CASE REPORT

The dangers of iodine-based contrasts in an elderly patient with thyroid disease

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SUMMARY

Iodine-based contrast agents are widely used in angiographic and other radiological procedures. Clinicians are familiar with many of the potential adverse events from contrast agents including allergic reactions and contrast-induced nephropathy. This case describes a lesser known adverse event: 'contrast-induced thyrotoxicosis' and its implications on the presentation and management of a patient with severe coronary artery disease. The management of this case was difficult and required a long inpatient admission with use of prednisolone, propylthiouracil and planned treatment with radioiodine to control the thyrotoxicosis, as well as the use of several rate-limiting agents and antianginal medications to control atrial fibrillation and prevent further episodes of angina.

BACKGROUND

In the UK, 87 676 coronary angioplasties were undertaken in 2010,¹ with an estimated 2.5 times as many coronary angiograms.² Iodine loads in the form of oral supplements,³ skin preparations,⁴ iodine-containing medications such as amiodarone⁵ and intravenous contrast agents⁶ have a well-documented potential to trigger thyrotoxicosis in susceptible patient groups, such as the elderly and those with pre-existing thyroid disease.

Thyroid hormones have widespread effects on the cardiovascular system. Large-scale reviews have identified that even subtle changes in thyroid function can have a significant impact on long-term cardiovascular outcomes. One analysis of 52 674 patients demonstrated that individuals with endogenous subclinical hyperthyroidism had an increased risk of coronary heart disease-related mortality (HR 1.29; 95% CI 1.02 to 1.65) and incident atrial fibrillation (AF; HR 1.68; 95% CI 1.16 to 2.43).⁷ In patients with pre-existing coronary artery disease there is significant risk from a hyperthyroid state. A thyroid hormone-induced increase in the body's metabolic rate coupled with an enhanced risk of arrhythmia and direct effects on myocardial and vascular smooth muscle tissue have the compound effect of increasing myocardial oxygen demand while reducing oxygen supply^{8 9} with alarming consequences on patient symptoms as illustrated in the following case.

CASE PRESENTATION

A 76-year-old Caucasian man presented to our chest pain assessment unit with a history of unstable angina worsening over the preceding 3–4 weeks, culminating in a 30 min episode of constrictive

chest pain shortly prior to presentation. He had an extensive cardiac history with a coronary artery bypass procedure in 1994, subsequent percutaneous coronary intervention to a vein graft in 2008 and impaired left ventricular function on recent echocardiogram. A repeat angiogram had been performed 2 months earlier to investigate gradually worsening angina, despite ongoing medical therapy. This had demonstrated severe three vessel coronary artery disease with new 90% stenosis to the distal right coronary artery unsuitable for further coronary revascularisation procedures. His symptoms had subsequently been managed with minimal change to symptoms through increasing his antiangina medications. At the time of the latest episode of chest pain he was taking 100 mg once daily of isosorbide mononitrate (modified release) and 5 mg once daily of amlodipine to prevent attacks of angina.

The patient's medical history was significant in that he had been under the long-term care of the endocrine team for management of a large toxic multinodular goitre. This was of sufficient size to produce dysphagia and radiological evidence of a 20% tracheal stenosis. The management of this goitre had been complicated by the development of agranulocytosis, during treatment with carbimazole. Thyroid surgery had been considered but his cardiovascular comorbidity had precluded the use of a general anaesthetic. Radioiodine treatment had also been considered but the patient had been concerned by the potential risk of airway occlusion secondary to swelling of the goitre following administration of radioiodine. His thyroid function tests prior to this admission had been only mildly thyrotoxic (free thyroxine (fT4) level of 23.4 pmol/L and thyroid-stimulating hormone (TSH) level 0.001 mIU/L) and hence he was currently being managed off treatment, with regular monitoring of his thyroid status.

At the time of this latest admission the patient reported acute onset palpitations in addition to chest pain. Twelve lead ECG confirmed a new diagnosis of AF with a ventricular response rate of 130 bpm. Fortunately serial troponin assessments ruled out NSTEMI. However, his biochemistry panel demonstrated a thyrotoxicosis with an undetectable TSH and an fT4 level of 43.2 pmol/L, almost double that of 2 months previously.

This steep increase in the patient's thyroid function was attributed to the use of iodine-containing contrast agents during his recent angiogram. His history of a probable myelodysplastic syndrome (agranulocytosis) meant that management of thyrotoxicosis with commonly used antithyroid therapies

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was difficult. Initial management with 40 mg of prednisolone therapy alone failed to control symptoms and after careful discussion with the haematologists low-dose propylthiouracil was added. He remained on prednisolone and propylthiouracil to control his hyperthyroidism and a combination of bisoprolol, nitrates and ranolazine for management of angina. He remained in AF throughout his admission, but continued to be rate controlled and was anticoagulated with warfarin to manage his stroke risk. The patient is currently awaiting radioiodine therapy.

DISCUSSION

Outside of the endocrine team, contrast-induced thyrotoxicosis is often overlooked in clinical settings. Yet, particularly within the context of cardiology, excess thyroid hormones can have significant implications for both myocardial tissue and systemic vasculature. In cases such as ours where myocardial perfusion is at a premium the consequences can be severe.

Iodine-induced thyrotoxicosis

Iodine-induced thyrotoxicosis has been recognised since 1821.³ Early studies in the 1920s suggested that as many as 12% of new-onset hyperthyroid cases could be attributed to the administration of exogenous iodine for treatment of endemic goitre.¹⁰ Case study evidence has identified that this can be triggered from a wide range of iodine loads, even from systemic absorption of topical iodine-based agents used in wound cleaning.⁴ Although the typical iodine load following use of intravenous contrast varies depending on the procedure and the exact contrast agent, a typical dose is ~13 500 µg of free I⁻ (iodide) and 15–60 g of bound iodine.^{11 12} This represents an iodine load potentially several hundred thousand times the recommended daily intake¹² of 150 µg.¹³

Several studies have looked at the effects of iodine-based contrasts on thyroid function. The impact is highly dependent on the presence or absence of underlying thyroid disease. In 1999 Hintze *et al* looked at the risks of developing thyrotoxicosis following coronary angiography in a group of patients with normal baseline thyroid function and no history of previous thyroid disease. By 12 weeks postadministration of iodine contrast agents only 2 of 788 patients had developed hyperthyroidism.¹⁴ A smaller study of only 28 patients looked at an elderly population in a geriatric hospital over a 20-month period, it found that 25% of new onset hyperthyroidism in patients could be attributed to the recent administration of iodine-containing contrast media. Four of these seven patients were scanned and identified as having a multinodular goitre.⁶

Thyroid hormone production is normally regulated by the negative feedback loop of the hypothalamic pituitary thyroid axis. An increased iodine load leads to reduced iodine uptake, thyroid hormone production and release. This autoregulatory process is called the Wolff-Chaikoff effect. In some individuals it can result in a self-limiting hypothyroidism which corrects with normalisation of iodine levels.¹⁵ In individuals with autonomous thyroid function the auto-regulatory process is impaired and the response to an iodine load is different. The increased uptake of iodine into the thyroid gland stimulates increased thyroid hormone synthesis and potential systemic thyrotoxicosis. This is known as the Jod-Basedow phenomenon.¹⁶ It is most commonly seen within the context of a toxic multinodular goitre or adenoma, although it can occur in patients with Grave's disease or who have a relative iodine deficiency.^{11 17} In the elderly population an iodine-induced thyrotoxicosis may be the first presentation of a previously silent multinodular goitre, a condition more commonly found in the elderly.⁶

Cardiovascular impact of hyperthyroidism

Thyroid hormones have complex interactions with the cardiovascular system. Within the context of ischaemic heart disease, angina is likely precipitated through a combination of mechanisms. Cardiac preload is increased both directly through stimulation of erythropoietin production and hence an increase in red cell mass and indirectly by thyroid hormone-mediated vasodilation of vascular smooth muscle. The latter results in reduced peripheral vascular resistance, consequent renal hypoperfusion and ultimately renal angiotensin system-mediated sodium and water retention. Thyroid hormones also have direct chronotropic and inotropic effects on the heart, via accelerated atrial pacemaker activity and upregulation of genes that enhance cardiac contractility respectively. All of these factors combine to enhance cardiac output such that in hyperthyroidism the cardiac output maybe 50–300% greater than in the euthyroid state.^{8 9} In addition the anatomy of the coronary vasculature means that the coronary arteries are effectively occluded during ventricular systole, hence myocardial perfusion occurs during diastole. The time spent in diastole is inversely proportional to heart rate; hyperthyroidism-induced tachycardia results in a significant reduction in coronary artery filling time causing reduced myocardial perfusion. The combination of increased myocardial oxygen demand with reduced supply results in myocardial ischaemia which in our patient produced the clinical picture of worsening angina.

AF is also commonly associated with hyperthyroidism, the prevalence of this varies depending on study population. A large study of over 40 628 patients with hyperthyroid in Denmark found 8.3% had developed AF.¹⁸ The mechanism underlying the link between AF and hyperthyroidism is unclear although likely reflects a number of both direct effects of thyroid hormone on myocardial tissue and indirect effects on the cardiovascular system as a whole.⁹ Our patient was admitted with a first episode of AF. Atrial activity is estimated to contribute to 20–25% of cardiac output in the normal heart. In a patient with previous myocardial infarctions and known poorly functioning ventricular myocardium this is likely an underestimate. Loss of the atrial kick results in a reduction in cardiac output, reducing coronary artery perfusion and placing increased demand on ventricular myocardium to match the systemic requirements of a thyrotoxic, high output state. This most likely further contributed to myocardial ischaemia.

Suggested management of contrast-induced thyrotoxicosis

The vast majority of patients who develop contrast-induced hyperthyroidism are completely asymptomatic. The usual scenario is an abnormal thyroid function test (TFT) result in an otherwise well patient, who has had a procedure requiring an iodine-based contrast within the past 1–3 months. Patients may have normal TFTs pre-contrast and still have a transient thyrotoxicosis. High-risk individuals that is, the elderly with known AF or ischaemic heart disease should have a full set of TFTs checked as part of their pre-assessment and if this suggests thyroid autonomy then the patient should be referred to an endocrinologist for further assessment and consideration of antithyroid medication prior to receiving radio-contrast. Potential strategies for these patients would be to start carbimazole therapy several weeks in advance of an elective angiogram. If the high-risk patient was to have an emergency angiogram then starting steroid therapy with antithyroid medication at the time of angiography would be appropriate. These prophylactic measures may mitigate the extent to which a patient becomes thyrotoxic.

Learning points

- ▶ Iodine-based contrast agents are widely used in clinical practice and the clinician needs to be aware of the potential complication of thyroid-induced thyrotoxicosis occurring 1–3 months postadministration.
- ▶ Iodine-induced thyrotoxicosis is most common in individuals with thyroid autonomy, for example multinodular goitre or toxic adenoma, however, the risk is increased in other hyperthyroid conditions and in patients from iodine-deficient regions.
- ▶ The clinician needs to be particularly aware of the potential for iodine-based preparations to unmask a previously clinically silent multinodular goitre in the elderly through generation of a thyrotoxic state.
- ▶ Thyroid hormones have multiple effects on the cardiovascular system. A hyperthyroid state increases cardiac output indirectly via an increase in preload, as well as directly via positive inotropic and chronotropic effects on myocardial tissue. In patients with coronary artery disease this added stress can result in cardiac ischaemia and infarction.
- ▶ In patients with pre-existing, severe coronary heart disease a thyrotoxic state can put significant strain on a cardiovascular system with minimal scope for adaptation and coping with a drive for increased cardiac workload. This can result in severe complications including heart failure, arrhythmias and acute coronary syndromes. Ideally the potential for contrast-induced thyrotoxicosis should be mitigated by early prophylaxis with corticosteroids and antithyroid hormones, or in cases such as our patient where there is difficulty with using antithyroid agents, preferably with definitive treatment in the form of radioiodine therapy or surgery prior to angiography where possible.

Contributors All authors were involved in the conception of the case study, DL wrote and researched the study while PC and SJ edited and reviewed the work.

Competing interests None.

Patient consent Obtained.

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