for amiodarone induced thyrotoxicosis (AIT). Type I AIT is common in patients with multinodular goiter or latent Graves disease and is due to increased synthesis of thyroid hormone due to increased iodine levels from the medication.<sup>9,13</sup> Type II AIT is common in euthyroid patients and is due to the direct toxic effect of amiodarone on the thyroid gland causing destructive thyroiditis with excess release of T4 and T3 hormones. For type II, the hyperthyroid phase can last weeks to months and may be followed by a hypothyroid phase.<sup>13-15</sup> Symptoms of AIT can include atrial arrhythmia, exacerbation of heart failure, unexplained weight loss, restlessness or low-grade fever. These hyperthyroid symptoms may be masked due to beta blocking activities of amiodarone making diagnosis more challenging.<sup>2</sup>

Amiodarone induced thyrotoxicosis is reported to have a threefold increase in major adverse CV events and increase mortality when compared with euthyroid controls.<sup>16</sup> Determining the type can be difficult because some patient may have element of both. Type I AIT tends to occur early, a median of 3.5 months after starting treatment while Type II AIT can occur later at 30 months.<sup>17</sup> Twenty-four hour radioiodine uptake is not able to distinguish between them because high level of iodine in amiodarone leads to very low 24 hour uptake of less than 1 percent in most case.<sup>18</sup> <sup>99m</sup>Tc -sestamibi imaging may also be used as it shows normal or increased uptake in Type I and decreased in Type II.<sup>19</sup> Color flow doppler sonography may distinguish between the two with Type I showing increased vascularity while that is absent in Type II.<sup>20</sup>

In AIT, amiodarone used for preventing life threatening ventricular arrhythmia should be continued while treating the hyperthyroid condition.<sup>21</sup> For non-threatening arrhythmia, amiodarone can be discontinued when the hyperthyroid symptoms are well-controlled to prevent worsening symptoms due to removing the beta-blocking effect of amiodarone.<sup>21</sup> In Type I AIT, higher doses of methimazole may be necessary until the measurement of urine iodine returns to normal which may take 6-18 months. For Type II, glucocorticoid therapy with prednisone 40-60 mg /day should be used for treating destructive thyroiditis rather than methimazole and should continue for 1-2 months before tapering.<sup>14,21</sup> In Type II AIT patients, hypothyroidism may develop when hyperthyroidism resolves and will require T4 replacement.<sup>5</sup> For AIT that is refractory to medical treatment, thyroidectomy should be considered especially if the patient is amiodarone-dependent. In these patients, the benefit of surgery outweighs the risk of uncontrolled hyperthyroidism over time.<sup>21,22</sup>

### *Case Discussion*

The case 1 patient had no underlying history of thyroid disease but presented with amiodarone-induced thyrotoxicosis leading to palpitations. It is unclear if the condition was acute due to restarting amiodarone recently or if was the result of prior amiodarone treatment, as it can take more than 30 months to develop symptoms due to the long half-life of amiodarone. He was diagnosed with Type II AIT based on the lack of prior history of thyroid disease. Because his amiodarone was recently restarted and his arrhythmia was not life threatening, the amiodarone was stopped and no steroid treatment was initiated. Due to destructive thyroiditis from Type II AIT, he subsequently became hypothyroid and required levothyroxine replacement. His is currently stable on the regimen and continues to be followed by endocrine and cardiology.

The case 2 patient had a history of hypothyroidism that had been well-controlled until the initiation of amiodarone which led to subclinical hypothyroidism. Her levothyroxine was increased to 3 times the original dose, but it was not until discontinuation of amiodarone that her thyroid level stabilized. She will need to have ongoing monitoring of her thyroid

function as she may need to decrease the levothyroxine dosage further when her thyroid function recovers.

It is prudent to monitor thyroid function closely when amiodarone is initiated regardless of patients' underlying thyroid status. The type of treatment depends on the type of thyroid dysfunction that occurs. Early diagnosis with early intervention can prevent unwanted long-term effects from thyroid dysfunction while achieving control of the cardiac arrhythmia.

## REFERENCES

1. **Latini R, Tognoni G, Kates RE.** Clinical pharmacokinetics of amiodarone. *Clin Pharmacokinet.* 1984 Mar-Apr;9(2):136-56. doi: 10.2165/00003088-198409020-00002. PMID: 6370540.
2. **Basaria S, Cooper DS.** Amiodarone and the thyroid. *Am J Med.* 2005 Jul;118(7):706-14. doi: 10.1016/j.amjmed.2004.11.028. PMID: 15989900.
3. **Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, Vidor G, Braverman LE, Medeiros-Neto G.** Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid.* 1998 Jan;8(1):83-100. doi: 10.1089/thy.1998.8.83. PMID: 9492158.
4. **Franklyn JA, Davis JR, Gammage MD, Littler WA, Ramsden DB, Sheppard MC.** Amiodarone and thyroid hormone action. *Clin Endocrinol (Oxf).* 1985 Mar;22(3):257-64. doi: 10.1111/j.1365-2265.1985.tb03238.x. PMID: 3978832.
5. **Roti E, Minelli R, Gardini E, Bianconi L, Braverman LE.** Thyrotoxicosis followed by hypothyroidism in patients treated with amiodarone. A possible consequence of a destructive process in the thyroid. *Arch Intern Med.* 1993 Apr 12;153(7):886-92. PMID: 8466380.
6. **Harjai KJ, Licata AA.** Effects of amiodarone on thyroid function. *Ann Intern Med.* 1997 Jan 1;126(1):63-73. doi: 10.7326/0003-4819-126-1-199701010-00009. PMID: 8992925.
7. **Trip MD, Wiersinga W, Plomp TA.** Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. *Am J Med.* 1991 Nov;91(5):507-11. doi: 10.1016/0002-9343(91)90187-3. PMID: 1951413.
8. **Diederichsen SZ, Darkner S, Chen X, Johannesen A, Pehrson S, Hansen J, Feldt-Rasmussen U, Svendsen JH.** Short-term amiodarone treatment for atrial fibrillation after catheter ablation induces a transient thyroid dysfunction: Results from the placebo-controlled, randomized AMIO-CAT trial. *Eur J Intern Med.* 2016 Sep;33:36-41. doi: 10.1016/j.ejim.2016.04.012. Epub 2016 Apr 26. PMID: 27129624.
9. **Fradkin JE, Wolff J.** Iodide-induced thyrotoxicosis. *Medicine (Baltimore).* 1983 Jan;62(1):1-20. doi: 10.1097/00005792-198301000-00001. PMID: 6218369.
10. **Mohammadi K, Shafie D, Vakhshoori M, Bondariyan N, Rezvanian H, Heidarpour M.** Prevalence of amiodarone-induced hypothyroidism; A systematic review and meta-analysis. *Trends Cardiovasc Med.* 2022 Jan 11;S1050-1738(22)00003-2. doi: 10.1016/j.tcm.2022.01.001. Epub ahead of print. PMID: 35026394.
11. **Christidis G, Lammert F, Krawczyk M.** Amiodarone and hypothyroidism. *Lancet.* 2021 Feb 20;397(10275):704. doi: 10.1016/S0140-6736(21)00204-X. PMID: 33610214.
12. **Martino E, Aghini-Lombardi F, Mariotti S, Bartalena L, Lenziardi M, Ceccarelli C, Bambini G, Safran M, Braverman LE, Pinchera A.** Amiodarone iodine-induced hypothyroidism: risk factors and follow-up in 28 cases. *Clin Endocrinol (Oxf).* 1987 Feb;26(2):227-37. doi: 10.1111/j.1365-2265.1987.tb00781.x. PMID: 3665117.
13. **Martino E, Bartalena L, Bogazzi F, Braverman LE.** The effects of amiodarone on the thyroid. *Endocr Rev.* 2001 Apr;22(2):240-54. doi: 10.1210/edrv.22.2.0427. PMID: 11294826.
14. **Bartalena L, Brogioni S, Grasso L, Bogazzi F, Burelli A, Martino E.** Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab.* 1996 Aug;81(8):2930-3. doi: 10.1210/jcem.81.8.8768854. PMID: 8768854.
15. **Lambert M, Unger J, De Nayer P, Brohet C, Gangji D.** Amiodarone-induced thyrotoxicosis suggestive of thyroid damage. *J Endocrinol Invest.* 1990 Jun;13(6):527-30. doi: 10.1007/BF03348618. PMID: 2258582.
16. **Yiu KH, Jim MH, Siu CW, Lee CH, Yuen M, Mok M, Shea YF, Fan K, Tse HF, Chow WH.** Amiodarone-induced thyrotoxicosis is a predictor of adverse cardiovascular outcome. *J Clin Endocrinol Metab.* 2009 Jan;94(1):109-14. doi: 10.1210/jc.2008-1907. Epub 2008 Oct 21. PMID: 18940876.
17. **Tomisti L, Rossi G, Bartalena L, Martino E, Bogazzi F.** The onset time of amiodarone-induced thyrotoxicosis (AIT) depends on AIT type. *Eur J Endocrinol.* 2014 Sep;171(3):363-8. doi: 10.1530/EJE-14-0267. Epub 2014 Jun 16. PMID: 24935933.
18. **Daniels GH.** Amiodarone-induced thyrotoxicosis. *J Clin Endocrinol Metab.* 2001 Jan;86(1):3-8. doi: 10.1210/jcem.86.1.7119. PMID: 11231968.
19. **Wang J, Zhang R.** Evaluation of 99m Tc-MIBI in thyroid gland imaging for the diagnosis of amiodarone-induced thyrotoxicosis. *Br J Radiol.* 2017 Mar;90(1071):20160836. doi: 10.1259/bjr.20160836. Epub 2017 Jan 20. PMID: 28106465; PMCID: PMC5601526.
20. **Eaton SE, Euinton HA, Newman CM, Weetman AP, Bennet WM.** Clinical experience of amiodarone-induced thyrotoxicosis over a 3-year period: role of colour-flow Doppler sonography. *Clin Endocrinol (Oxf).* 2002 Jan;56(1):33-8. doi: 10.1046/j.0300-0664.2001.01457.x. PMID: 11849244.
21. **Bogazzi F, Bartalena L, Martino E.** Approach to the patient with amiodarone-induced thyrotoxicosis. *J Clin Endocrinol Metab.* 2010 Jun;95(6):2529-35. doi: 10.1210/jc.2010-0180. PMID: 20525904.
22. **Cappellani D, Papini P, Pingitore A, Tomisti L, Mantuano M, Di Certo AM, Manetti L, Marconcini G, Scattina I, Urbani C, Morganti R, Marcocci C,**

**Materazzi G, Iervasi G, Martino E, Bartalena L, Bogazzi F.** Comparison Between Total Thyroidectomy and Medical Therapy for Amiodarone-Induced Thyrotoxicosis. *J Clin Endocrinol Metab.* 2020 Jan 1;105(1):dgz041. doi: 10.1210/clinem/dgz041. PMID: 31545358.