ORIGINAL RESEARCH

Graves' disease treated with thyroid arterial embolization

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Abstract

Purpose: To study pathological changes in the thyroid gland of patients with Graves' disease (GD) treated with thyroid arterial embolization.

Methods: Thirty-seven patients with GD were treated through transcatheter thyroid arterial embolization. Of these patients, twenty-two had biopsy of the thyroid gland at different time points before and after the embolization for the study of pathology. Serum thyroid hormones, TSH and TRAb were also studied at these time points. Thyroid size was evaluated in all patients using color Doppler ultrasound or CT scan.

Results: Thyroid size decreased immediately or several days following embolization. Pathological study demonstrated mainly acute infarction and necrosis at 7 days post embolization. At 6 months, chronic inflammation and fibrous hyperplasia were the primary findings in the gland, and at 3 years following embolization, mesenchyma hyperplasia and follicle atrophy were primarily present in the embolized thyroid tissue. The thyroid hormones and TSH gradually resumed to normal range after embolization while TRAb decreased significantly.

Conclusion: Thyroid arterial embolization can cause GD thyroid gland a series of pathological changes of acute ischemia and necrosis and later, chronic inflammation, fibroplasia and atrophy to decrease secretion of thyroid. The pathological changes within the thyroid gland after embolization form the basis of thyroid arterial embolization in treating GD hyperthyroidism.

Graves' Disease (GD) is one of the most frequent endocrine diseases and occurs primarily in younger adults with a peak incidence between the ages of 20 and 40 yr. Women, with an incidence of the disease as high as 1.9%, are affected up to seven times more frequently than men.¹⁻⁴ The disease is characterized by hyperthyroidism, goitre and, in some cases, ophthalmopathy, caused by a variety of autoantibodies in the serum including antibodies to the TSH receptor, thyroid peroxisomes and thyroglobulin to stimulate excessive production of thyroid hormones.⁵⁻⁸ Surgery, radioactive iodine and antithyroid medication are the currently established modalities used to treat this disease. Recently, thyroid arterial embolization, due to considerable progress in the endovascular technology, has been employed to treat GD.⁹⁻¹⁴ Arterial embolization is usually applied for treatment of hyperfunction of parenchymatous organs to preserve normal organ function, similar to partial surgical resection. This approach involves embolization of most of the thyroid tissue to reduce thyroid hormone secretion, resulting in euthyroidism. After thyroid arterial embolization, the vessels in the thyroid gland are occluded, embolized tissue becomes ischemic, and aseptic necrosis

and fibrosis ensue, thus reducing thyroid function to euthyroidism. This approach is effective in the treatment of GD. However, minimal experience has been gained with this therapy, and further research is needed. This study investigated the pathological thyroid changes in combination with changes in thyroid hormones and key autoantibody caused by thyroid arterial embolization for the treatment of GD hyperthyroidism.

Methods

The study protocol was approved by the Institutional Review Board and the Ethics Committee of the First Affiliated Hospital of Kunming Medical College. Patients provided signed informed consent prior to the study. Thirty-seven patients (7 male, 30 female) with the clinical features and laboratory of GD were enrolled for thyroid arterial embolization in the period from November 2001 to November 2006. Inclusion criteria were noncompliance or serious side effects to antithyroid drugs and refusal of surgical and radioactive iodine therapy. Aged 14 to 50 yr (mean 33.1 yr), all patients had goitre, grade I in 5 cases, II in 12, and III in 20, classified according to the World Health Organization recommendations.¹⁵ All patients had vascular murmurs in the anterior neck corresponding to the thyroid area. No patients had a history of any other autoimmune, endocrinological or infectious diseases or tumour.

Experienced interventional radiologists performed thyroid arterial embolization using similar techniques. A detailed embolization protocol and efficacy assessment of thyroid embolization had been described previously.¹³ In brief, the bilateral superior thyroid arteries were embolized in each case using a mixed product of polyvinyl alcohol, papaverine and a non-ionic contrast agent (Omnipaque 300, Amersham Health, Shanghai, China) because these arteries are usually the major supplying vessels to the thyroid. In patients with moderate to severe goitre, an inferior thyroid artery was also embolized to enforce the ef-

fect. Since the parathyroid glands are supplied mainly by the thyroid bilateral inferior arteries, one inferior artery would usually be left unembolized to avoid parathyroid hypo-function.¹³ Special attention was paid during the procedure to prevent regurgitation of the embolic agent to avoid mis-embolization of other arteries.

All patients had either CT scan or ultrasound scan before embolization and at 7 days, 6 months and 3 years after embolization. Venous blood was also sampled on an empty stomach to test the thyroid hormones and the auto-antibodies at different time points. Twenty-two patients agreed to thyroid biopsy, 7 cases prior to arterial embolization, 2 cases at 7 days, 6 at 6 months and 7 at 3 years post embolization. After thyroid puncture for biopsy, the punctured side of thyroid was compressed for 10 minutes, with no occurrence of hematoma or any other complications.

Statistical analysis

SAS application software package, version 6.12 (SAS Institute Inc., North Carolina State University, N.C., USA) was employed to perform statistical analysis. Continuous data were expressed as mean ($\bar{x}$) $\pm$ SD, or as the median and range if not normally distributed. Various tests were used, including the chi-squared test, ANOVA, Pearson correlation, and q-test. A *P* value <0.05 was considered significant, and a *P* value <0.01 highly significant statistically.

Results

Complications and Efficacy

No severe complications occurred immediately after the embolization procedure except slight to moderate neck pain. Vascular murmurs in the anterior neck area disappeared, vascular regions in the thyroid decreased, and the enlarged thyroid gland was dwindled following embolization (Table 1 and Fig.1&2). Thirty seven patients had been followed up for one to three years following embolization, with 26 being euthyroid

TABLE 1. Changes of thyroid gland size before and after arterial embolization

	n	Normal	I° goiter	II° goitre	III° goitre	Blood supply
PrE	37	0	5	12	20	Abundant with typical sign of goiter
7 d PoE*	37	5	15	10	7	Scarce with large ischemic regions
6 m PoE*#	19	9	6	3	0	Scarce with small ischemic regions
3 y PoE*#	14	7	5	2	0	Relatively scarce

* $P < 0.05$ compared with pre-embolization values ; # $P < 0.05$ compared with values at 7 days post-embolization.

PrE=pre-embolization, d=day, PoE=post embolization, m=month, y=year

(70.3%), 4 improved (10.8%) and 7 recurrent (18.9%). No side effects occurred during the long-term follow-up.

Pathological changes of thyroid gland

Seven patients had fine needle biopsy before embolization, including 3 with a primary diagnosis of GD and 4 who had been treated using anti-thyroid drugs from 3 months to 1 year. In three patients, with a primary diagnosis of GD, pathological changes were typical of hyperthyroidism (Fig3 A). In the other four patients who had been treated previously, hyperthyroidism was not so typical with large follicles and flat epithelial cells. At 7 days following embolization, the primary pathological changes were acute infarction and necrosis of the glandular epithelium and interstitium (Fig.3 B). Six months after embolization, chronic inflammation and fibroplasia were mainly present in the thyroid gland with some atrophic follicles (Fig. 3 C). At three years, pathological changes included interstitial fibroplasia, lymphocyte infiltration and follicular atrophy (Fig.3 D).

Serum thyroid hormone and thyrotropin receptor antibody (TRAb) changes

Changes in serum thyroid hormones, autoimmune function (TRAb) and corresponding pathological characteristics after embolization are shown in Table 2 and Fig.4. After embolization, serum thyroid hormones and TRAb all decreased, with a significant difference at 6 months and 3 years. Conversely, TSH index gradually increased over time. At 3 yr, all serum values of thyroid hormones and TSH returned to nor-

mal except TRAb which decreased to near the normal range.

Discussion

GD is a common autoimmune thyroid disease and no studies have focused on the thyroid pathological changes caused by thyroid arterial embolization. This pathological study was performed to understand better the role of thyroid arterial embolization in treating GD, the most common cause of hyperthyroidism.^{1-8,10,12,13,16} The mechanism of thyroid arterial embolization, for the treatment of GD hyperthyroidism, is to block most of the blood supply to the thyroid gland, thus leading to necrosis and later fibrosis of most of thyroid tissue to decrease thyroid hormone secretion in the future. The bilateral superior thyroid arteries account for over 70% of the total blood supply in the majority of patients^{2,10,12,13}, and embolization of the bilateral superior thyroid arteries (plus one additional inferior artery in patients with severe goitre) will block 70-80% of the blood supply of the gland, thereby achieving an effect similar to subtotal surgical thyroidectomy.

In this study, we investigated the macroscopic and microscopic changes of the thyroid glands before and after thyroid arterial embolization in comparison with the thyroid hormone levels (Table 2). In GD, the degree of thyrotoxicosis varies from case to case and may be less conspicuous than other manifestations of the disease. Diffuse enlargement of the thyroid was present in all cases of GD, and increased blood flow through the hyperactive gland often produces an audible bruit.⁶ Embolization of the thyroid arteries oc-

FIGURE 1. A 31-year-old male with ultrasound examination before and after thyroid arterial embolization. A. Pre-embolization Doppler scan showed abundant blood supply within the thyroid gland consistent with hyperthyroidism. B. Seven days after embolization, ultrasound scan demonstrated that the blood supply within the thyroid had greatly decreased, with some low-level echo areas implying tissue necrosis. C. Six months later, grayscale ultrasound revealed greatly reduced size and blood supply of the gland. D. Ultrasound at 3 yr demonstrated decreased thyroid volume with some echo areas, indicating tissue fibrosis of the gland.

FIGURE 2. Super-selective thyroid angiography of 40-yr-old female patient with hyperthyroidism caused by GD. A. Angiography of the right superior thyroid artery demonstrated obvious staining of the gland. B. Post-embolization angiography of the same artery revealed occlusion of the artery with no abnormal staining.

FIGURE 3. Microscopy of thyroid tissue with HE staining in GD. A. Typical hyperthyroidism before arterial embolization. B. Coagulation necrosis was present in the thyroid at 7 days following embolization. C. At 6 months after embolization, fibroplasia and atrophic follicles were present simultaneously in the thyroid gland. D. At 3 years, atrophic follicles and fibrosis of the interstitial tissues were demonstrated in the thyroid.

cludes most of the vessels and no bruit could be heard immediately following the procedure. On the very first day post embolization, the thyroid gland begins to decrease in size and continues to decrease long after embolization. At 7 days, the primary pathological changes were acute infarction and necrosis of the glandular epithelium and the interstitium (Fig.3 B), consistent with short-term pathological changes caused by arterial embolization¹⁷⁻²². Later on, the thyroid gland started a process of repair with presence of chronic inflammation, fibroplasia and some atrophic

follicles (Fig. 3 C). At three years, the major pathological changes were apparent interstitial fibroplasia, lymphocyte infiltration and follicular atrophy (Fig.3 D) and, consequently, thyroid function was decreased greatly and even returned to the normal range. These pathological changes within the thyroid gland formed the basis for thyroid arterial embolization in treating GD hyperthyroidism.

Shortly after the arterial embolization, secretion of thyroid hormones decreased because the embolized thyroid tissue became acutely chemically thyroiditic

FIGURE 4. Thyroid hormone changes, TSH and TRAb before and after arterial embolization. PrE: pre-embolization. A. TT3 gradually decreased while TSH increased over time following embolization. B. All the indexes including TT4, FT3, FT4 and TRAb decreased significantly over time after arterial embolization.

and necrotic. With time, chronic inflammation and fibrosis occurred and synthesis and release of thyroid hormones decreased further, reflecting that most of the thyroid tissue had become dead and fibrotic, resulting in euthyroidism. The change of TSH index was caused by negative feedback of the serum thyroid hormones. After thyroid arterial embolization, the value of TRAb was also significantly decreased (Table 2). TRAb, especially TSAb (thyroid stimulating antibody), was thought to be the key autoantibody to stimulate the thyroid gland for hyperblastosis and hyperfunction by combining with the major antigen peptide of thyroid stimulating hormone receptor (TSHR) to stimulate the TSHR.²³⁻²⁵ After embolization, the value of TRAb decreased compared with before embolization, and continued to drop with gradual decomposition of the existing TRAb and reduction of newly synthesized autoantibodies because most thyroid tissue had been embolized and necrotic. Finally, the synthesis and the destructive metabolism of the key autoantibodies gradually reach a balance, and the TRAb value maintains relatively stable.

To date, no hypothyroidism occurred as a result of thyroid arterial embolization. At 6 months, massive necrosis which was frequent in other tissues or organs with arterial embolization^{17,19,20,22,26} had not occurred within the embolized thyroid tissue, and only sporadic focal necrosis with concurrent degenerative atrophy and fibrous hyperplasia was present. At three years, new small vessels and capillary network were regenerated within the interstitial hyperplastic fibrous tissue, which suggested partial recovery of the blood supply of the gland. No parathyroid hypo-function occurred as a result of embolization. The parathyroid glands are primarily supplied by the bilateral inferior thyroid arteries^{27, 28}, and embolization of bilateral inferior arteries may cause hypoparathyroidism. Therefore, we usually embolized bilateral superior arteries and one inferior artery, leaving one inferior thyroid artery unblocked for the maintenance of blood supply to the parathyroids.

This study has some limitations. One was the diminution of the embolized thyroid gland which might affect thyroid biopsy even under CT guidance.

TABLE 2. Changes of serum thyroid hormones, TSH and TRAb before and after embolization

group	n	TT3 (nmol/L)	TT4 (nmol/L)	FT3 (pmol/L)	FT4 (pmol/L)	TSH (uIU/ml)	TRAb (U/L)	Associated Pathology
NR		1.1-3.4	58-161	2.3-7.7	12.2-28.7	0.25-4	<14	-
3d PrE	37	6.2±3.3	198.3±78.5	12.6±7.6	39.1±19.4	0.1±0.1	193.1±186.6	Hyperthyroidism
7d PoE	37	4.7±2.5	211.2±83.7	12.6±8.5	35.8±15.8	0.3±0.4	112.3±107.7*	Acute infarction & necrosis
6m PoE	19	3.2±1.3*	147.7±50.6*	7.4±3.4*	29.1±14.0*	2.4±3.8*	50.1±37.9*	chronic inflammation & fibroplasia
3y PoE	14	2.5±0.9*	130.7±43.5*	7.3±3.2*	28.5±11.3*	1.14±1.51*	25.8±4.2*#	Atrophy and fibroplasia

TT4, total T4; TT3, total T3; FT4, free T4; FT3, free T3; TSH: thyroid-stimulating hormone; TRAb: thyrotropin receptor antibody; NR: normal range; d: day; m: month; y: year; PrE: pre-embolization; PoE: post-embolization.

* $P < 0.05$ vs. pre-embolization values; # $P < 0.05$ vs 6 months after embolization.

Another factor may be the embolization material. We applied polyvinyl alcohol as a particle embolus agent in thyroid arterial embolization. This agent was very effective but we have not tried other material. The search for a better embolus agent may produce even better embolization results.

In conclusion, GD is a disease with complicated etiopathogenesis which has not been clearly stated. Thyroid arterial embolization can occlude the major blood supply to the thyroid gland in GD patients and cause acute ischemia and necrosis and later chronic inflammation, fibroplasia and atrophy of the thyroid follicles, consequently decreasing the secretion of thyroid hormones and restoring hyperthyroidism to euthyroidism. The pathological changes within the thyroid gland after embolization form the basis of thyroid arterial embolization in treating GD hyperthyroidism.

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