Contrast Induced Thyrotoxicosis in a Patient with New onset Atrial Fibrillation: A Case Report and Review

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Abstract

The development of thyrotoxicosis following the administration of iodinated contrast is a rare occurrence. The effect, referred to as the Jod-Basedow effect, is often observed in patients with underlying thyroid disease who develop thyrotoxicosis subsequent to the exposure of exogenous iodide. An example of an iatrogenic cause for this event may be seen when a large iodide load is given intravenously for studies or procedures. Thyrotoxicosis can also lead to cardiac arrhythmias including atrial fibrillation. This is a case presentation of a 74 year old female who developed thyrotoxicosis as well as new onset atrial fibrillation approximately one week after receiving iodinated contrast dye for a diagnostic CT of the abdomen. We further review the prior published literature in regard to atrial fibrillation and thyrotoxicosis.

Introduction

Case Presentation

A 74-year-old Caucasian female, with no prior history of thyroid disease, presented to our facility for intractable abdominal pain and diarrhea. She had been diagnosed with diverticulitis by an outside hospital approximately one week prior to her presentation to our facility. She had undergone a diagnostic contrast CT of the abdomen and pelvis and was treated for one day with intravenous antibiotics before being discharged on a course of oral ciprofloxacin and metronidazole. She was unable to complete her prescribed regimen due to intolerance of the medications and presented to our hospital with persistent symptoms and failure of outpatient therapy. Her past medical history was limited to depression and hypertension. The only medication she had been taking was duloxetine 60mg daily.She had no known drug allergies and no known family history of thyroid disease. She also denied tobacco, alcohol, and illicit substance use.

Findings on Admission

Her vital signs on presentation were as follows: temperature 97.2F, heart rate 80 and regular, blood pressure 128/85, respiratory rate 22, pulse oximetry 95% on room air, weight 220lbs, and BMI 35.7. The patient was awake, alert, and oriented. She appeared dehydrated with dry mucous membranes. Cardiac auscultation revealed a normal heart rate without appreciable murmurs or audible extra heart sounds. Her abdomen was diffusely tender to palpation without guarding or rebound and bowel sounds were active. Laboratory data showed a white blood cell count of 13.1, otherwise BMP and CBC were within normal limits. Liver enzymes, amylase, lipase, albumin, total protein, and urinalysis were also within normal limits. A CT withoutcontrast of the abdomen and pelvis showed sigmoid diverticulitis, without abscess, perforation, or obstruction. Because of failed treatment as an outpatient, she was admitted to the internal medicine service for IV ciprofloxacin and metronidazole.

Subsequent Findings

On her second day of admission she was found to be in atrial fibrillation with rapid ventricular response, which responded to IV beta-blockade. A workup for the etiology for her new onset atrial fibrillation included the following:

Troponin I: Three serial enzymes were negative

Echocardiogram: Mild left ventricular hypertrophy, preserved internal dimension and overall normal systolic function 60-65%, bi-atrial enlargement, left greater than right, thickening of the mitral leaflet with preserved excursion and moderate mitral annular calcification, mild mitral regurgitation, mildtricuspid regurgitation with right sided pressures estimated to be mildly to moderately elevated, trace aortic and pulmonic insufficiency

Thyroid stimulating hormone: 0.002 mIU/L (reference range 0.465-4.68)

Free T4: 5.01 ng/dl (reference range 0.78-2.19)

Disclosures:
None.

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Free T3: 13.8 pg/ml (reference range 2.3-4.2)
Thyroperoxidase antibody: Negative
Thyroglobulin antibody: Less than 20 IU/ml (reference range 0-40)
Thyroid ultrasound: Diffusely heterogeneous, hypoechoic, and hyperemic gland with a 1.3cm in greatest dimension nodule within the isthmus

Treatment and Short-Term Outcome

The patient was diagnosed with thyrotoxicosis secondary to contrast administration. Because of her thyrotoxicosis, she developed atrial fibrillation and was treated with propylthiouracil 100mg tid, propranolol 20mg tid, and digoxin 0.125mg daily. She was placed on anticoagulation with warfarin for a target INR of 2-3 given her CHADS$_2$ score of two. Her hospital course was marked by frequent reversions between sinus bradycardia in the range of 50-60bpm, and atrial fibrillation with rapid ventricular rate in the range of 110-150bpm.

Her medications were titrated and she remained asymptomatic with respect to her cardiac condition and without other stigmata of hyperthyroidism. She completed antibiotics for diverticulitis as an inpatient and was discharged in stable condition after having demonstrated several days of heart rate control. She was additionally instructed to follow up as an outpatient with a cardiologist and an endocrinologist for continued monitoring and management.

Approximately one month later when seen by her outpatient primary care physician, she had remained in rate controlled atrial fibrillation and was asymptomatic in regard to her thyrotoxicosis.

Discussion Risk Factors for Atrial Fibrillation in Hyperthyroid Patients

Jod-Basedow Phenomenon

There are numerous extrathyroidal and intrathyroidal adverse effects related to iodide exposure. The Jod-Basedow phenomenon describes an intrathyroidal induced thyrotoxic state precipitated by exogenous iodide. The impact of iodine on thyroid function is well documented. The extensive review by Fradkin and Wolff reported on the increased incidence of thyrotoxicosis, toxic nodular goiter, thyroidectomies, and deaths from hyperthyroidism in the United States shortly after the introduction of iodized salts in the 1920's.[1] Similarly, they addressed the increased incidence of hyperthyroidism in Holland, Tasmania, Serbia, and Austria in the mid-1900s following the widespread introduction of iodide into consumer products. While the development of hyperthyroidism secondary to exogenous iodide has been well documented in iodide deficient regions, thyroid dysfunction has also been reported in iodide sufficient areas among patients with non-toxic goiters and in patients with otherwise normal thyroid glands.[2,3] With the advent of iodide based contrast agents, there have been several other reports of contrast-induced hyperthyroidism.[4-9] Contrast induced thyrotoxicosis could potentially occur in individuals who undergo pulmonary vein mapping for catheter ablation in patients who have atrial fibrillation, however there have been no reported cases to date. Patients on amiodarone therapy would be at further increased risk in this clinical scenario.

Risk Factors for Atrial Fibrillation in Hyperthyroid Patients

There is a known relationship between atrial fibrillation and hyperthyroidism; however, sinus tachycardia is the most common cardiac manifestation of hyperthyroidism. Atrial fibrillation may present in 5-15% of hyperthyroid patients.[10] An observational study of 2007 patients >60 years old conducted over a ten year follow-up showed that low baseline serum thyrotropin levels were a significant risk factor for atrial fibrillation (AF).[11] Patients with thyrotropin concentrations <0.1mU/L had a near three fold increased risk of developing AF when compared to individuals with normal thyrotropin concentrations (0.4-5mU/L; RR 3.1, CI 1.7-5.5,P<0.001). Furthermore, there was a trend towards increased risk of AF even in those with slightly low thyrotropin levels (TSH: 0.1-0.4mU/L; relative risk of 1.6, P=0.05). A series of 23,638 patients revealed a >5 fold greater prevalence of AF in patients with subnormal TSH levels when compared euthyrotropic subjects (13.3% vs. 2.3% respectively).[12] They did not discover a significant difference in the prevalence of AF between overt and subclinical hyperthyroid individuals (13.8% and 12.7%). The utility of screening for thyroid disease in patients with new onset atrial fibrillation was addressed in a study of 726 patients with recent onset AF (<3months).[13] Approximately 5% of their patients were found to have subnormal TSH levels, with only 1% of their cohort diagnosed with 'clinical hyperthyroidism'. The results lead the authors to conclude that routine TSH screening would generally be of low yield in patients with new onset AF. However, they pointed out that there might be greater utility in screening patients who have symptoms specific to thyroid disease, present with palpitations without documented heart disease, or without initial symptoms of AF. It is difficult to say how their recommendations may have differed had AF been considered for their diagnosis of 'clinical hyperthyroidism'. A study looking at patients presenting with atrial fibrillation with no obvious cardiovascular cause, found that 13% had evidence of thyrotoxicosis.[14] However, not all of their patients had elevated serum thyroid hormone levels and none of them showed signs of hyperthyroidism. Among these patients, treatment with either I-131 uptake or carbimazole resulted in 80% reverting to stable sinus rhythm.

Another study attempted to identify patient characteristics that may increase the risk of developing AF in association with hyperthyroidism. This study included 40,628 patients between the ages of 20 and 89 whose records were obtained from the Danish National Registry between 1977 and 1999.[15] They found 3362 (8.3%) had been newly diagnosed with AF/flutter +/- 30 days of their diagnosis of hyperthyroidism. Major risk factors for AF were male sex (OR, 1.8; 95% CI, 1.6-1.9), age (OR, 1.7; 95% CI, 1.7-1.8) per 10-year increment starting at 20, ischemic heart disease (OR, 1.8; 95% CI, 1.6-2.0), congestive heart failure (OR, 3.9; 95% CI,3.5-4.4), and heart valve disease (OR, 2.6; 95% CI, 1.9-3.4).

Proposed Mechanisms of Hyperthyroidism Inducing Atrial Fibrillation

The mechanism by which hyperthyroidism may cause AF is still an active area of research. The biological effects of thyroid hormone appear to be principally mediated by combined nuclear and extranuclear activities of tri-iodothyronin.[16] Tri-iodothyronin mediated nuclear activities include effects on components of the cardiac contractile machinery, proteins involved in the regulation of intracellular calcium, as well as cell surface receptor molecules.[16-18] Extranuclear effects of T3 may be related to alterations in the performance characteristics of ion channels in cardiac myocytes.[10]

A study that investigated the effects of thyroid hormone on the electrophysiological characteristics of single rabbit pulmonary vein

cardiomyocytes found that incubation with L-tri-iodothyronin shortened the action potential duration of pulmonary vein and atrial cardiomyocytes.[19] They postulated that these effects could facilitate the genesis of re-entrant circuits through shortening of the refractory period, which may account for the high incidence of atrial tachyarrhythmias in hyperthyroid patients. These findings are supported by another study that showed that patients with hyperthyroidism and paroxysmal AF have significantly shorteratrial effective refractory periods (ERP) than controls and those with lone AF.[20] They hypothesized that the shortening of ERP in the context of the conduction delays that are seen more often among hyperthyroid subjects could increase the propensity of AF. It has also been found that hyperthyroid subjects with normal hearts have increased supraventricular ectopy, and that these arrhythmogenic foci may represent an important link between hyperthyroidism and AF.[21]

Prognosis and Mortality

There is significant cardiovascular and cerebrovascular related mortality associated atrial fibrillation in hyperthyroid subjects. The finding of a single low serum thyrotropin level in individuals over the age of 60 is associated with increased mortality from all causes, andparticularly from cardiovascular and cerebrovascular diseases.[22] Analysis of 551 AF patients within the first year of diagnosis of thyrotoxicosis with AF identified only age as a significant risk factor for cerebrovascular events.[23] Atrial fibrillation and sex were not independent predictors of cerebrovascular events; however a trend towards more events was seen in the AF class. The impact of hyperthyroidism on the prognosis of AF was also investigated in a retrospective study of 162 patients for a mean follow up of 34 months.[24] Thyrotoxicosis was controlled with either radioactive iodine combined with anti-thyroid drugs in 143 patients (87 percent), with anti-thyroid drugs alone in 15 patients (9 percent), and by thyroidectomy after initiation of anti-thyroid drugs in five patients (3 percent). Treatment of hyperthyroidism was associated with reversion of AF. In their study there were 101 patients who had spontaneous reversions to sinus rhythm and 62 patients who had persistent AF. Among those who did revert to sinus rhythm following correction of thyrotoxicosis, 20% reverted despite elevated T3 and T4 but at levels markedly decreased from baseline, and approximately 75% reverted to sinus rhythm within 3 weeks of becoming euthyroid. If AF persisted beyond 15 weeks after establishing a euthyroid state there were no further reversions. The longest duration of AF prior to achieving a euthyroid state was 13 months. Therefore, it appeared that patients who were hyperthyroid and in AF for greater than 13 months were unlikely to revert. Furthermore, had AF persisted beyond 15 weeks of being euthyroid, it was also unlikely to see spontaneous reversion. Among those with persistent AF (i.e. AF persisting beyond a year of being euthyroid) the shortest time before achieving a euthyroid state was 8 months, and the longest was 33 months. Taken together, an earlier return to a euthyroid state may confer a benefit in promoting spontaneous reversion to sinus rhythm; however, spontaneous reversion may not be anticipated if the total duration of AFboth before and after stabilization of thyroid disease is prolonged.

Conclusions:

This case report and review demonstrates the importance of considering the potential repercussion of the widespread use of IV contrast agents, particularly in the elderly population. As a population, they are at higher risk for developing thyrotoxicosis after the administration of iodinated contrast. This would also include individuals who undergo pulmonary vein mapping for catheter ablation who have atrial fibrillation, especially for patients who are taking amiodarone. Thyrotoxicosis can precipitate other serious conditions including atrial fibrillation which could potentially lead to cerebrovascular accidents. Careful selection of patients for IV contrast should include screening for symptoms of underlying thyroid dysfunction and obtaining screening laboratory data in high risk patients who are scheduled for non-emergent contrast scans.

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