Section Editor: Neil R. Miller, MD

A Case of Extraocular Muscle Enlargement Causing Diplopia: Thinking Beyond Thyroid Eye Disease

Kian Eftekhari, MD, Collin M. McClelland, MD, Roberta E. Gausas, MD, Bo Jian, MD, PhD, John Woo, MD, Nicholas J. Volpe, MD, Madhura A. Tamhankar, MD

Dr. Eftekhari and Dr. McClelland:

A 64-year-old woman complained of insidious onset of binocular vertical diplopia for 4 weeks. The diplopia was present in upgaze and downgaze and was worse in the morning and improved as the day progressed. She denied pain with eye movements, eyelid droop, generalized weakness, or difficulty swallowing. Her medical history was significant for colon cancer that was treated with surgery and chemotherapy 4 years previously and cardiac arrhythmia. She had a history of narrow anterior chamber angles treated with laser peripheral iridotomies. She worked as a dog groomer.

The patient's visual acuity was 20/20 in the right eye, and 20/15 in the left eye, with normal color vision bilaterally. External examination showed bilateral eyelid retraction and lid lag in downgaze (Fig. 1). Evaluation of extraocular movements revealed mild decrease in elevation and depression of the right eye and normal motility of the left eye. Despite the lack of diplopia in primary gaze, her sensorimotor examination showed a 12–prism diopter (PD) right hypertropia that increased in downgaze to 16 PD. The hypertropia measured 10 PD in right gaze and 6 PD in left gaze. In addition, the patient had 18 PD of comitant exotropia. The pupils and funduscopic examination were normal in both eyes.

Orbital echography (A and B scans) showed mild, diffuse thickening of all extraocular muscles in both orbits and marked enlargement of the right inferior rectus muscle (Fig. 2). The right inferior rectus muscle showed low internal reflectivity on A scan, whereas the other extraocular muscles had high internal reflectivity. We considered the possibilities of thyroid eye disease, orbital pseudotumor, a mass lesion of the inferior rectus muscle, or a combination of these processes. Thyroid studies revealed an elevated thyroid stimulating hormone level of 6.12 mIU/L (normal, 0.40–5.50 mIU/L), a normal thyroid-stimulating immunoglobulin level, and negative acetylcholine receptor–binding antibodies. Magnetic resonance imaging (MRI) of the brain and orbits was obtained.

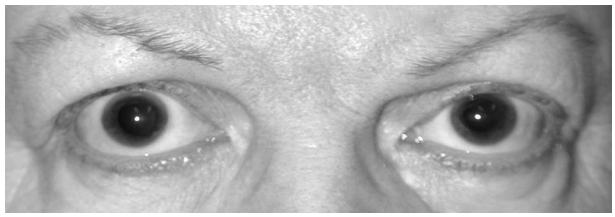

FIG. 1. At presentation, the patient has retraction of both lower eyelids and the right upper lid.

Dr. Woo:

MRI of the orbits revealed enlargement of the extraocular muscles bilaterally and a heterogeneously enhancing mass involving the midportion of the right inferior rectus muscle (Fig. 3). The mass measured approximately 10 mm in diameter. Brain MRI showed changes consistent with microvascular ischemia but was otherwise normal.

Dr. Eftekhari and Dr. McClelland:

In view of the patient's clinical presentation and the results of ultrasonography and MRI, a biopsy of the right inferior rectus muscle was performed.

Dr. Gausas:

The patient underwent biopsy of the right inferior rectus muscle via an inferior transconjunctival approach combined with a lateral canthotomy and cantholysis to obtain additional exposure. The periosteum of the orbital floor was elevated and incised to obtain access to the inferior rectus muscle from which multiple specimens were obtained.

Divisions of Oculoplastics Surgery (REG) and Neuro-Ophthalmology (MAT), Scheie Eye Institute (KE), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Department of Ophthalmology and Visual Sciences (CMM), Washington University School of Medicine, St Louis, Missouri; Pathology and Laboratory Medicine (BJ), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Division of Neuroradiology, Department of Radiology (JW), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and Department of Ophthalmology (NJV), Feinberg School of Medicine, Northwestern University.

The authors have no financial or conflicts of interests in the products mentioned in this case report.

Address correspondence to Madhura A. Tamhankar, MD, Scheie Eye Institute, 51 N. 39th Street, Philadelphia, PA 19104; E-mail: madhura.tamhankar@uphs.upenn.edu

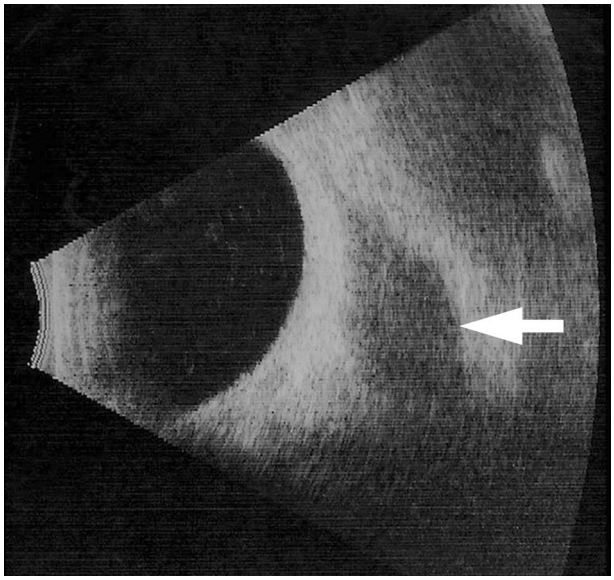

FIG. 2. B-scan ultrasound showing a massively thickened inferior rectus muscle (arrow).

Dr. Jian:

The biopsy specimen from the right inferior rectus muscle showed fibrotic skeletal muscle with a dense mononuclear infiltrate. The cells were intermediate to large in size with scant cytoplasm, round to slightly irregular nuclei, and finely granular chromatin without cytological atypia. No cytological atypia, mitotic figures, or necrosis were noted (Fig. 4). Immunohistochemical stains showed that these cells were positive for chromogranin, synaptophysin, and pancytokeratin (Fig. 5). Additionally, the cells were positive for CD10, and a substantial portion were Ki-67 positive, indicating active proliferation. Because of the patient's history of colonic adenocarcinoma, the slides from her hemicolectomy specimen were obtained from an outside institution and reviewed. The colectomy specimen was consistent with adenocarcinoma, and it did not have the same features of the mass in the right inferior rectus muscle. The final diagnosis was a neuroendocrine tumor most consistent with a carcinoid.

Dr. Eftekhari and Dr. McClelland:

The patient underwent a systemic screening for a primary lesion. Computed tomography (CT) of the chest and abdomen revealed a 2.5-cm mass in the lower lobe of the left lung and 2 suspicious lesions in the liver. Laboratory studies including urinary 5-hydroxyindoleacetic acid levels were normal, suggesting that she did not have a functional carcinoid syndrome. Biopsies of the lung and liver lesions revealed a low-to-intermediate grade neuroendocrine tumor, consistent in appearance with the specimen from the right inferior rectus muscle.

Final Diagnosis

Metastatic bronchial carcinoid.

Dr. Eftekhari and Dr. McClelland:

The patient received palliative stereotactic radiation therapy to the right orbit. She developed a large right hypotropia from radiation-induced fibrosis of the right inferior rectus muscle and underwent strabismus surgery.

Dr. Volpe and Dr. Tamhankar:

Intraoperatively, the patient had positive forced ductions in depression as well as elevation, indicating restriction of both superior and inferior rectus muscles of the right eye. Accordingly, she underwent recession of the right inferior rectus and superior rectus muscles. Postoperatively, the patient had significant improvement in her symptoms, with a larger field of single vision in primary gaze.

Dr. Eftekhari and Dr. McClelland:

A positron emission tomography/CT 9 months after the diagnosis revealed enlargement of the lung and liver lesions. The patient was placed on octreotide and underwent palliative hypofractionated stereotactic radiosurgery for her lung and liver lesions. However, the patient's disease progressed, and she ultimately succumbed to her illness less than 2 years after the diagnosis.

Dr. Tamhankar:

Carcinoid tumors comprise 0.49% of all malignancies and are derived from enterochromaffin cells that are found mainly in the gastrointestinal tract (67%) but also are present in the

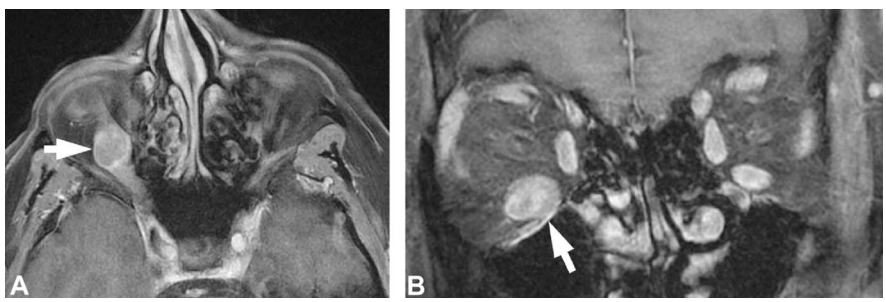

FIG. 3. Contrast-enhanced, fat-suppressed T1 axial (**A**) and coronal (**B**) magnetic resonance imaging reveals enlargement of the extraocular muscles in both orbits. There is a heterogeneously enhancing mass within the right inferior rectus muscle (arrows).

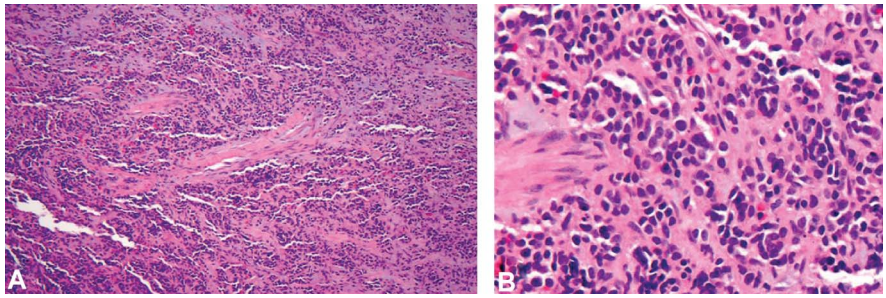

FIG. 4. Biopsy specimen from the right inferior rectus muscle showing fibrotic skeletal muscle with a dense infiltration of mononuclear cells with scant cytoplasm without atypia, mitoses, or necrosis (hematoxylin and eosin: ×10 (**A**), ×40 (**B**)).

bronchopulmonary tract (25%), ovaries, biliary tract, and testes (1). The term *karzinoide* was first used by Oberndorfer in 1907 to classify these tumors as benign compared with the more malignant intestinal adenocarcinoma (1). Carcinoid tumors commonly are slow growing, although they can be aggressive and lethal. The most common site for carcinoid metastases is the liver, while ocular metastases are rare (2,3). In patients with metastatic carcinoid, the 5-year survival is approximately 38% (1). About 10% of patients with carcinoid tumors secrete vasoactive substances that can lead to the carcinoid syndrome characterized by paroxysmal facial flushing, diarrhea, asthma, cardiac arrhythmias, and cardiac valvular abnormalities (1).

Carcinoid tumors comprise 4%–5% of orbital metastases (2) and 1% of uveal mestastases (3). There are at least 33 reported cases of carcinoid metastatic to the orbit, involving one or more extraocular muscles, the retrobulbar soft tissues, or a combination of both (4,5). Previous studies have reported that bronchial carcinoid tumors are more likely to metastasize to the uveal tract and gastrointestinal carcinoid tumors tend to metastasize to the orbit (6–8). However, there are reports of bronchial carcinoids metastasizing to the orbit (5,9–12). The apparent association between the site of origin of the carcinoid tumor and the site of metastasis may reflect the frequency of gastrointestinal and bronchial carcinoid tumors rather than a true relationship.

An interesting aspect of our case was that the orbital metastasis was the presenting feature of an undiagnosed primary neoplasm. In a large series of orbital carcinoid metastases, 69% of patients had a known carcinoid prior to presentation (4). On average, these patients were diagnosed with the primary carcinoid tumor 10 years before presenting with orbital metastases. An analysis of published data revealed that about one-fifth of patients (22%) with orbital carcinoid metastases present with orbital disease before discovery of the primary tumor (4).

The most common presenting symptom of carcinoid tumor metastatic to the orbit is diplopia, followed by decreased vision, ptosis, and pain. In our patient, the differential diagnosis for diplopia and an enlarged extraocular muscle included a neoplasm, thyroid eye disease, and idiopathic orbital inflammatory syndrome (IOIS). The absence of pain and the insidious onset of her symptoms made IOIS unlikely. Thyroid eye disease was a diagnostic consideration in our patient because of the insidious onset of diplopia, the presence of eyelid retraction, diffuse enlargement of all hyperreflective extraocular muscles on ultrasonography, and an elevated thyroid stimulating hormone level. It is possible that our patient had thyroid eye disease. However, we were suspicious of another disease process for a variety of reasons: the pattern of her ocular misalignment indicated that her diplopia was due, in part, to paresis of the right inferior rectus muscle rather than restriction, the muscle had low internal reflectivity, and MRI demonstrated focal, heterogeneous enlargement of the right inferior rectus muscle, which is unusual for thyroid eye disease. In addition, the patient had a history of a colonic neoplasm, and a biopsy was necessary to exclude a malignancy of the inferior rectus muscle.

It is important for the clinician to be aware of the nonthyroid causes of extraocular muscle enlargement and to

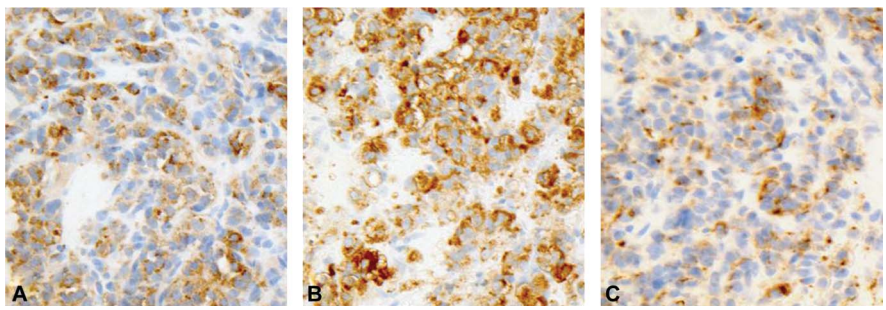

FIG. 5. The right inferior rectus biopsy specimen showing positivity for chromogranin (**A**), synaptophysin (**B**), and pancytokeratin (**C**), indicating a neuroendocrine tumor (**A**, **B**, **C**, ×40).

have a high index of suspicion in patients presenting with diplopia with atypical clinical and imaging features. This was highlighted in a series of 103 patients by Lacey et al (13) who reported that inflammatory, vascular, and neoplastic disorders (including melanoma, breast cancer, and lymphoma) were the most common nonthyroid causes of extraocular muscle enlargement, with rare disorders such as cysticercosis also in the differential diagnosis (13).

REFERENCES

1. **Modlin IM,** Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97:934–959.
2. **Goldberg RA,** Rootman J, Cline RA. Tumors metastatic to the orbit: a changing picture. Surv Ophthalmol. 1990;35:1–24.
3. **Shields CL,** Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. Ophthalmology. 1997;104:1265–1276.
4. **Mehta JS,** Abou-Rayyah Y, Rose GE. Orbital carcinoid metastases. Ophthalmology. 2006;113:466–472.
5. **Kiratli H,** Yilmaz PT, Yildiz ZI. Metastatic atypical carcinoid tumor of the inferior rectus muscle. Ophthal Plast Reconstr Surg. 2008;24:482–484.
6. **Shetlar DJ,** Font RL, Ordonez N, El-Naggar A, Boniuk M. A clinicopathology study of three carcinoid tumors metastatic to the orbit. Immunohistochemical, ultrastructural, and DNA flow cytometric studies. Ophthalmology. 1990;97:257–264.
7. **Aburn NS,** Whitehead K, Sullivan TJ. Bronchopulmonary atypical carcinoid tumour metastatic to the orbit. Aust N Z J Ophthalmol. 1995;23:241–244.
8. **Albert DM,** Zimmerman AW Jr, Zeidman I. Tumor metastasis to the eye. 3. The fate of circulating tumor cells to the eye. Am J Ophthalmol. 1967;63:733–738.
9. **Riddle PJ,** Font RL, Zimmerman LE. Carcinoid tumors of the eye and orbit. A clinicopathologic study of 15 cases, with histochemical and electron microscopic observations. Hum Pathol. 1982;13:459–469.
10. **Kulvin MM,** Sawchak WG. Tumor of orbit metastatic from malignant bronchial adenoma. Am J Ophthalmol. 1960;49:833–838.
11. **Nida TY,** Hall WA, Glantz MJ, Clark HB. Metastatic carcinoid tumor to the orbit and brain. Neurosurgery. 1992;31:949–952.
12. **Khaw P,** Ball D, Duchesne G. Carcinoid tumour of the orbital muscles. A rare occurrence. Australas Radiol. 2001;45:179–181.
13. **Lacey B,** Chang W, Rootman J. Nonthyroid causes of extraocular muscle disease. Surv Ophthalmol. 1999;44:187–213.