Unusual presentation of more common disease/injury

Development of Graves' disease after long-standing hypothyroidism on treatment, with acute toxicity to thionamides and lithium

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Summary

Thyroid hyperfunction in a patient with long-standing hypothyroidism is uncommon. Here, we describe and discuss the unusual scenario of development of severe skin rash to carbimazole, with subsequent acute toxicity to lithium in clinically indicated doses, in a patient who manifested hyperthyroidism after being on treatment for hypothyroidism for 7 years.

BACKGROUND

Autoimmune thyroid disease is among the most common autoimmune diseases. It is a complex disease with genetic and environmental factors contributing to its aetiology. The hallmark of disease is infiltration of the thyroid gland with thyroid reactive lymphocytes. The clinical manifestation is variable, hypothyroidism (Hashimoto's thyroiditis) and hyperthyroidism (Graves' diseases) being the two ends of the spectrum. About 15–20% of patients with Graves' hyperthyroidism develop hypothyroidism 10–15 years after discontinuation of medical therapy or subtotal thyroidectomy. There are anecdotal reports of development of hyperthyroidism in patients who manifest with hypothyroidism initially.^{1–6} Here we describe a patient with history of treatment for hypothyroidism for 7 years before manifesting persistent state of hyperthyroidism. We also describe and discuss the acute toxicity in the same patient to thionamides and subsequently lithium, who finally was rendered euthyroid by radioiodine ablation.

CASE PRESENTATION

Ms M, 66 years was diagnosed to have hypothyroidism in 2003 during evaluation for easy fatigability. Her plasma thyroid stimulating hormone (TSH) was 13.18 mIU/l (normal 0.55–4.78 mIU/l), Anti-thyroid peroxidase (TPO) antibody was 1920.6 U/ml (normal <60 U/ml). T₄ or FT₄ report was not available from records of patient. She was advised to start thyroxine 75 µg daily. The TSH was 10.77 mIU/l 6 months after starting thyroxine. The dose of thyroxine was increased to 100 µg daily. During the next 7 years, she continued the same dose of medication as she was asymptomatic and periodic thyroid function tests were within normal limits. However in December 2010 she experienced palpitations, easy fatigability and heat intolerance. She did not notice goitre or any eye symptoms. Thyroxine dose was reduced and stopped subsequently in view of suppressed TSH. Three months later, she was initiated on carbimazole (10 mg three time a

day). Her lab data at that time were FT₄ 30.9 pmol/l (normal 10.3–25.8 pmol/l), FT₃ 10.4 pmol/l (normal 3.55–6.48 pmol/l), TSH 0.003 mIU/l and anti-TPO antibody 3156 U/ml. She developed erythema multiforme 7 days after starting carbimazole. Carbimazole was stopped, and after resolution of skin lesions (2 months later) she was initiated on propylthiouracil 25 mg once in a day and was referred to our hospital for radioactive iodine ablation in August 2011.

At the time of presentation, she had complaints of weight loss (16 kg during the previous 8 months), excess sweating, palpitations and complaint of occasional redness in right eye. There was no diminution of vision, feeling of grittiness in eyes or history of diplopia. She had difficulty in getting up from squatting position and climbing upstairs. On examination, her blood pressure of 160/60 mm Hg (on amlodipine 5 mg and telmisartan 40 mg daily), pulse rate was 64/min, good volume and regular, height and weight was 151 cm and 49 kg, respectively, with body mass index (BMI) of 21.5 kg/m². She was not on any β-blocker at the time of presentation. She had moist and warm hands and mild thyroid enlargement. There were no tremors, signs of ophthalmopathy, dermatopathy or acropachy. Apart from muscle power of 4/5 at proximal muscles of the lower limb, systemic examination was essentially normal.

Her medical history revealed that she had syncopal attacks 20 years back, which decreased symptomatically on cinnarizine. She underwent CT as part of an evaluation, which was normal as per patient. The records of same were not available. In 2006, she underwent a detailed evaluation for her symptoms. MRI revealed multiple small chronic bilateral infarcts seen as hypodense non-enhancing areas in the left parietal paraventricular parenchyma, left frontal parenchyma, bilateral thalami and the right parafalcine occipital parenchyma. There was no history suggestive of transient ischaemic attacks or paresis. Carotid Doppler was suggestive of atherosclerotic changes in common carotid arteries and their branches on

Figure 1 Holter strip showing sinus bradycardia with intermittent sinus arrest and junctional escape rhythm.

both sides without any evidence of any significant stenosis. Holter study done outside in 2006 was reported as normal. She was taking clonazepam 0.5 mg/day, rosuvastatin 10 mg/day, cinnarizine 25 mg three times a day for giddiness, telmisartan 40 mg and amlodipine 5 mg combination (1 tab/day) and pantoprazole 40 mg/day.

INVESTIGATIONS

Her T_4 at time of admission was 182.2 nmol/l (normal 66.1–182.7 nmol/l), free T_4 was 31.8 pmol/l (normal 12–21.9 pmol/l) and TSH was <0.005 mIU/l. Her renal and liver function tests were normal. Considering her age, recent weight loss and low BMI, she was hospitalised for controlling the thyrotoxic state before ablation.

TREATMENT

She was initiated on lithium 600 mg in two divided doses for initial 5 days and subsequently increased to 900 mg in three divided doses. She complained of giddiness and had tremors after increasing the dose of lithium (lithium levels done on day 7 was 1.08 mmol/l; normal 0.6–1.2 mmol/l). Lithium was reduced to 600 mg/day on day 9, in view of her symptoms. On day 11 of lithium therapy, she developed bradycardia (ECG was suggestive of sick sinus syndrome, sinus arrest with junctional escape rhythm). About 24-h holter recording was again consistent with sinus node dysfunction with sinus bradycardia, intermittent sinus arrest with ectopic atrial/junctional escape rhythm (figure 1). Her pulse rate before initiation of treatment was 64/min and regular. She had fine hand tremors, no focal neurological deficit or gait disturbances. Plasma lithium was 1.54 mmol/l at the time of developing bradycardia.

Cardiology opinion was taken, lithium was stopped, after which the patient improved. Her symptoms got alleviated and pulse rate became regular with sinus rhythm with rate recorded between 52 and 60/min. Cardiology clearance was obtained and the patient was planned for radioactive iodine ablation. She underwent radioactive iodine uptake study for dose estimation which surprisingly revealed low uptake (2 h uptake 1.6% and 24 h uptake 9.3%), T_4 levels were 134.8 nmol/l at this time. In view of low uptake (suggestive of thyroiditis like picture) ablation was withheld, and she was discharged with a plan to repeat radioactive-iodine uptake after 1 month. Repeat holter done 6 weeks after the stoppage of lithium revealed sinus rhythm with heart rate varying between 50 and 100 beats/min and occasional supraventricular ectopics. There was no evidence of sinus arrest (figure 2). Her T_4 level on repeat admission was 211.2 nmol/l and radioactive iodine uptake was 4.6% at 2 h and 25.2% at 24 h. In view of previous toxicity to thionamides and lithium, patient underwent radioactive iodine ablation with 5 millicurie of radioactive iodine under close observation in the hyperthyroidism state. There was no postablation complication.

OUTCOME AND FOLLOW-UP

She was discharged after 1 week in the euthyroid state, with a plan to follow-up in OPD. Post ablation T_4 and fT_4 levels were within the normal limit (134.8 nmol/l and 19.57 pmol/l) at the time of discharge. T_4 and TSH at last follow-up at 10 weeks was 97.2 nmol/l (58.3–162 nmol/l) and 0.3 mIU/l (0.17–4 mIU/l), respectively. Her pulse rate was 60/min and regular.

Figure 2 Holter strip showing sinus rhythm with a heart rate of 55/min.

DISCUSSION

Graves' disease after long-standing hypothyroidism is rare.^{1–6} The exact pathogenesis of this relatively rare phenomenon of hyperthyroidism following hypothyroidism has not been elucidated. Takasu *et al*¹ described seven cases of Graves' disease following hypothyroidism. On the basis of the clinical course he divided them into three groups, (1) transient hyperthyroidism due to Graves' disease, (2) persistent hyperthyroidism due to Graves' disease and (3) persistent hypothyroidism with positive thyroid stimulating antibody (TSAb). They suggested that the changes in thyroid function and clinical course could be due to three factors: (a) TSAb; (b) TSH stimulation blocking antibody (TSBAb) and (c) the responsiveness of the thyroid gland to TSAb.¹ TSAb and TSBAb are TSH receptor antibodies which block binding of TSH to thyroid cells. TSBAb causes hypothyroidism while TSAb causes thyroid hyperplasia and hyperfunction. A potential trigger for autoimmunity is thyroid gland damage. There are reports of hyperthyroidism due to Graves' disease following painless lymphocytic thyroiditis, painful Hashimoto's thyroiditis, subacute thyroiditis, etc. Most of these cases have occurred in 1–2 years although it has been reported after 7 years also.⁷

The present case had been on treatment for 7 years for hypothyroidism prior to diagnosis of hyperthyroidism. Thyroid receptor antibodies were not tested in this case. TPO antibody was positive. Additional problems in this patient included adverse effects with carbimazole and lithium.

Thionamides (carbimazole, methimazole and propylthiouracil) are the primary treatment modality for the first episode of Graves' disease and they also used prior to radioiodine therapy and surgery to reduce the risk of thyroid storm. Rarely serious side effects have been reported with these drugs. Cross-reactivity between carbimazole and propylthiouracil has been reported to be upto 50%.⁵ Therefore, replacing carbimazole with propylthiouracil or vice versa in patients developing serious side effects poses a risk. In such patients, definitive treatment such as surgery or radioiodine is often indicated. But, before these can be offered, it is safer to ameliorate the degree of thyrotoxicosis medically to reduce the risk of thyrotoxic crisis that may be precipitated by the stress of surgery or postradioiodine thyroiditis. The choice of drugs in patients intolerant to thionamides is nonetheless limited. Iodide compounds, although effective, interfere with subsequent uptake of radioiodine. Therefore, it is not used before radioactive iodine ablation.

Lithium is most commonly used as a treatment for bipolar disorder. The common clinical side effects of the drug are goitre in up to 40% and hypothyroidism in about 20%.⁸ The most important clinically relevant action is the inhibition of thyroid hormone release.⁸ The mechanism of inhibition of hormone release involves an alteration in tubulin polymerisation as well as inhibition of action of TSH on cyclicAMP. As lithium inhibits thyroid hormone release from the thyroid gland, it can be used as an adjunct therapy in the management of severe hyperthyroidism.⁸ It also increases thyroidal radioiodine retention and is effective in reducing administered activity in hyperthyroidism as well as reducing the increase in thyroid hormone concentrations observed after radioiodine treatment.

Ng *et al*⁹ used lithium therapy in doses ranging from 500 to 1500 mg/day for preparing patients for definitive therapy in patients in whom thionamides were contraindicated due to adverse reactions or failure of treatment. One of their patients developed lithium toxicity (neurological) at a dose of 500–750 mg/day with plasma lithium reaching 3.4 mmol/l.

Lithium overdose has been associated with a wide range of cardiovascular complications including cardiac arrhythmias and interstitial myocarditis. Asymptomatic electrocardiogram changes are the most common (10–30%) including T wave changes such as flattening, isoelectricity or inversion.¹⁰ This is thought to be due to intracellular substitution of potassium by lithium. Infrequently, clinically evident cardiac manifestations occur including sinus node dysfunction.⁶ Rarely the lithium cardiotoxicity can manifest as prolonged QT interval, atrial flutter, atrioventricular block, right bundle branch block, left anterior hemiblock, ventricular tachycardia and ventricular fibrillation.¹¹ The lithium enters the cardiac cell during depolarisation, but is not removed as effectively as sodium ions.¹² It decreases the spontaneous rate of depolarisation of the sinus node and decreases the conduction velocity in the atrioventricular and intraventricular conduction system. These electrophysiological effects of lithium might account for lithium-induced sinus nodal dysfunction in man.¹³ Other postulated mechanisms are reduced response to adrenergic stimulation, interference with calcium ion influx in pacing cells of sinus node and sinus node dysfunction due to hypothyroidism induced by lithium in some cases.^{14 15}

Our patient had several unusual events like development of persistent hyperthyroidism due to Graves' disease after 7 years of hypothyroidism, serious adverse event with carbimazole and acute cardiotoxicity and neurotoxicity with lithium.

Learning points

- Development of persistent hyperthyroidism due to Graves' disease, although rare, can occur in course of hypothyroidism.
- As lithium inhibits thyroid hormone release from the thyroid gland, it can be used as an adjunct therapy in the management of severe hyperthyroidism.
- Lithium overdose has been associated with a wide range of cardiovascular complication including cardiac arrhythmias and interstitial myocarditis. Lithium toxicity can occur at clinically indicated doses and with shorter duration of therapy.
- Radioactive iodine ablation is a preferable option in elderly patients, who are intolerant to medical therapy.

Competing interests None.

Patient consent Obtained.

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