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Case Report

Thyrotoxic Graves' Disease-induced by Interferon-ribavirin Therapy in a Patient with Amiodarone-induced Hypothyroidism on Thyroxine Replacement

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Abstract

An unusual type of drug-induced thyroid dysfunction is described. Thyrotoxicosis was seen in association with the use of interferon therapy despite prior established amiodarone-induced hypothyroidism. A 63-year-old female patient with a history of hypertension, high-grade ventricular arrhythmia on sotalol 80 mg daily was diagnosed to have amiodarone-induced hypothyroidism previously. She has been receiving thyroxine replacement therapy for 4 years. During the second cycle of interferon for hepatitis C virus relapse. She developed autonomous thyrotoxicosis. Her anti-thyroid peroxidase antibody was persistently negative before, during, and after either amiodarone or interferon while anti-thyroid stimulating hormone receptor antibody titer. Thyroid Tc-99m scan showed a high uptake during interferon therapy. To the best of the author's knowledge, this is the first report of a case of long-term hypothyroidism-induced by amiodarone therapy evolving into thyrotoxic Graves' disease-induced by interferon/ribavirin combination therapy in Libya reflecting an interaction of drugs and the background autoimmune disease.

Keywords: Amiodarone, Graves' disease, Interferon, Libya, thyroid dysfunction

Introduction

Amiodarone is an effective class III antiarrhythmic drug used in the treatment of ventricular and supraventricular arrhythmias. Pharmacologically, it is an Iodine-containing compound with some structural similarity to thyroxine.[1] Some adverse effects of amiodarone are relatively mild, others can require intervention, for example, thyroid dysfunction (hypothyroidism 1%–22%, hyperthyroidism 2%–10%), pneumonitis 2%–17%, and hepatitis <3%.[1] Amiodarone-induced thyrotoxicosis (AIT) is more prevalent in iodine-sufficient areas and predominantly occurs in men, and may develop anytime during amiodarone therapy or even after the drug is discontinued. AIT in a patient with preexisting thyroid abnormality such as diffuse or nodular goiter or latent Graves' disease is called AIT Type I, whereas AIT in a patient with apparently normal thyroid gland is called AIT Type II.[2] AIT Type II may be related to destructive inflammatory thyroiditis caused by the increased iodine load.[3] In fact, mixed forms often exist.[3] In Type I AIT, 24-h uptake of radioactive iodine by the thyroid gland is normal to high, conversely, in Type II, uptake is low.[2] Amiodarone-induced hypothyroidism is believed to result from the inability of the thyroid to escape from the Wolff–Chaikoff effect after an iodine load and to resume normal thyroid hormone synthesis. It mostly affects old females with anti-thyroid peroxidase (TPO) antibodies from iodine sufficient areas.[2] On the other hand, the interferons are a group of proteins with antiviral activity is used therapeutically in chronic hepatitis B and C and in certain malignancies. It can precipitate or exacerbate autoimmune endocrine diseases, especially of the thyroid gland.[3] The thyroid gland dysfunction affects 4%–14% of patients.[4,5] Secondary appearance on interferon therapy of elevated thyroid auto antibodies (anti-microsomal, anti-thyroglobulin, and/or anti-thyroid stimulating hormone [TSH] receptor antibodies) was a risk factor.[6] The most common type is interferon-induced thyroiditis, others include Graves' such as thyrotoxicosis and diphasic thyroiditis.[7,8] The addition

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of ribavirin to interferon α does not seem to increase the incidence of thyroid dysfunction.[9,10] Hepatitis C infection itself is associated with autoimmune diseases.[11]

Case Report

A 63-year-old female patient was referred to the endocrine clinic in May 2011 with a history of hypertension on perindropril 4 mg. She received the first cycle of interferon/ribavirin combination in 2008 for hepatitis C with no complications. Thyroid function and anti-TPO at baseline and after interferon were negative. Her past medical history revealed that in 2009, she had had high-grade ventricular arrhythmia for which she was treated with amiodarone therapy in Tunisia. After 6 months of amiodarone therapy, she developed primary hypothyroidism, and her anti-TPO antibodies remained negative. Amiodarone was stopped, and the patient was started on sotalol 80 mg daily. Since hypothyroidism persisted, she was started on levothyroxine 75 mcg. On this dose, she remained euthyroid for 4 years. During the present episode (2011), she was biochemically and clinically euthyroid on thyroxine 75 mcg daily. In October 2012, her hepatologist restarted her on interferon/ribavirin combination therapy. After 5 months on this treatment, she became clinically thyrotoxic. Therefore, thyroxine doses were gradually tapered and eventually discontinued. Anti-TPO antibodies remained negative. At this stage, she traveled elsewhere for second opinion and treatment where anti-TSH receptor antibodies which was found to be positive and a Tc-99m scan revealed a high diffuse uptake [Figure 1]. Interferon was stopped, and the patient received an ablation dose of radioiodine. After 8 weeks of arrival back home, thyroid function was revealed a high serum TSH at 100 mU/L and very low serum T_4 and T_3 diagnostic of post-radioiodine hypothyroidism. The patient started on levothyroxine 100 μg daily which was later adjusted to 125 mcg daily. She remained well till the time of this report.

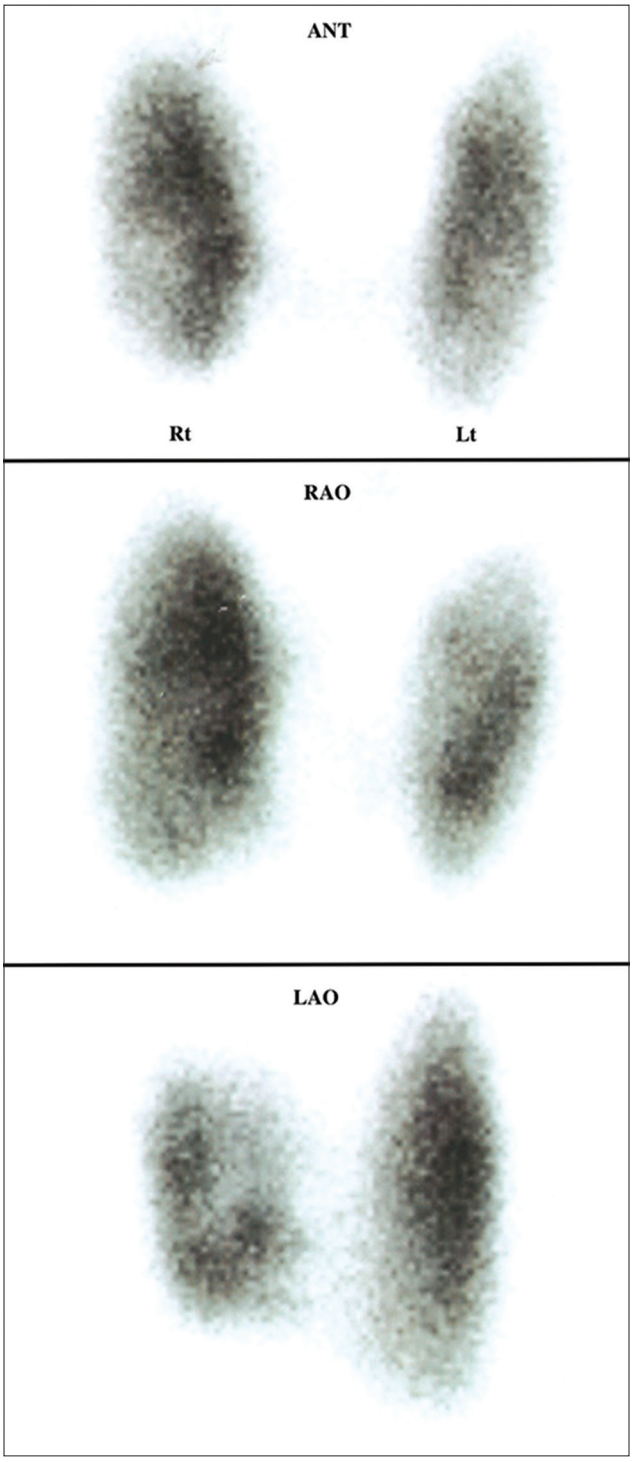

Figure 1: Tc-99m scan of the patient to illustrate the high uptake

Discussion

This case presents an example for the interaction of side effects of medications with autoimmune disease. The patient is an elderly female, so her sex and age predispose her more to an autoimmune disorder induced by drugs such as amiodarone and interferon. She developed high-grade ventricular arrhythmia a few months after finishing the first cycle of interferon therapy. It is well known that interferon therapy may induce a different type of arrhythmias during therapy but whether it can induce arrhythmia even few months after treatment had stopped this is not clear.

The use of amiodarone for the control of arrhythmia in this patient having been treated with interferon recently may have predisposed her more to thyroid dysfunction and choosing beta blocker as the first choice for this patient may be was more prudent. The patient resided in Benghazi which is a coastal city presumed to be iodine-sufficient despite the lack of formal studies to confirm this. This at variance to many other cities in the south of Libya, far from the sea to be safely presumed to be iodine-deficient. Consequently, she would theoretically be more likely to develop hypothyroidism with amiodarone treatment because the inability of the thyroid to escape from the Wolff–Chaikoff effect and less likely due to autoimmune thyroiditis because her anti-TPO antibody was negative during and after treatment with amiodarone. The present patient developed

thyroid disease after 6 months of therapy in line with the predicted course of events in amiodarone-induced thyroid dysfunction typically occurring between 6 and 12 months of treatment (2).

The development of thyrotoxicosis with evidence of high radioactive uptake and positive high titer of anti-TSH receptor antibodies may point to Graves' disease, probably being induced by interferon therapy. Most cases of Graves' disease develop in patient with preexisting anti bodies, especially anti-TPO. This patient is unique in that anti-TPO was negative before and after she developed autoimmune disease. However, there is a reported case of negative preexisting anti-TPO which turn to be positive after the development of Graves' disease.[12]

As the patient was a case of hepatitis C virus treating her with the anti-thyroid drug was not a choice so she underwent RAI therapy (with increasing dose of beta-blocker) which render here hypothyroid again. The persistently negative anti-TPO antibodies make the diagnoses of hashitoxicosis very unlikely. Furthermore, the high and diffuse radioactive Tc-99m uptake with positive high titer of the anti-TSH receptor antibodies makes thyroiditis unlikely. This case lends support to the notion that follow up of thyroid function in every patient treated with either amiodarone or interferon is important. In addition, when a patient develops thyroid dysfunction the careful evaluation and determination of the specific underlying pathology and the exact type should lead to a rational management.

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Author's contribution

Single author.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

None required for non-identifiable single case reports. Patient consented for case report on anonymous basis.

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