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CLINICAL CASE SEMINAR

Carotid Cavernous Fistula in a Patient with Graves' Ophthalmopathy

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The clinical manifestations of carotid cavernous fistula, an abnormal arteriovenous connection between the cavernous sinus and the carotid artery, can closely mimic the cardinal signs of Graves' ophthalmopathy, an inflammatory disorder of the orbit usually associated with autoimmune thyroid disease. Therefore, carotid cavernous fistulas are generally considered in the differential diagnosis of Graves' ophthalmopathy, especially when the eye involvement is unilateral or asymmetric, and there is the need for exclusion of rarer etiologies of orbital disease. This is the first report of the simultaneous occurrence of Graves' ophthalmopathy and carotid cavernous fistula. The patient was a 67-yr-old woman who presented with a history of Graves' disease with mild bilateral ophthalmopathy treated with radioiodine following a 10-yr therapy with methimazole; after radioiodine treatment, ophthalmopathy deteriorated. At the time of our initial clinical evaluation the ocular involvement of the patient was symmetric, and no evidence of any associated condition was found. However, the response of eye disease to corticosteroid treatment was markedly unequal, resulting in evident asymmetry. This prompted a reconsideration of the diagnosis and a new evaluation of the patient with sensitive techniques, leading to the further diagnosis of carotid cavernous fistula. (*J Clin Endocrinol Metab* 88: 3487–3490, 2003)

GRAVES' DISEASE IS an autoimmune disorder characterized by diffuse goiter, thyrotoxicosis, infiltrative orbitopathy, and, occasionally, infiltrative dermopathy. The hyperthyroidism of Graves' disease is caused by autoantibodies directed to the TSH receptor, whereas the extrathyroidal manifestations are due to immunologically mediated activation of fibroblasts in the extraocular muscles and skin, with accumulation of glycosaminoglycans, leading to the trapping of water and edema. Graves' disease is associated with specific eye signs (Graves' ophthalmopathy) that may include proptosis, ophthalmoplegia, orbital congestion, periorbital edema, conjunctival injection and chemosis, and, uncommonly, compression of the optic nerve. This condition is also known as thyroid-associated ophthalmopathy, as it occurs in the absence of Graves' disease in 10% of patients (1).

Carotid cavernous fistulas are abnormal arteriovenous connections between the cavernous sinus and carotid arteries. They are classified as direct and indirect. Direct fistulas usually result from trauma and are characterized by dramatic signs produced by high flow, high pressure shunting. Indirect fistulas generally occur spontaneously and cause more subtle signs. Symptoms include eye pain, proptosis, loss of vision, double vision, conjunctival injection and chemosis (related to increased blood flow), and inability to move the affected eye (2). Due to the similarities of clinical signs, carotid cavernous fistulas are usually considered in the differential diagnosis of Graves' ophthalmopathy. We describe the simultaneous occurrence of both Graves' ophthalmopathy and indirect carotid cavernous fistula in the same patient.

Abbreviations: CT, Computed tomography.

Case Reports

A 67-yr-old woman presented with a history of Graves' disease with mild bilateral ophthalmopathy, diagnosed almost 11 yr earlier and treated for about 10 yr with methimazole, then with ^{131}I. Radioiodine treatment was followed by a progressive improvement of hyperthyroidism together with a consistent worsening of the clinical signs of ophthalmopathy.

Our initial evaluation in September 2000 revealed moderate bilateral periorbital edema, scleral injection, and conjunctival chemosis, with mild proptosis (Fig. 1, *upper panel*). The patient complained of eye discomfort, excess tearing, and diplopia. The clinical examination at this time provided no evidence of any associated condition. Laboratory results were consistent with subclinical hyperthyroidism, with suppressed levels of serum TSH and normal values for free thyroid hormones. TSH receptor antibodies were positive, whereas thyroid peroxidase antibodies proved negative.

The patient underwent iv steroid treatment with 1 g methylprednisolone acetate in 500 ml saline infused over 24 h for 3 consecutive d, followed by an oral regimen of 75 mg prednisone/d for 3 wk, with subsequent tapering and discontinuation after 3 months. After the treatment, improvement of congestive symptoms in the left eye was noticed, whereas only mild contralateral changes were observed.

A few months after discontinuation of oral steroid treat-

ment, the persistence of severe ocular signs involving the right eye (Fig. 1, *middle panel*) prompted another extensive evaluation.

Materials and Methods

The clinical evaluation of ophthalmopathy was based on the atlas for clinical assessment of active thyroid-associated orbitopathy by Dickinson and Perros (3). Hormone measurements were performed using commercial immunoassay kits. The orbits were examined by means of computed tomography (CT); axial and coronal sections with a thickness of 3–5 mm were obtained. Four-vessel cerebral digital subtraction angiography was performed according to a standard technique, via puncture of the right femoral artery.

Results

Clinical findings, before and after steroid treatment, are summarized in Table 1. Laboratory results were still consistent with the diagnosis of subclinical hyperthyroidism. A CT scan of the orbits revealed a moderate enlargement of the right extraocular muscles, particularly of the superior rectus, as well as a marked prominence of the ipsilateral superior ophthalmic vein (Fig. 2). Only minor abnormalities were shown in the left orbit. Cerebral angiography showed a dural carotid cavernous fistula, mainly receiving supply from meningeal branches of the right ascending pharyngeal artery, and draining exclusively into the ipsilateral superior ophthalmic vein (Fig. 3). A minor supply from the contralateral external carotid was also demonstrated.

After 2 months of conservative therapy, which proved ineffective, the patient underwent endovascular treatment by transvenous embolization (4, 5), and immediate clinical and subjective improvement was obtained (Fig. 1, *lower panel*). No complications occurred.

Discussion

Graves' disease is a relatively common condition, occurring in up to 2% of women and in a much smaller proportion of men. The disorder typically occurs between 20 and 50 yr of age, although it is also observed in the elderly. Ophthalmopathy is its most frequent extrathyroidal manifestation (1). Although fewer than 5% of patients with Graves' disease experience severe ocular problems (6), CT reveals some evidence of extraocular muscle involvement in the majority of them (7–9).

Asymmetric eye involvement is quite common in patients with Graves' ophthalmopathy, whereas true unilateral disease is rare (7–10). Its underlying mechanisms remain poorly defined, although local anatomical factors, such as susceptibility to venous obstruction on the involved side, have been suggested (1). In fact, it has been postulated that superior rectus muscle enlargement alone may cause reduced venous outflow from susceptible orbits through simple external compression and/or periphlebitis (due to extension of the muscle inflammatory process) of the superior ophthalmic

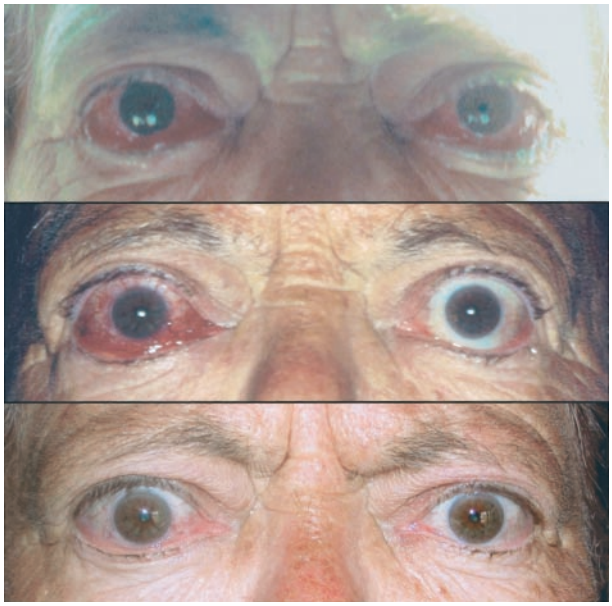

FIG. 1. Ocular manifestations before steroid treatment (*upper panel*), a few months after completion of steroid treatment (*middle panel*) and 2 months after embolization treatment (*lower panel*).

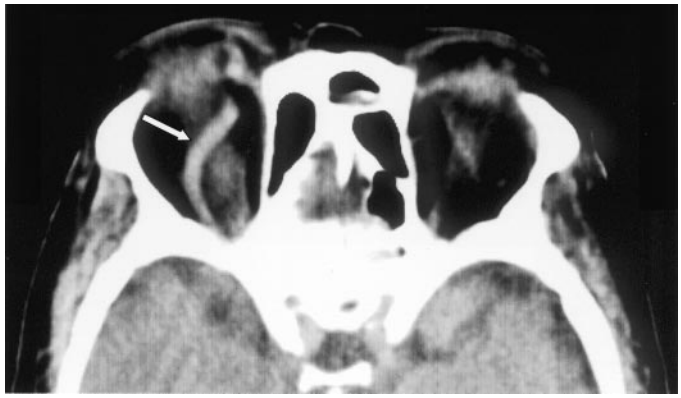

FIG. 2. High orbital axial section of CT scan showing prominence of the right superior ophthalmic vein (*arrow*).

TABLE 1. Clinical findings before and a few months after steroid treatment

	Before steroid treatment		After steroid treatment	
	Right eye	Left eye	Right eye	Left eye
Conjunctival injection	Severe	Severe	Severe	Mild
Eyelid/periorbital swelling	Moderate	Moderate	Moderate	Absent
Eyelid erythema	Absent	Absent	Absent	Absent
Injection of the lateral rectus vessels	Severe	Severe	Severe	Mild
Caruncle and plical swelling	Present	Present	Present	Absent
Chemosis	Moderate	Moderate	Severe	Absent
Upper eyelid retraction	Absent	Absent	Absent	Absent
Lagophthalmos	Present	Present	Present	Absent
Proptosis	Mild	Mild	Mild	Absent

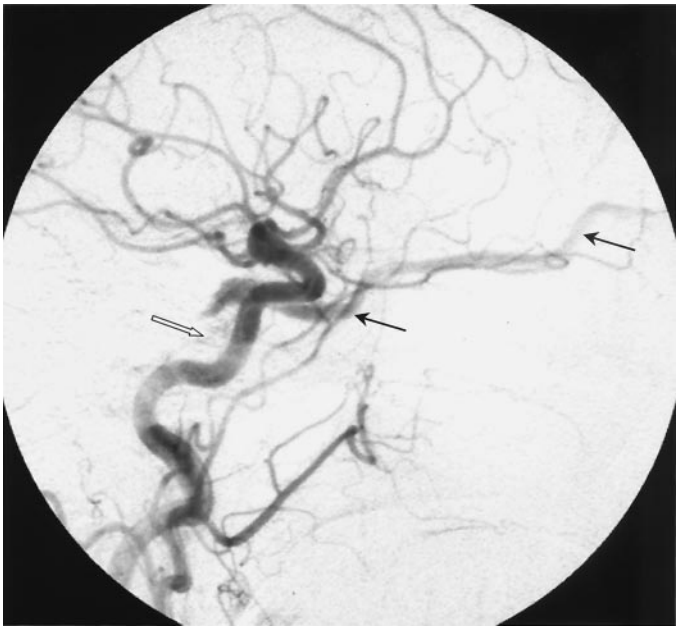

FIG. 3. Cerebral arteriography, arterial phase, lateral cranial projection, demonstrating the supply to the carotid cavernous fistula from multiple clival meningeal branches (*white arrow*) of the right ascending pharyngeal artery. *Black arrows* indicate the enlarged right superior ophthalmic vein.

vein (11). Asymmetric ocular involvement in Graves' disease may also result from an unequal response to the treatment of ophthalmopathy. In particular, an asymmetric response to steroid treatment is not exceptional.

It is generally agreed that when the ocular involvement is bilateral and clearly related to a clinical picture of Graves' disease, the diagnosis can easily be established. On the contrary, when the asymmetry of eye involvement is marked, particularly in euthyroid individuals (12), an anatomical assessment with sensitive diagnosis techniques, such as CT or magnetic resonance imaging, is required to exclude the presence of a space-occupying lesion in the orbit (13–16). The differential diagnosis of such lesions comprises a variety of serious and treatable conditions, including orbital pseudotumor (an idiopathic, inflammatory orbital syndrome), orbital cellulitis, primary or metastatic tumors of the orbit, and carotid cavernous fistulas (10, 15, 17).

Direct (or type A) carotid cavernous fistulas are usually single hole connections between the internal carotid artery and the ipsilateral cavernous sinus. Indirect (or dural) arteriovenous fistulas are relatively rare lesions, although they account for up to 15% of intracranial vascular malformations (18). They display a female predominance and are observed most frequently in perimenopausal women (19). Three types of indirect fistulas have been described (B, C, and D). Type B fistulas are supplied solely by dural branches of the internal carotid artery and are uncommon. Type C fistulas are supplied exclusively by dural branches of the external carotid artery. Type D fistulas are the most common dural type, receiving supply from meningeal branches of both the internal and external carotid arteries (20).

The mechanisms leading to the development of indirect carotid cavernous fistulas are still unclear. Available clinical (21) and experimental (22) data indicate the possible causative role of local vascular factors, such as venous hypertension, vascular stagnation, and sinus thrombosis, in promoting the development and proliferation of intrinsic arteriovenous shunts.

Although Graves' ophthalmopathy and the passive congestion of the orbit seen in carotid cavernous fistula are often clinically and radiologically confused (23), to the best of our knowledge the simultaneous occurrence of Graves' ophthalmopathy and carotid cavernous fistulas has never been reported. This is not surprising if the finding of cavernous carotid fistula in a patient with Graves' disease is to be considered purely coincidental. Actually there is no reason why a patient with Graves' ophthalmopathy could not also develop other orbital processes, such as a primary or metastatic tumor or a carotid cavernous fistula. Therefore, we believe that the endocrinologist should be aware that a clearly asymmetric response to steroid treatment in Graves' ophthalmopathy, such as that observed in our patient, requires reconsideration of the diagnosis and further evaluation with sensitive techniques.

The present case is unusual not only due to the clinical aspects described, but also because of the singularity of the medical decision-making process it required. Differential diagnosis generally aims to identify a disease by excluding other pathological conditions with similar manifestations. On the contrary, in our patient we had to consider the possible coexistence of two distinct diseases causing similar signs with different origins.

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