

# Recurrent Graves' Disease after Successful Radioiodine Therapy Induced Hypothyroidism: A Rare Occurrence

<sup>1</sup>Bhargav PRK, <sup>2</sup>Amar V, <sup>3</sup>Uday SK

<sup>1</sup>Associate Professor, Department of Endocrine and Metabolic Surgery, MMC/MGH, Khammam, Andhra Pradesh, India

<sup>2</sup>Consultant Advanced Laparoscopic Surgeon, Prime Hospitals, Hyderabad, Andhra Pradesh, India

<sup>3</sup>Associate Professor, Department of General Surgery, MMC/MGH, Khammam, Andhra Pradesh, India

**Correspondence:** Bhargav PRK, Associate Professor, Department of Endocrine and Metabolic Surgery, Mamata Medical College and Hospital (MMC/MGH), Rotary Nagar, Khammam-507002, Andhra Pradesh, India, e-mail: kingbhargav@gmail.com

## ABSTRACT

One of the three principal therapies of Graves' disease is radioiodine treatment. Hypothyroidism is considered as a treatment end point of successful radioiodine treatment for Graves' disease. The radioiodine-induced hypothyroidism is mostly irreversible. Though, early recurrences can be due to treatment failure, inadequate radioiodine dose or rarely due to Marine-Lenhart syndrome. Here, we report a rare case of recurrent Graves' disease, 3 years after successful radioiodine therapy induced hypothyroidism in a 50-year-old lady.

**Keywords:** Graves' disease, Recurrence, Radioiodine therapy, Marine-Lenhart syndrome.

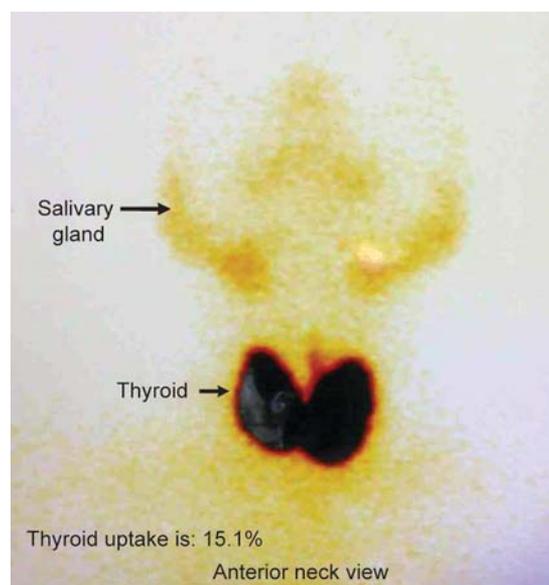
## INTRODUCTION

Graves' disease is usually treated with antithyroid drugs with or without definitive therapy in the form of radioiodine (RAI) or thyroidectomy. RAI is administered in single or occasionally multiple doses to achieve remission.<sup>1</sup> The debatable end point of successful RAI treatment may be sustained euthyroidism or hypothyroidism. Incidence of hypothyroidism progressively increases as a function of time after RAI therapy.<sup>2</sup> Once hypothyroidism is reached, it is mostly irreversible with patient requiring life-long thyroxine replacement. Early recurrences can be due to inadequate RAI therapy or rarely Marine-Lenhart syndrome (MLS). Here, we report and discuss a rare case of recurrent Graves' disease after successful RAI therapy appearing 3 years after attaining hypothyroidism.

## CASE REPORT

A 50-year-old woman presented to us with features of hyperthyroidism (excess sweating, goiter, fine tremors and palpitations) of 2 months duration. There was no history of diabetes, hypertension, drug abuse or psychiatric illness. Medical history and records revealed history of similar complaints, 4 years back and was treated with RAI of 8 milliCurie (mCi) after being diagnosed as Graves' disease. She became euthyroid 5 months after RAI treatment and during the transition period, she was treated with antithyroid drugs (ATD). Serum thyroid stimulating hormone (TSH) was measured at 4 to 6 months interval with radioimmunoassay (0.35-5.0  $\mu$ IU/ml) and 6 monthly clinical follow-up. After 1 year post-RAI, she became hypothyroid (TSH titer was 12.11  $\mu$ IU/ml)

and was kept on thyroxine replacement at 2  $\mu$ g/kg dose. Three years after achieving hypothyroidism, there was recurrence of Graves' hyperthyroidism [TSH < 0.03  $\mu$ IU/ml and T4 titer = 20.2 ng/ml (3.2 – 12)]. On examination, there was a grade 2 diffuse, firm goiter without any evidence of ophthalmopathy. Radioiodine scan revealed diffuse uptake in entire gland (Fig. 1). We put her on 30 mg of carbimazole and 60 mg of propranolol per day. She became euthyroid 6 weeks later (TSH = 1.56  $\mu$ IU/ml). In view of post-RAI late recurrence, we performed total thyroidectomy as patient was reluctant to



**Fig. 1:** Diagnostic RAI scan shows diffusely increased uptake throughout the goiter

receive repeat RAI therapy, inspite of offering the option higher dose of RAI. Figure 2 shows *ex vivo* specimen of total thyroidectomy. Postoperative period was uneventful without any sequelae of hypoparathyroidism or recurrent laryngeal nerve palsy. Histopathology confirmed it as diffuse hyperplastic goiter with no evidence of malignancy or nodularity.

## DISCUSSION

Graves' disease is an organ-specific autoimmune disease caused by stimulatory autoantibodies targeting TSH receptors leading to hyperthyroidism and its associations. Graves' disease is known to have undulant clinical course with multiple relapses and remissions in up to 30% of cases. Three principle options for the treatment of Graves' disease are antithyroid drugs (ATD), radioiodine and thyroidectomy. In general, the most commonly used definitive treatment is RAI, though there are substantial regional variations in practice.<sup>3</sup> Typically, the patient is started on antithyroid drugs till reasonable euthyroidism is achieved, followed by RAI. Majority of the patients require single dose of RAI, though 10 to 20% require more than one dose at 6 to 12 months interval for optimal therapy.<sup>1</sup> A successful treatment of RAI is followed by a latency of 3 to 6 months to achieve non-ATD-dependent euthyroidism. In the follow-up, progressively increasing proportion of subjects land in hypothyroidism to the extent that by 10 to 15 years up to 55 to 80% are hypothyroid, though 10 to 90%, achieve hypothyroidism as early as within 1 year.<sup>3-5</sup> The response depends on multiple factors like underlying autoimmune thyroiditis, age of the patient, severity of hyperthyroidism, dose of RAI, nodularity and nature of autoantibodies. The clinical course of disease after successful RAI therapy is early or late hypothyroidism, which is debatably accepted as a sequel or treatment end point by most of the clinicians.<sup>6</sup>

The quest to achieve long-term euthyroidism with RAI by methods like dosimetry, low dose or fixed dose regimen have

been largely unsuccessful.<sup>7</sup> Post-RAI recurrences are reported in 20 to 54% of cases, usually occur with low dose or inadequate dose of RAI.<sup>8-10</sup> However, close analysis of the reported post-RAI recurrences suggest that majority occurred within 3 to 6 months, often necessitating repeat RAI therapy.<sup>8</sup> Though, there is no cutoff time to differentiate persistent *vs* recurrent disease, it is arbitrarily considered as 3 to 6 months. But, even this is debatable as severe hyperthyroidism is controlled by ATD before administering RAI and continued till euthyroidism is achieved and mild hyperthyroidism may undergo temporary remission due to stunning of thyrocytes by RAI. A true recurrence is a situation, wherein the patient achieves the desired end point (hypothyroidism or permanent euthyroidism) and relapsed after a definite time period (a period beyond the therapeutic effect of administered RAI). Majority of the studies are biased due to improper definition, study design or confounding factors like ATD treatment or shorter follow-up. If analyzed from this view point, there is no reported case of true recurrent Graves' disease after successful RAI-induced hypothyroidism. One unique cause of post-RAI recurrence could be Marine-Lenhart syndrome (MLS), which occurs due to autonomous toxic nodule within diffuse toxic goiter.<sup>11-12</sup> The conventional doses of RAI dose may be insufficient for MLS and can lead to recurrence later. But, MLS was ruled out in our case based on RAI scan finding (which shows an area of increased uptake within diffuse uptake of goiter) and gross cut section of specimen, which shows no nodularity. Associated Hashimoto's thyroiditis was excluded on histopathology. To the best of our knowledge and searched literature, this case is a true recurrence of Graves' disease after RAI-induced hypothyroidism. We speculate, this may be due to *de novo* emergence of dormant hyperactive cell clones probably triggered by RAI-induced mutations or mutations in proliferation control of TSH receptors. Similar pathophysiology has been proposed for MLS.<sup>12</sup> Of course, these hypotheses commend intensive basic and clinical research.

This case report highlights that (1) RAI may not be a definitive therapy in few cases; (2) close long-term follow-up of patients treated with RAI may reveal more cases of late recurrences or (3) this may be a unique phenomenon of RAI triggered emergence of cell clones causing recurrence.

## REFERENCES

1. Holm LE, Lundell G, Dahlqvist I, et al. Cure rate after 131I therapy for hyperthyroidism. *Acta Radiol* 1981;20:161.
2. Cunnien AJ, Hay ID, Gorman CA, et al. Radioiodine-induced hypothyroidism in Graves' disease: Factors associated with the increasing incidence. *J Nucl Med* 1982;23:978.
3. Wartofsky L, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan and the United States. *Thyroid* 1991;1:129.
4. Sridama V, et al. Long-term follow-up study of compensated low dose 131I therapy for Graves' disease. *N Engl J Med* 1984;311:428.
5. Goolden AW, Stewart JS. Long-term results from graded low dose radioactive iodine therapy for thyrotoxicosis. *Clin Endocrinol (Oxf)* 1986;24:217.

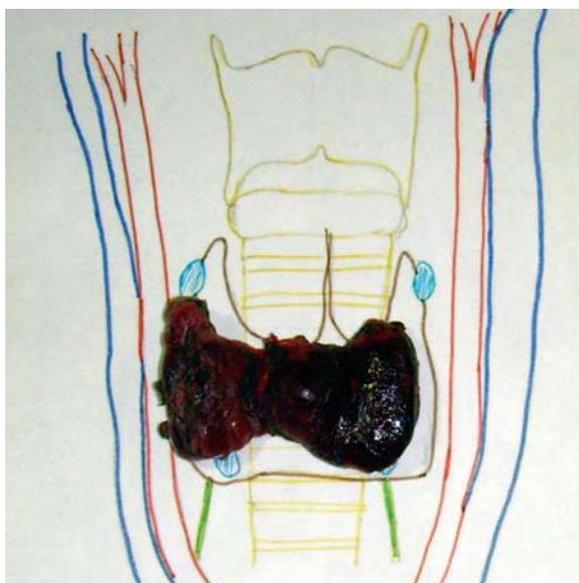


Fig. 2: *Ex vivo* specimen of total thyroidectomy on the grossing chart

6. Metso S, Jaatinen P, Huhtala H, Luukkaala T, Oksala H, Salmi J. Long-term follow-up study of radioiodine treatment of hyperthyroidism. *Clin Endocrinol (Oxf)* 2004;61:641-48.
7. Jarlov AE, Hegedus L, Kristensen LO, Nygaard B, Hansen B. Is calculation of the dose in radioiodine therapy of hyperthyroidism worthwhile? *Clin Endocrinol (Oxf)* 1995;43:325-29.
8. Joyce SY Yau, Chu KS, et al. Usage of a fixed dose of radioactive iodine for the treatment of hyperthyroidism: One-year outcome in a regional hospital in Hong Kong. *Hong Kong Med J* 2009;15:267-73.
9. Sankar R, Sekhri T, Sripathy G, Walia RP, Jain SK. Radioactive iodine therapy in Graves' hyperthyroidism: A prospective study from a tertiary referral centre in North India. *JAPI* 2005;53: 603-06.
10. Ustun F, Yuksel M, et al. The incidence of recurrence and hypothyroidism after radioiodine treatment in patients with hyperthyroidism in Trakya, a mild iodine deficiency area, during the period 1991-2003. *Annals of Nuclear Medicine* 2005;19(8): 737-42.
11. Nishikawa M, Yoshimura M, Yoshikawa N, Toyoda N, Yonemoto T, Ogawa Y, et al. Coexistence of an autonomously functioning thyroid nodule in a patient with Graves' disease: An unusual presentation of Marine-Lenhart syndrome. *Endocr J* 1997;44(4):571-74.
12. Lamata HF, Sanchez BJ, Artigas Marco MC, Gonzalez GM, et al. [Graves' disease with associated thyroid nodules (nodular Graves' disease). Clinical, diagnostic and therapeutic considerations]. *An Med Interna* 2003;20(8):403-09.