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CASE REPORT

Exacerbation of thyroid associated ophthalmopathy after arterial embolization therapy in a patient with Graves' disease

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Abstract A novel treatment approach to Graves' disease (GD), embolization of the thyroid gland arteries, is evaluated with respect to its indications and adverse effects. We describe an exacerbation of thyroid associated ophthalmopathy (TAO) following thyroid artery embolization in a woman with GD and mild stable TAO (NOSPECS classification, class I grade a). A 45-year-old woman with GD and inactive TAO, in whom thyroid function was stable following blockade of hormone release combined with replacement therapy, underwent embolization of three thyroid arteries. Initially, there were neither adverse effects nor complications; however, the patient developed severe TAO (NOSPECS classification, class IV grade b) 3 months after the arterial embolization. Steroid pulse treatments followed by total thyroidectomy resulted in improvement of the eye signs and symptoms. The clinical course and the serial changes of the thyroglobulin and thyroglobulin-antibody titers suggested that the destruction of thyroid follicles, induced by the arterial embolization, triggered the exacerbation of her TAO. Our experience argues for the use of caution when arterial embolization is considered for GD patients with even the mildest TAO (NOSPECS classification, class I).

Keywords Thyroid associated ophthalmopathy · Graves' disease · Arterial embolization therapy · Orbital MRI · Total thyroidectomy

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Introduction

To date, a perfect treatment for Graves' disease (GD) has yet to be developed. Antithyroid drugs, radioiodine, and surgery are safe and effective; however, each has adverse effects, and complications do occur [1, 2]. Additionally, some cases are resistant to the aforementioned therapies. Xiao et al. [3] recently demonstrated that embolization of the thyroid gland arteries was a safe and effective treatment of GD. While promising additional information is needed regarding its indications, effectiveness, and adverse effects. Here we describe an exacerbation of thyroid associated ophthalmopathy (TAO) following thyroid artery embolization in a woman with GD and mild stable TAO (NOSPECS classification, class I grade a) [4].

Case report

A 45-year-old woman, with suspected Graves' disease (GD), was referred to our Division of Endocrinology for treatment. She exhibited eye signs and had suffered from thyrotoxic symptoms for the preceding 8 weeks. Her past

medical history included facial nerve palsy, but was otherwise noncontributory, and her family history was likewise unremarkable. She had smoked 10–20 cigarettes per day for 25 years. Physical examination demonstrated redness and swelling of eyelids, lid retraction, absence of proptosis (16 mm in the right eye and 14 mm in the left eye by an exophthalmometer), no disturbance of eye muscle motility (NOSPECS classification, class II grade b), and a goiter that was 7.4 cm in its transverse diameter.

The diagnosis of GD was confirmed by elevated levels of thyroid hormones (free thyroxine 6.2 ng/dl [79.79 pmol/l] [normal range: 0.90–1.70 ng/dl] and tri-iodothyroinine 490 ng/dl [7.55 nmol/l] [normal range: 80–160 ng/dl]) associated with decreased thyrotropin (TSH: <0.010 mU/l) (normal range: 0.340–5.000 mU/l), and a high level of TSH receptor antibody (TRAb 73.9%) (normal value: <15%). The thyroid gland volume estimated by ultrasound was 57.0 ml. We collaborated with our Department of Ophthalmology and began treatment with 15 mg of methimazole, 10 mg of prednisolone, a beta-blocker and betamethasone eye drops. Despite being advised to stop smoking to prevent deterioration of her TAO, the patient was unable to quit. The medications improved her eye signs (NOSPECS classification, class I grade a) and thyrotoxic symptoms, and subsequently the methimazole was tapered and the prednisolone and beta-blocker discontinued. Due to the instability of her thyroid function, we added levothyroxine following blockade of the thyroid hormone release. Though she desired definitive therapy, the patient refused surgery for cosmetic reasons, so medical management was continued.

At the time the patient presented, we were in the process of evaluating arterial embolization therapy for GD. The indications were reviewed and the procedure was approved by the ethics committee of Osaka Medical College. After obtaining informed, written consent, the patient underwent thyroid artery embolization in our institution about 12 months after her initial visit.

The cardinal procedure was based upon the method of Xiao et al. [3]. Selective arteriography of the bilateral common carotid and subclavian arteries was performed using the Seldinger technique. The left and right superior thyroid arteries and right inferior artery were embolized with a total of 5 ml of the following mixture: Embosphere Microspheres® 300–500 μm (Biosphere Medical, Massachusetts, USA) were mixed in the same amount of contrast medium and injected using a 1-ml syringe. Arteriographic images after the embolization showed occlusion of the three thyroid arteries and patency of the bilateral common carotid arteries and its branches. In the subsequent weeks, no serious complications developed. The thyroid gland volume rapidly decreased for 4 weeks. This was followed by a slight increase in thyroid volume, after the initial blockade and replacement therapy had been tapered (Fig. 1). The serum TSH levels in the first 3 months after the intervention ranged from 0.166 to 5.070 mU/l, and the patient remained nearly euthyroid.

The patient complained of eye discomfort and diplopia 3 months after the arterial embolization. Physical examination showed proptosis (20 mm in the right eye and 17 mm in the left eye), and severe restriction of eye muscle

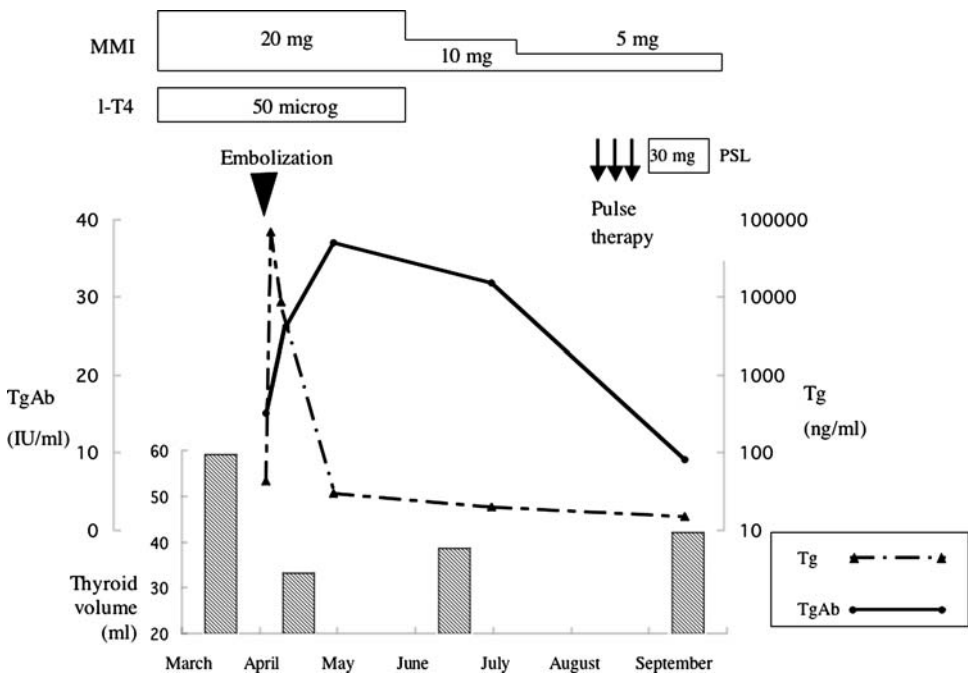

Fig. 1 Clinical course of the patient. *MMI*: methimazole, *l-T4*: levothyroxine, *PSL*: methylprednisolone, *Tg*: thyroglobulin, *TgAb*: thyroglobulin-antibody

motility (NOSPECS classification, class IV grade b). A test of field of single binocular vision demonstrated severe diplopia, although flicker photometer tests were normal in both eyes. MR T2-weighted images (inversion recovery) of the orbit revealed swelling of the extraocular muscles, more pronounced on the right, with a high intensity. A series of the orbital MR-T2 images along with their time course is shown in Fig. 2. Based on these findings, the patient was diagnosed with an exacerbation of her TAO.

Over the 4 months following embolization, the patient was treated with three courses of steroid pulse therapy. This was coupled with 30 mg prednisolone orally per day with subsequent tapering and discontinuation after 3 months. Levels of the TSH receptor antibody, h-TRAb (DYNO test TRAb human, Yamasa Co., Chiba, Japan) and the TSH receptor stimulating antibody TSAb (TSAb kit, Yamasa Co.) were measured in a series of the patient's sera, retrospectively. Serum h-TRAb levels before the treatment, and on days 7, 26, 63 and 140 after arterial embolization (day 140 was after the steroid pulse therapy), were 8.5, 8.1, 8.5, 7.7, and 3.1 IU/l, respectively. TSAb for the same days were 1,194, 1,132, 984, 1,171, and 424%, respectively. The steroid therapy resulted in a certain degree of improvement in the extraocular muscle swelling that was associated with the high intensity areas on the T2 images (Fig. 2c). However, the eye signs and symptoms remained (NOSPECS classification, range between class II and III) and antithyroid drug therapy was continued. Ultimately, the patient agreed to undergo total thyroidectomy about 10 months after arterial embolization. The weight of the removed thyroid tissue was 36.2 g. Microscopic findings were similar to those presented by Xiao et al. [3] and are shown in Fig. 3. Nineteen months after the operation, the patient was euthyroid on 100 μg of levothyroxine and her eye signs and symptoms were stable (NOSPECS classification, class I grade a) with eye drops alone.

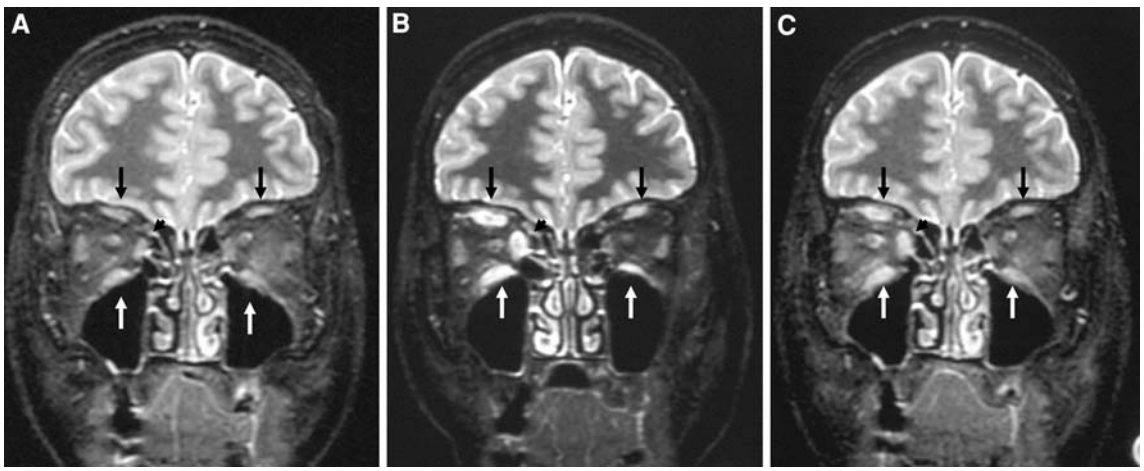

Fig. 2 Orbital magnetic resonance T2-weighted images (inversion recovery) in frontal sections have the following findings: **a** slight swelling of the eye muscles. **b** High signal intensity and swelling of the eye muscles predominantly on the right side. **c** Improvement in the same regions in Fig. 2**b**. *Black arrows*, *white arrows* and *black arrow-heads* indicate the superior rectus, inferior rectus, and medial rectus, respectively

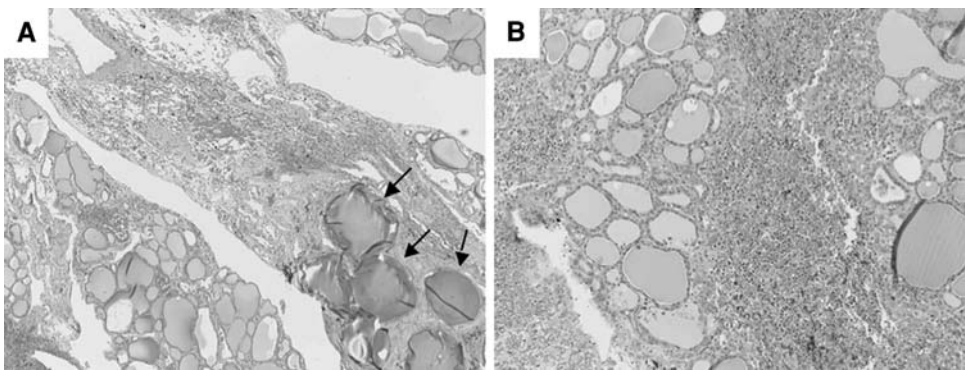

Fig. 3 Histological sections stained by Hematoxylin–eosin, magnification ×4 for **a**; ×10 for **b**. Finer arteries filled with the embolic agent were observed (note the *arrows* in **a**). Lymphoid cells infiltrated in collapsed foci near the embolized capillaries and the volume of colloid in the follicles decreased. Microphotograph **a** and **b** are from different locations of the same slide

Discussion

This is the first report of an exacerbation of TAO following thyroid artery embolization in GD. This novel technique, first described by Galkin et al. [5] and later enhanced by Xiao et al. [3], was found to be minimally invasive, safe, and effective [6, 7]. No serious adverse effects or complications were described in these studies. In the present patient, however, mild and stable TAO (NOSPECS classification, class I grade a) worsened rapidly after arterial embolization. Arterial embolization is currently being evaluated with respect to its efficacy and complications. We still believe that arterial embolization has excellent potential, particularly in patients who are resistant or otherwise unable to undergo conventional treatments. However, one must exercise caution when using it in patients with TAO. We recommend that the degree of TAO be estimated by orbit MRI prior to performing arterial embolization in these patients.

The clinical course of our patient supports the hypothesis that a worsening of TAO results from the release of thyroid antigens after the destruction of follicular cells. As shown in Fig. 1, the titer of serum thyroglobulin after the intervention was very high. Subsequently, the titer of thyroglobulin-antibody rapidly increased, and after 5 months, the thyroid volume diminished to about 56% of its initial volume. This hypothesis has also been used to explain TAO exacerbation after radioiodine therapy [8]. However, in this patient, the exacerbation occurred without the influence of radiation thyroiditis or transient hypothyroidism, both of which are risk factors for TAO exacerbation after radioiodine therapy [9]. In addition, there was no direct effect of radioiodine on the immune system, including T cells, B cells, or macrophages. TAO is widely accepted as an autoimmune inflammatory disorder of the orbital tissue and extraocular muscles, and there is consensus regarding the relationship between radioiodine therapy and the subsequent worsening of TAO [8]. The present case is another illustration of this hypothesis.

Levels of h-TRAb and TSAb after the arterial embolization did not change. In our interpretation, the h-TRAb or TSAb levels were high enough prior to the intervention to accelerate the TAO. Accordingly, if thyroid destruction triggered by arterial embolization modulates the immune system, exacerbation of TAO is more likely to follow.

We ultimately recommended total thyroidectomy to this patient, with the intention of both improving the TAO as well as curing the Graves' hyperthyroidism. Several studies have suggested that complete removal of thyroid tissue is a more effective means of improving TAO [10, 11]. Moleti et al. [12] also argued that both the short and long term inactivation of TAO could be achieved subjoining radioiodine therapy to near-total thyroidectomy, which is equal to complete ablation of the thyroid tissue. These findings, combined with the disease's failure to completely respond to steroid pulse therapy, persuaded us to recommend total thyroidectomy to the patient.

In conclusion, we report an exacerbation of TAO after arterial embolization therapy in a GD patient with previously mild stable TAO (NOSPECS classification, class I grade a). Our experience argues for the use of caution when arterial embolization is considered for GD patients with even the mildest TAO (NOSPECS classification, class I).

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