Hashimoto's Thyroiditis: An Unusual Sequela

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In this case report, too much preoccupation with obscure laboratory values prevented prompt treatment of the patient's condition. Although a rare sequela of Hashimoto's thyroiditis, the following illustrates the point that, at times, laboratory data can be a hindrance rather than a help in treating patients.

CASE REPORT

A 38-year-old woman first presented with symptoms of tiredness, irritability, cold intolerance, and heavy frequent menstrual periods in 1974. Past history showed an asymptomatic goiter on a prenatal examination in 1964, which was not treated. Family history revealed an uncle with a goiter. Physical examination showed an obese patient with a diffuse goiter. Pulse was 60/min and blood pressure was 120/80 mmHg. Deep tendon reflexes were normal. Results of thyroxine radioimmunoassay (T_4-RIA) were 12.87 nmol/L (1.0 μg/dL). A presumptive diagnosis of Hashimoto's thyroiditis was made, and she was started on levothyroxine, 0.1 mg/d. A repeat T_4-RIA in May 1975 was 104 nmol/L (8.2 μg/dL).

The patient remained clinically euthyroid until February 1981, when she presented with heavy menstrual periods and dry skin. Thyroid indices were all normal except for an elevated thyroxine-stimulating hormone (TSH). Because of her symptoms and elevated TSH, her levothyroxine was increased to 0.2 mg/d. She improved clinically, although her pulse remained at 60/min.

Although her thyroid indices on routine follow-up had become markedly abnormal by October 1982 (Table 1), she denied any symptoms suggestive of hypothyroidism or hyperthyroidism. Findings on physical examination were normal except for the palpable goiter. She remained on levothyroxine, 0.2 mg/d, and she was sent to an endocrinologist for consultation.

Before performing thyroid function tests and thyroid scan, the endocrinologist took the patient off all her levothyroxine for three weeks. Thyroid studies done in January 1983 are shown in Table 1. The thyroid scan at six hours had an uptake of 0.06 (normal 0.06 to 0.16) and at 24 hours of 0.10 (normal 0.07 to 0.36), suggesting chronic thyroiditis. The patient was restarted on levothyroxine, 0.1 mg/d, because she had developed headaches on the 0.2-mg dosage. The increased triiodothyronine (T_3) was felt to be due to too much thyroid medication.

In May 1983 the patient was referred to a second endocrinologist because her T_3-RIA remained markedly elevated. Before her thyroid function tests were done at the laboratory, the patient was taken off all medication for four weeks. Results showed a low T_4-RIA with a very low T_3-RIA and an elevated TSH (Table 1). A thyrotropin-releasing hormone (TRH) test was performed with 200 μg of TRH. The initial TSH was 167 mU/L (167 μU/mL); at 20 minutes the TSH was 240 mU/L (240 μU/mL), and at 60 minutes the TSH was 240 mU/L (240 μU/mL), suggesting hypothyroidism. Although clinically euthyroid, she was put on levothyroxine, 0.1 mg/d. As her T_3-RIA values remained obscure, either being very high or very low depending on the endocrinologist's laboratory, the patient's blood was sent to a university for special analysis.

At the university laboratory, the patient's serum was initially extracted with 95 percent ethanol and then reconstituted in calf serum free of triidothyronine. The triidothyronine was then determined along with a sample of the whole serum. In the whole or unextracted serum, the T_3-RIA was 12.9 nmol/L (800 ng/dL). In the extracted serum, it was 2.8 nmol/L (185 ng/dL) (Table 1).

The patient was diagnosed as having Hashimoto's thyroiditis, and she had subsequently developed autoantibodies to her triiodothyronine. She was treated with levothyroxine in amounts to bring her TSH to within normal values.

DISCUSSION

This patient's abnormal T_3-RIA levels were due to T_3 autoantibodies interfering with the radioimmunoassay.

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TABLE 1. LABORATORY DATA

Date	T_4-RIA nmol/L	T_3 Resin Uptake	T_3-RIA nmol/L	TSH mU/L	Comments	Treatment
October 1982	2.5		12*	60	Clinically euthyroid L-thyroxine stopped one week before performing tests	L-thyroxine 0.2 mg/d
January 1983	45.05	0.14	12*	50	Antimicrosomal antibodies 1:6400 Antithyroglobulin antibodies negative Thyroid scan suggests chronic thyroiditis	L-thyroxine 0.1 mg/d
July 1983	47.0	0.28	0.0**	146.4	Blood sent to university laboratory 10/83	L-thyroxine 0.1 mg/d
October 1983	37.0	0.20	2.8*	82	Antimicrosomal antibodies 1:6, 513,000 Antithyroglobulin antibodies negative Blood extracted with ethanol prior to performing tests	L-thyroxine 0.2 mg/d
Normal range	60–155	0.25–0.35	1.2–3.4	0–8		

** Double-antibody technique*
*** Single-antibody technique*

The technique of radioimmunoassay for T_3 or T_4 is performed with either a single- or double-antibody technique (Figure 1). With the single-antibody technique (ie, rabbit immunoglobulin G [IgG]), a bound or radioactive triiodothyronine is added to the patient's serum along with the rabbit antibody. Both the bound and free T_3 will compete for sites on the rabbit IgG. The rabbit antibody is then precipitated out with either polyethylene glycol, dextran charcoal, or ammonium sulphate. The percentage of T_3 that is bound is measured and plotted on a reference curve. Because the percentage of bound T_3 is inversely proportional to T_3, a value for T_3 can be calculated from the curve (Figure 2). In a patient with T_3 autoantibodies, both the rabbit IgG and the T_3 autoantibodies compete for the bound T_3. As the polyethylene glycol does not differentiate one antibody from the other, both are precipitated out. The precipitant gives a very high value for the radioactive T_3 from the graph (Figure 2).

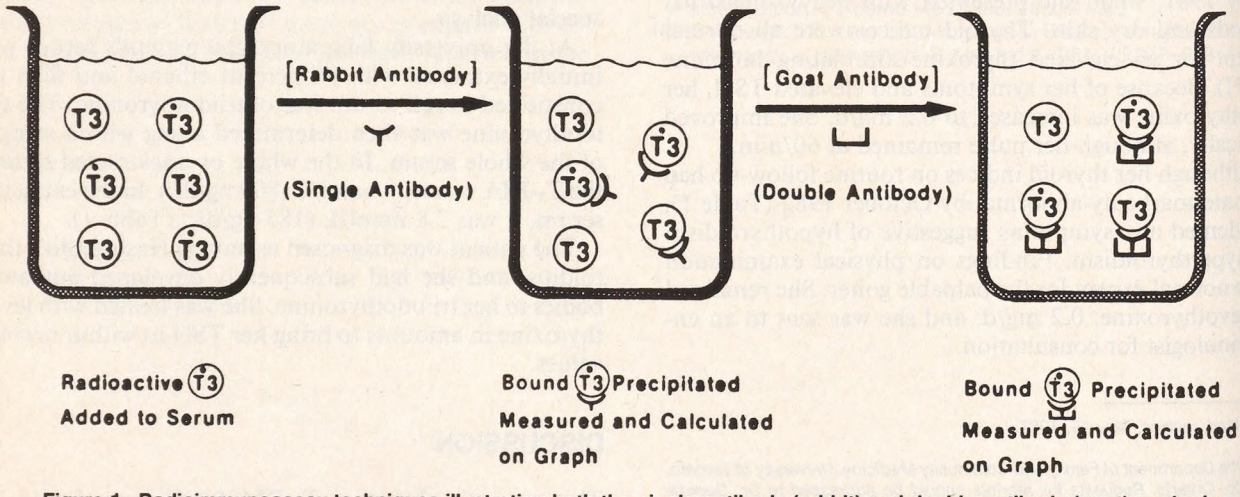

Figure 1. Radioimmunoassay techniques illustrating both the single-antibody (rabbit) and double-antibody (goat) method

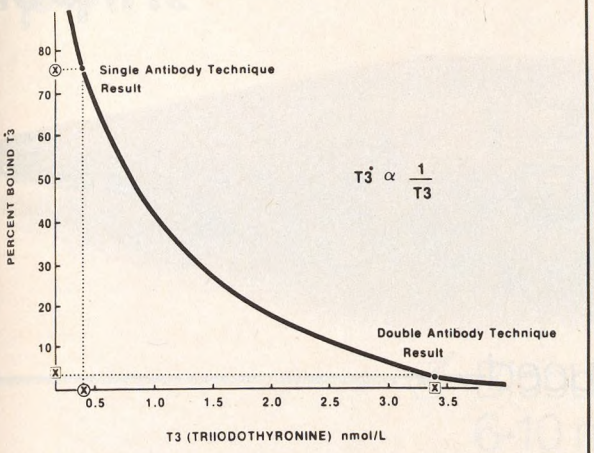

Figure 2. Reference curve showing the percentage of bound fraction plotted against T_3 concentration. The two points on the graph illustrate the spuriously high and low values when thyroid hormone autoantibodies are present

In the double-antibody technique, a second antibody (eg, goat immunoglobulin G) is specifically directed against the rabbit antibody and then precipitated out. When the T_3 autoantibodies are present, less radioactive T_3 will be bound to the first antibody (ie, rabbit IgG). Because the second antibody recognizes only the rabbit antibody, less bound T_3 will be picked up. When this is plotted on the graph, it will yield a falsely high calculated result for T_3. In this case, the patient had astronomically high and low values for her T_3-RIA on different occasions (Table 1), which were due to one laboratory using a single-antibody technique and the other using a double-antibody technique. Once extraction had been performed on her serum and the T_3 autoantibody removed, her thyroid function test results were in keeping with Hashimoto's thyroiditis. The T_3 autoantibody can be shown by immunoelectrophoresis using tracer triiodothyronine or thyroxine,[1] but as this method was not readily available, simple extraction with ethanol proved more efficacious.

This condition of unusual binding of thyroid hormones by immunoglobulins was first described by Robbins et al[2] in 1956 in a patient with thyroid carcinoma. Cases of Hashimoto's thyroiditis with thyroid hormone autoantibodies have been described as well.[3,4] Other authors have reported this condition in patients with Grave's disease,[5] primary hypothyroidism,[6] and in patients who are euthyroid.[7–9]

The origin of autoantibody production is not known, but several theories exist. One suggests that the immunogen responsible for the formation of the thyroid hormone autoantibody is thyroglobulin and that the antibodies produced to this immunogen cross react with the thyroid hormones.[3,5,9–11] It is possible that the antimicrosomal antibodies could induce this same phenomenon in this patient. Another theory suggests that incompletely digested fragments of ingested desiccated thyroid are partially absorbed and could be immunogenic.[7] Other theoretical possibilities include a hereditary disorder or a benign monoclonal gammopathy.[6]

Treatment of this condition is with levothyroxine in amounts sufficient to bring the TSH values to within normal limits.[12] The TSH values are monitored, as T_3 values will be unreliable using radioimmunoassay. If available, simple ethanol extraction before radioimmunoassay or T_3-RIA on Sephadex[13] will prevent abnormal results.

References

1. Premachandra BN, Walfish PG: Effects and clinical significance of exogenous thyroxine therapy in patients with circulating thyroid hormone autoantibodies. Am Clin Pathol 1982; 78:63–68
2. Robbins J, Rall JE, Rawson RW: An unusual instance of thyroxine binding by human serum gamma-globulin. Clin Endocrinol Metab 1956; 16:573–579
3. Premachandra BN, Blumenthal HT: Abnormal binding of thyroid hormone in sera from patients with Hashimoto's disease. Clin Endocrinol Metab 1967; 27:931–936
4. Foerch TA, Hojslet PE, Mose C, Paby P: Thyroid hormone autoantibodies in a case of Hashimoto's disease. Scand J Clin Lab Invest 1980; 40:263–269
5. Inada M, Nishikawa M, Oismi M, et al: Triiodothyronine binding immunoglobulin in a patient with Grave's disease and its effect on metabolism and radioimmunoassay of triiodothyronine. Am J Med 1980; 68:787–792
6. Beckett GJ, Todd JA, Hughes GJ, Campbell IW: Primary hypothyroidism and grossly elevated plasma total thyroxine and triiodothyronine levels. Clin Endocrinol 1983; 19:295–303
7. Wu SY, Green W: Triiodothyronine (T_3)-binding immunoglobulins in a euthyroid woman: Effects on measurement of T_3 RIA and on T_3 turnover. Clin Endocrin Metab 1976; 42:642–652
8. Neeley WE, Alexander NM: Polyclonal 3,5,3-triiodothyronine (T_3) antibodies in a euthyroid woman and the effect on radioimmunoassays for T_3. Clin Endocrinol Metab 1983; 57:851–854
9. Beck-Peccoz P, Romelli PB, Faglia C: Circulating antitriiodothyronine autoantibodies in two euthyroid patients: Apparent lack of interference in total T_3 radioimmunoassay based on second antibody or solid phase separation techniques. J Endocrinol Invest 1983; 6:333–340
10. Pearce CJ, Byfield PGH, Edmonds CJ, et al: Autoantibodies to thyroglobulin cross reacting with iodothyronine. Clin Endocrinol 1981; 15:1–10
11. Staeheli V, Vallotton MB, Burger A: Antibodies in different thyroid conditions. Clin Endocrinol Metabol 1975; 41:669–675
12. Ginsberg J, Segal D, Ehrlich RM, Walfish PG: Inappropriate triiodothyronine (T_3) and thyroxine (T_4) radioimmunoassay levels secondary to circulating thyroid hormone autoantibodies. Clin Endocrinol 1978; 8:133–139
13. Alexander NM, Jennings JF: Radioimmunoassay of serum triiodothyronine on small reusable Sephadex columns. Clin Chem 1974; 20:1353–1361