Type 2 Amiodarone-induced Thyrotoxicosis Which Present with Nodular Goiter

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Amiodarone, an iodinated benzo-furanic derivative, was introduced in the 1960s as an antianginal agent for its coronary vasodilator property. Later it was broadly applied as an antiarrhythmic agent. Amiodarone affects thyroid function as a result of both iodine release and intrinsic drug properties. The incidence of Amiodarone induced thyrotoxicosis (AIT) is 5-10% in reports of most studies. There are two types of AIT, designated as type 1 and type 2. Type 1 AIT occurs in abnormal thyroid glands (nodular goiter, latent Graves’ disease) and type 2 AIT in apparently normal thyroid glands. But mixed or indefinite form, the combination of these 2 forms does exist. This form maybe caused by both pathogenic mechanisms. Here we reported a patient with type 2 AIT who presented not only with common manifestations of type 1AIT but also gained euthyroid state with steroid therapy.

Key words: Amiodarone-induced thyrotoxicosis, Amiodarone

INTRODUCTION

Amiodarone induced thyrotoxicosis (AIT) is a challenging problem and often faces difficult diagnostic and therapeutic decisions. There are two main forms of AIT. Type 1 AIT occurs in patients with preexisting thyroid gland abnormalities and is due to iodine-induced increased synthesis of thyroid hormone. Type 2 AIT is typically seen in patients with a previously normal thyroid gland and is due to the release of preformed hormone by iodine induced cytotoxic damage of the gland.

Mixed or indefinite AIT can occur in the same patient¹⁻³. The affected person may present with or without cardiac manifestations of thyrotoxicosis due to the antiadrenergic action of amiodarone and its inhibition of conversion of T4 to T3. Although radioactive iodine uptake (RAIU) and color flow Doppler sonography (CFDS) are essential for differentiation between type 1 and type 2 AIT, careful history and physical examination are usually enough to discriminate them¹⁻³. Here we reported a case of type 2 AIT but with common manifestations of type 1 AIT, such as goiter and autoimmune autoantibodies.

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Case presentation

A 76 year-old man was diagnosed with coronary artery disease (CAD) 16 years ago and a bypass surgery was performed at Cheng Hsin General Hospital then. Because of his recurrent CAD, percutaneous transluminal coronary angioplasty (PTCA) was administered on Nov. 2006. Unfortunately it failed because of short run ventricular tachycardia when PTCA was undertaken. Thereafter, amiodarone was initiated. Other medical histories included hypertension, dyslipidemia, old cerebrovascular accident, Parkinsonism and benign prostate hyperplasia. On Sep 9, 2011, he visited endocrine outpatient department (OPD) with chief complain of left lower neck mass associated with compression sensation. His body weight was 75kg and height was 167cm. He had no history of thyroid disease problem in the past and he never received neck ultrasound before. Moreover, he denied history of neck radiation and trauma before. He had no medication history like lithium, interferon and any other history of illness within these days. Upon physical examination, he has no proptosis, but a 3x3 cm nodule was found over left lower neck, which was not associated with tenderness. No bruit was appreciated over the gland. There were no symptoms or signs of thyrotoxicosis, such as body weight loss or palpitation. Thyroid sonogram was done immediately. At that time, there was no any information about thyroid function. Thyroid sonogram showed small thyroid cysts over the right lobe and a big cyst (4.92x3.86x3.72cm) on the left lobe (Figure 1a). Fine needle aspiration was done and 0.5 ml clear fluid was extracted. Cytology of the aspiration disclosed mixed population of colloid and a few inflammatory cells in the background. Nodular goiter with cystic change was impressed initially by the findings of sonogram. However, lab test revealed thyrotoxicosis with positive autoantibodies: free T4 (FT4) at 2.58ng/dl (reference range: 0.89-1.76ng/dl ); TSH at 0.034μIU/ml (0.35-5.5μIU/ml); anti-thyroglobulin antibody at 92.6U/ml (0-60U/ml); and anti-thyroperoxidase antibody at 65.6U/ml (0-60U/ml). The patient was assumed to be type 1 AIT in the beginning according to nodular goiter on physical examination and thyroid sonogram, as well as positive autoantibodes. Therefore anti-thyroid drug with carbimazole 20mg/day was prescribed for four weeks. However, the patient took carbimazole with dose of 40mg/day instead of 20mg/day. Therefore, he ran out of medication after two weeks. During the two weeks, the patient experienced poor appetites and dysphagia. In addition profound body weight loss of 4 kg was noticed. Therefore he consulted with gastroenterologist for further evaluation. Endoscopic examination showed gastroesophageal reflux disease (GERD) Grade B and superficial gastritis. Proton pump inhibitor (PPI) with supportive medicine was prescribed accordingly. On Oct 18, 2011, one month after prescription of carbimazole, he returned for the scheduled follow-up. Significant body weight loss of 7kg within this month (from 75Kg to 68Kg) was observed. In addition, aggravated thyrotoxicosis with FT4 at 9.39ng/dl associated with elevated ALT at 151U/L (reference range: 10-60U/L) were disclosed. His TSH receptor antibody(TSH-r-Ab) was 7% (normal:<14%). In order to prevent the emergence of thyroid storm, he was admitted to our ward immediately.
Thyroid sonogram was done on the following day after admission and it revealed a large echo-free cystic lesion (5.09x3.13x3.32cm), which occupied nearly the whole left lobe. Color flow doppler scan (CFDS) showed no increased vascularity over the non-cystic part of both lobes (Figure 1b). Tc-99m thyroid scan on the following day unveiled prominently decreased (very low) activity on the thyroid bed/anterior neck. The uptake ratio was only 0.1% (reference range: 0.5-3.75%) (Figure 2). 99mTc-sestaMIBI thyroid scan of this patient also showed persistent low activity in both thyroid glands from 2 to 15 minutes imaging (Figure 3). After these examinations, type 2 AIT was suspected, instead of type 1 AIT. Hydrocortisone sodium succinate (solucortef) 50 mg q6h was started intravenously and anti-thyroid drug was discontinued. After one week of hospitalization, the patient was discharged with prednisolone 20mg/day. Euthyroidism (FT4: 1.44ng/dl; T3: 44.89ng/dl; TSH: 0.845μIU/ml) was achieved after six weeks and prednisolone was gradually tapered and discontinued. The last thyroid function on Dec 16, 2011 showed FT4 at 1.2ng/dl; T3 at 65.34ng/dl and TSH at 0.827μIU/ml. Follow-up sonogram revealed a smaller thyroid cyst (2.41x1.26x1.32cm) comparing to previous scans (Figure 1c).

Figure 1a Thyroid sonogram in 100/09/09 revealed a cystic lesion (4.92*3.86*3.72cm) in left lobe.

Figure 1b Color flow doppler scan (CFDS) in 100/10/19 revealed no increased vascularity over the non-cystic part of both lobes.
Figure 1c Thyroid sonogram in 100/12/30 revealed that the cystic lesion (2.41*1.26*1.32cm) of left lobe was smaller than it was in 100/9/9.

Figure 2 The technetium-99m pertechnetate thyroid study shows prominently decreased (very low) activity on the thyroid bed/anterior neck. Tc-O4 thyroid uptake ratio: 0.1 % (normal range 0.5 - 3.75 %).
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Figure 3  Tc-99m MIBI revealed relatively symmetric decreased activity through both thyroid glands at 2, 10, 15 and 60 minutes imaging, which showed persistent low activity from 2 to 15 minutes imaging.

Figure 4  A patient with type 2AIT who achieved euthyroidism after steroid therapy.
Discussion

Amiodarone, a benzofuranic iodine-rich antiarrhythmic drug, causes thyroid dysfunction in 15-20% of people with amiodarone\(^1\)-\(^3\). Since iodine consists of 37% of its weight, recipients are exposed to 75 mg iodide daily with a standard dose of amiodarone 200 mg/day\(^3\). The daily intake of iodine recommended by the National Research Council of the US National Academy of Sciences in 1989 was 150 μg/day for adolescents and adults. It has also a long period of effect after drug discontinuation due to its prolong half-life (40-60 days)\(^1\)-\(^3\). In euthyroid subjects who are on amiodarone therapy, the serum T4 usually increases and serum T3 decreases because of the inhibition of type I 5′-deiodinase (5′-D) activity in the conversion from T4 to T3 in the peripheral tissues, particularly the liver, and the T4 entry into peripheral tissues by amiodarone\(^1\)-\(^3\). The affected person may present with or without cardiac manifestations of thyrotoxicosis due to the antiadrenergic action of amiodarone and its inhibition of conversion of T4 to T3. In our case, he didn’t suffer from any symptoms or signs when he came to OPD in the beginning. Therefore, regular thyroid function evaluation is always important when patient is receiving amiodarone, even when patient doesn’t have symptoms of thyrotoxicosis.

The challenge regarding AIT is not to diagnose thyrotoxicosis, but to differentiate between type 1 and 2 AIT. Type 1 AIT usually develops in patients with latent autonomy due to thyroid nodular or autoimmune disease. In contrast, type 2 AIT usually exists in patients with normal thyroid gland\(^1\)-\(^3\). In a previous study, patients with apparent thyroid abnormalities, like nodular goiter and/or thyroid autoimmune disease, were usually with normal to high radioiodine uptake (RAIU) and normal level of interleukin-6 (IL-6). Whereas patients with no apparent thyroid abnormalities were with low RAIU and high IL-6\(^4\). In the current case, the patient presented a large nodular goiter with cystic change, as well as positive thyroid autoantibodies. These are typical signs of type 1 AIT. Therefore, type 1 AIT was assumed initially in our case. However about 8% of type 2 AIT could present with positive thyroid autoantibody tests\(^3\). In a small prospective study, TPOAb developed in 46% of patients with recent myocardial infarction who started to receive amiodarone, comparing to none with placebo use\(^5\). Therefore, thyroid autoimmunity cannot exclude the possibility of type 2 AIT. Moreover, many thyroid diseases can present with thyroid cyst, there is no role of steroid therapy in treatment of thyroid cyst. In our case, thyroid cyst was apparently reduced in size with steroid therapy. This also approved the underlying thyroid disease in our patient is type 2 AIT.

For further differential diagnosis, CFDS and RAIU are considered the best tools. CFDS findings correlate well with the pathophysiology of the AIT. In type 1 AIT, the CFDS displays an increased vascularity due to a iodine induced increase of thyroid function whereas it shows no vascularity in type 2 AIT due to iodine induced destruction of thyroid gland\(^1\)-\(^3\)-\(^6\). RAIU value is normal to high in type 1 AIT. Conversely, like other thyroiditis, the uptake is low or none in type 2 AIT\(^1\)-\(^3\). Even with the combination of RAIU and CFDS in the diagnostic work up, nearly one third of thyroidologists cannot make a clear-cut diagnosis of type 1 or type 2 AIT in a index case with the presence of a nodular...
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goiter, negative thyroid autoantibody tests, low-normal thyroid RAIU values and increased vascularization[9]. Fortunately, RAIU was very low in our case and vascularity could be evaluated on the other side of big cyst by sonogram. It leads us to think about the diagnosis of type 2 AIT.

99mTc-sestaMIBI is a lipophilic monovalent cation. It shows an increased uptake in epithelial cells containing high numbers of mitochondria[8-10]. It is currently used in detecting hyperparathyroidism. 99mTc-sestaMIBI had been shown in diagnosing hyperfunctioning thyroid tissue before[11,12]. Recently, a study carried out in Italy claimed that 99mTc-sestaMIBI thyroid represents the best single test to differentiate type 1 AIT from type 2 AIT. 99mTc-sestaMIBI uptakes were normal or increased in patients with type 1 AIT and absent in patients with type 2 AIT. In mixed type AIT, the MIBI uptake will be faint or transient due to incomplete thyroid destruction associated with different degrees of hyperfunctioning tissue[13]. In our patient, Tc-99m MIBI revealed relatively symmetric decreased activity through the both thyroid glands at 2,10,15 and 60 minutes imaging, which showed persistent low activity from 2 to 15 minutes imaging. So our case is consistent with type 2 AIT.

In conclusion, the differentiation between the two main forms of AIT has crucial therapeutic implications and is based on clinical, biochemical and imaging results. A clear-cut differentiation between the two main forms is difficult, despite recent diagnostic advances. Although many case reports had already presented that type 1 AIT usually occurs in abnormal thyroid glands with positive thyroid autoantibodies. Exception in few cases of type 2 AIT can develop in small goiters, majority of type 2 AIT develops in apparently normal thyroid glands. In the literature, there is no case report of type 2 AIT presented with apparently abnormal thyroid gland as well as positive thyroid autoantibodies. We believed the case we presented here is the first case of type 2 AIT presented with large nodular goiter and positive thyroid autoantibodies. Indeed, differentiation between type 1 AIT and type 2 AIT is not simple and easy one. Clinically AIT patient can also present either with mixed/indefinite forms or with atypical features like our case. For all AIT patients, detailed examination in addition to careful history and physical examination is warranted.

Reference

induced thyrotoxicosis. Thyroid 7:541-545.


以甲狀結節來表現的第二型 Amiodarone 導致的甲狀腺機能亢進症

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Amiodarone 是一個碘化的苯丙夫喃 (benzofuran) 衍生物，因其具有冠狀動脈擴張的效果，在 1960 年代被用來當成抗心絞痛藥物。之後他被廣泛用來當作抗心律不整的藥物。Amiodarone 藥物本身及其會釋放碘，雙雙都會影響甲狀腺的功能。Amiodarone 導致的甲狀腺毒血症 (AIT) 的發生率在大部分的研究當中大約是 5-10%。Amiodarone 導致的甲狀腺毒血症有兩種類型，分別是第一型和第二型。第一型 AIT 發生在不正常的甲狀腺（甲狀腺結節，潛伏性葛瑞夫茲氏症 (Graves' disease)），第二型 AIT 則發生在正常的甲狀腺。我們這位病人罕見的是以甲狀腺結節來表現的第二型 AIT。

關鍵字：Amiodarone 導致的甲狀腺毒血症