Therapeutic Plasmapheresis in Amiodarone-Induced Thyrotoxicosis Resistant to Medical Therapy

Medikal Tedaviye Dirençli Amiodaron ile İlişkili Tirotoksikozda Terapötik Plazmaferez Tedavisi

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Case Report

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Introduction

Amiodarone, a class 3 anti-arrhythmic drug, commonly used in the treatment of ventricular and supraventricular tachyarrhythmias, contains 37% by weight iodine, and a significant amount of this iodine is released during metabolism (1). The high iodine content of amiodarone increases the amount of plasma inorganic iodine by 40 times and causes approximately 15,000 mcg/day urinary iodine excretion (1,2). Due to these changes, 25% of patients suffer from thyroid dysfunction (2-4). A wide range of amiodarone-induced thyroid abnormalities have been reported, from hypothyroidism to thyrotoxicosis (3).

Amiodarone-induced thyrotoxicosis (AIT) is divided into two main groups (3,5). Type 1 thyrotoxicosis occurs in iodine-deficient areas, in patients with baseline thyroid disease, conversely type 2 thyrotoxicosis occurs in iodine sufficient areas in patients without any prior thyroid disease. Type 1 AIT is iodine associated thyrotoxicosis (Jod Basedow phenomenon), and type 2 AIT is thyroiditis associated (3,6). The overlapping form of both types is referred to as mixed or indeterminate type (7).
In type 1 AIT, refractory hyperthyroidism may occur despite amiodarone cessation and a high dose of thionamide treatment \((4,5,8)\). High solubility in adipose tissue and long half-life of amiodarone may be responsible for some challenges in controlling AIT \((2)\). Amiodarone-associated thyrotoxicosis may also worsen the underlying cardiac abnormality \((9)\). Thus urgent surgery may be considered in patients with impaired cardiac function or severe cardiac arrhythmia \((7,10)\). A therapeutic plasmapheresis is a possible option for ensuring preoperative euthyroidism in patients resistant to thionamide or if thionamide is contraindicated \((11,12)\). In this article, we aimed to discuss plasmapheresis treatment in surgery preparation of medical treatment-resistant type 1 AIT.

**Case Report**

A 48-year-old male was admitted to the emergency department with dyspnea and palpitation. A cardiologist evaluated and diagnosed the patient with ventricular tachycardia. The patient was hospitalized, and amiodarone treatment was started \((300\, \text{mg IV bolus followed by 900 mg/day infusion})\). The patient was evaluated for tachycardia etiologies, and the thyroid function tests revealed thyrotoxicosis \(fT3\: 12.3\, \text{ng/L},\, fT4\: 3.82\, \text{ng/dL},\, \text{TSH}\: 0.22\, \text{mIU/L}\). The patient was further consulted at the endocrinology clinic.

According to his medical history, the patient had a 10-year history of aortic valve replacement, one year of congestive heart failure \(25\%\, \text{ejection fraction})\), and he received treatment for ventricular tachycardia. One year ago, an implantable cardioverter-defibrillator (ICD) was placed in the patient due to frequent ventricular tachycardia attacks despite anti-arrhythmic therapy \(\text{amiodarone})\). Furthermore, four years ago, he received methimazole treatment for one year with a diagnosis of Graves' disease. His medications included coumadin \(5\, \text{mg/day},\, \text{spironolactone}\: 25\, \text{mg/day},\, \text{ramipril}\: 5\, \text{mg/day} and \text{amiodarone}\: 200\, \text{mg/day}.

In physical examination, his general condition was moderate; he was conscious, restless, and cachectic. In vital signs, fever was \(36.5\, ^\circ\, \text{C}\), heart rate was 110 beats/min, blood pressure was 140/80 mm/hg and respiratory rate was 25/min. In addition, eye examination revealed eyelid retraction. In thyroid examination, he had stage 2 diffuse goiter. Laboratory findings were all normal, except thyrotoxicosis and thyroid antibody positivity \(\text{Table 1}\). Thyroid scintigraphy showed normal uptake \(2.6\%\), and thyroid ultrasonography revealed chronic thyroiditis characterized by a diffuse reduction in parenchymal echogenicity. Type 3 blood flow was observed in the color flow Doppler \(\text{Figure 1A and 1B})\). With these findings, the patient was considered with type 1 AIT, amiodarone treatment was discontinued, and methimazole and propranolol were started with \(2\times10\, \text{mg/day} and 3\times20\, \text{mg/day})\). Although a dose of methimazole was increased to \(2\times30\, \text{mg/day} on follow up after one month, fT4 and fT3 levels were \(2.35\, \text{ng/dL} and 5.70\, \text{ng/L})\), respectively, and the patient continued to suffer from frequent ventricular tachycardia. Subsequently, five sessions of therapeutic plasmapheresis were performed on the patient. Plasmapheresis was

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient</th>
<th>Normal Reference Range</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>88</td>
<td>74-100 mg/dL</td>
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<tr>
<td>BUN</td>
<td>14</td>
<td>6-20 mg/dL</td>
</tr>
<tr>
<td>Cr</td>
<td>0.7</td>
<td>0.2-1.3 mg/dL</td>
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<tr>
<td>AST</td>
<td>28</td>
<td>13-40 U/L</td>
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<td>ALT</td>
<td>18</td>
<td>7-45 U/L</td>
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<tr>
<td>T. Bilirubin</td>
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<td>0.3-1.2 mg/dL</td>
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<tr>
<td>WBC</td>
<td>6.83</td>
<td>3.39-8.86 10^9/L</td>
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<tr>
<td>Neutrophil</td>
<td>4.77</td>
<td>1.5-5 10^9/L</td>
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<tr>
<td>Hg</td>
<td>14.3</td>
<td>11.1-16.6 g/dL</td>
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<tr>
<td>Plt</td>
<td>191</td>
<td>171-388 10^9/L</td>
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<tr>
<td>TSH</td>
<td>0.000</td>
<td>0.35-5.5 mIU/L</td>
</tr>
<tr>
<td>fT3</td>
<td>12.3</td>
<td>2.3-4.2 ng/L</td>
</tr>
<tr>
<td>fT4</td>
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<tr>
<td>AntiTPO</td>
<td>150</td>
<td>0-35 IU/mL</td>
</tr>
<tr>
<td>AntiTg</td>
<td>355</td>
<td>0-40 IU/mL</td>
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</table>

BUN: Blood urea nitrogen; Cr: Creatinine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; T. Bilirubin: Total bilirubin; WBC: White blood cell; Hg: Hemoglobin; TSH: Thyroid-stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine; AntiTPO: Thyroid peroxidase antibody; AntiTg: Thyroglobulin antibody.
performed with a Multifiltrate Pro device (Fresenius Medical Care, Germany), and 40 mg/kg of fresh frozen plasma was used for 2 h in each session. Classical heparin (2500 IU) was used as the anticoagulant. The change in thyroid function test after plasmapheresis is shown in Figure 2. After ensuring clinical euthyroidism, total thyroidec- tomy was performed by general surgery without intraoperative or postoperative complications. The patient is still being followed up in our clinic with levothyroxine treatment.

Discussion
Type 1 AIT is a form of iodine-induced hyperthyroidism typically characterized by an uncontrolled increase in thyroid hormone due to excessive iodine exposure in patients with baseline nodular goiter or latent graves (3). Amiodarone-induced thyrotoxicosis is diagnosed by increased fT4, fT3, and decreased TSH levels. In rare cases, fT3 may be normal due to severe non-thyroidal illness (13). Although the levels of fT4 and fT3 are higher in type 2 AIT, they are not useful in the differential diagnosis, whereas thyroid autoantibody positivity may be beneficial. Also, antithyroid peroxidase (anti-TPO) is positive in type 1 AIT but negative in type 2 (14). However, the presence of antibodies for the diagnosis of Type 1 AIT is not necessarily required (15). On the contrary, scintigraphy and ultrasound may be used for diagnosis (1). Although the standard thyroid USG has a low diagnostic value, there is an increase in type 1 vascularity in color Doppler ultrasound, and no vascularity in type 2 (16). Radioactive iodine uptake (RAIU) may be low, normal, or high in type 1 AIT. Inversely, RAIU is suppressed in type 2 AIT (17). Our case was diagnosed as Type 1 amiodarone-induced thyrotoxicosis because of the presence of underlying Graves’ disease, anti-TPO positivity, type 3 blood flow in the color Doppler USG and normal uptake in the scintigraphy.

Amiodarone-induced thyrotoxicosis may cause cardiac dysfunction or increase underlying cardiac abnormality, even in asymptomatic patients. The left ventricular function may also be impaired, especially in elderly patients (9,18,19). Moreover, AIT and left ventricular systolic dysfunction are associated with mortality and morbidity (9,18). For this reason, treatment should be considered in all patients with AIT. If medical

![Figure 1A, B: Normal uptake in thyroid scintigraphy and type 3 blood flow in color flow Doppler ultrasound.](image)

![Figure 2: Changes in thyroid function tests before and after plasmapheresis.](image)
treatment is applicable, the primary treatment of type I AIT is thionamide (carbimazole, methimazole, propylthiouracil). However, surgical treatment may be an alternative option in people who cannot be controlled or contraindicated with medical treatment.

Furthermore, urgent surgery may be considered in patients with impaired cardiac function and/or severe arrhythmia (10,20). Surgical treatment provides euthyroidism quickly and improves cardiac function in patients with severe left ventricular systolic dysfunction in two months and thus decreases mortality (10). In our case, we started treatment with thionamide, similar to previous studies. However, we could not provide euthyroidism despite high dose methimazole treatment. Furthermore, our patient had severe left ventricular systolic dysfunction and developed severe arrhythmia, thus requiring urgent surgery.

Therapeutic plasmapheresis is a safe and useful procedure in which blood is separated by centrifugation or filtration into plasma and cells. The cells are returned to the patient, and the patient’s plasma is replaced by fresh frozen plasma, albumin, or similar colloidal solution (21,22). Since the therapeutic aim of the plasmapheresis is the removal of harmful substances (like immune complexes, cytokines, toxins or hormones), patients with severe hyperthyroidism may benefit from this procedure. Therefore, it can be used to decrease thyroid hormone levels in medical treatment-resistant AIT patients. This effect is usually temporary and causes exacerbation of thyrotoxicosis after treatment; nevertheless, it is a useful procedure in preparation for surgery (23). Therapeutic plasmapheresis was first used in the treatment of hyperthyroidism and thyroid storm in the 1970s and 1985, respectively (24,25). In general, it was used in severe hyperthyroidism when antithyroid drugs were contraindicated (22). In the case of accompanying diseases, preoperative antithyroid drug intolerance/resistance, or other insufficient treatment options, plasmapheresis is an alternative and effective therapeutic tool (22,26). In a retrospective case series, 20 of 22 patients with severe hyperthyroidism due to Graves’ disease or toxic multinodular disease are reported to show clinical improvement from plasmapheresis (22). In another case series, plasmapheresis provided euthyroidism without any complication in eight patients with thyrotoxicosis before thyroid surgery (24). In the study by Lukomskii et al. (12), plasmapheresis was found to be effective in preoperative preparation of 73 thyrotoxic patients resistant or intolerant to antithyroid drugs. Yamamoto et al. (27) also reported that preoperative plasmapheresis was applied successfully in a patient with medical treatment-resistant amiodarone-induced thyrotoxicosis. Plasmapheresis has been shown to be effective and prompt to correct thyrotoxicosis in a series of 46 patients with 40 Graves’ disease, 4 with AIT, and 2 with toxic nodular goiter (28). Our case also benefited from therapeutic plasmapheresis in providing preoperative euthyroidism. In our case, we applied plasmapheresis five times and provided clinical euthyroidism at the end of the 5th session.

In conclusion, preoperative TP was found to be an effective method in light of this case and the literature, in providing euthyroidism in patients with AIT requiring emergency surgery.

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Conflict of Interest
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