Kindred With Prominent Corneal Nerves Associated With a Mutation in Codon 804 of RET on Chromosome 10q11

Multiple endocrine neoplasia (MEN) type 2 has a potentially lethal outcome. The syndrome can be subdivided into types 2A, 2B, and familial medullary thyroid carcinoma (MTC). Both MEN type 2 and familial MTC have been associated with prominent corneal nerves, along with other features. Here we describe an incidental finding of prominent corneal nerves as the first manifestation of MEN type 2A associated with a codon V804M (RET; OMIM 171400) mutation.

Report of Cases. The proband, a 20-year-old male college student, presented in November 2006 accompanied by his parents for a second opinion regarding the recent diagnosis of lattice corneal dystrophy. Besides hyperlipidemia, migraines, and mild myopia, the patient was otherwise healthy and asymptomatic. Family history was negative for any medical conditions. Results of ocular examination including visual acuity assessment were normal apart from the presence of easily visible corneal nerves bilaterally (Figure 1). There was no evidence of lattice corneal dystrophy. On examination of the parents, the 53-year-old father had less prominent but still easily visible corneal nerves of which he was unaware. The patient and his father were evaluated for the MEN syndromes. Genetic testing in both revealed a mutation in the RET proto-oncogene at exon 14 (V804M) specific for MEN type 2A. Results of further evaluation of the son for MTC, hyperparathyroidism, and pheochromocytoma were negative. He had a prophylactic total thyroidectomy in June 2007. On histologic examination, there was no evidence of MTC or C-cell hyperplasia. The father also had a total thyroidectomy and lymph node dissection in October 2007. Two foci of MTC were found in the thyroid, together with tumor deposits locally in the soft tissue and level VI metastasis in the lymph node.

Screening of additional family members revealed a 63-year-old paternal great aunt of the proband with a remote history of carcinoid tumor found on incidental appendectomy. Although she tested positive for the V804M mutation in September 2007, results of thyroid ultrasound and fine-needle aspiration as well as calcitonin and resting metanephrine levels were normal. Results of ophthalmic examination were normal. She had a prophylactic thyroidectomy in January 2008. On pathological examination, there was no evidence of MTC. Screening of remaining family members was attempted (Figure 2); however, this was only partially successful because several were not able to be contacted while others declined to be tested for the mutation.

Comment. Corneal nerves are occasionally identifiable on careful biomicroscopic examination of the normal cornea and are seen commonly in a number of corneal conditions. In an otherwise normal cornea, the finding of prominent corneal nerves as exemplified in these 2 patients should arouse suspicion of an underlying MEN syndrome.

The prominent corneal nerves in the index case were observed and attributed to lattice corneal dystrophy, although the usual error is to confuse them with ghost stromal blood vessels.

Multiple endocrine neoplasia was first There are now 3 subtypes of the syndrome, MEN 2A and 2B and familial MTC. The incidence of MEN 2 is 1 in 30 000. Inheritance is autosomal dominant. The MEN 2 syndromes are caused by mutations in the RET proto-oncogene on chromosome 10q11. By different mechanisms, these mutations ultimately re-
sult in the activation of an intracellular tyrosine kinase domain that is involved in growth factor signaling.

The MEN 2A subtype accounts for 60% to 90% of MEN type 2. The incidence of MTC in this subtype is as high as 95%, with the possibility of multiple and/or multifocal tumors. The incidence of parathyroid tumors is 20% to 30% and of pheochromocytomas is 50%. The MEN 2A subtype differs from MEN 2B in that patients do not display the characteristic mucocutaneous neviomas, marfanoid habitus, and other skeletal abnormalities.

The treatment of patients who carry a mutation for one of the MEN syndromes requires an evaluation for all of the life-threatening manifestations, specifically MTC and pheochromocytoma.1 This would include determination of baseline calcitonin and carcinoembryonic antigen levels (MTC), 24-hour urine catecholamines, metanephrines and vanillylmandelic acid or plasma-free metanephrines (pheochromocytoma), serum calcium, and parathyroid hormone levels (parathyroid tumors). Based on laboratory testing, further imaging may be necessary. Management of thyroid cancer has been stratified based on codon mutation.2

Prominent corneal nerves are a well-known manifestation of MEN 2B and have been described in patients with MEN 2A.3,4 Among patients with MEN-2 disease, this specific codon mutation (V804M) has been associated with MTC but the association with prominent corneal nerves had not been noted until the study of a kindred with familial medullary carcinoma by Kasprzak et al in 2001.4 This particular mutation has highly variable expression of invasive MTC.5

While this kindred and the one described herein are in many respects similar, the diagnosis in the proband from the first kindred was made only on presentation of advanced thyroid carcinoma despite the presence of prominent corneal nerves noted some 15 years earlier.4 The corneal findings in the proband of our kindred led to identification of the syndrome and the decision to perform a prophylactic thyroidectomy. Because patients with MEN 2A do not exhibit the other classic phenotypic features of MEN 2B, it is essential that the clinical significance of prominent corneal nerves is recognized and acted on. Based on this case series, given that there were no other concerning features on history or examination of the index case, it is reasonable to consider genetic testing in all patients with prominent corneal nerves. However, as this study shows, not all individuals with this mutation will show evidence of prominent corneal nerves. To detect those with systemic manifestations of the MEN 2A syndrome, screening of family members is indicated regardless of the finding of normal corneas.

The astute ophthalmologist can play a potentially life-saving role in the early detection and rapid referral of patients with this finding. Regrettably, the prominent corneal nerves were not discovered in the father of the proband until his son’s presentation. He had already developed metastatic MTC.

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1. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1

Figure 2. Family pedigree of 2 related patients with prominent corneal nerves associated with a mutation in codon 804 (RET) on chromosome 10q11. The pedigree is incomplete because several members could not be contacted while others declined to be tested. MTC indicates medullary thyroid carcinoma; ?MTC, MTC status unknown; PCN, prominent corneal nerves; ?PCN, corneal nerve status unknown.
Intravitreous Ranibizumab (Lucentis) for Radiation Maculopathy

Radiation maculopathy is the most common cause of irreversible radiation-related vision loss in patients treated for choroidal melanoma. In our series, radiation maculopathy affects up to 52% of patients with posteriorly located tumors following plaque brachytherapy and appeared at a mean of 26 months after plaque brachytherapy.

Radiation maculopathy has been treated with nonsteroidal anti-inflammatory agents, laser photocoagulation, and steroids (topical, intravitreous, and peribulbar) with limited success. Anti–vascular endothelial growth factor (anti-VEGF) bevacizumab was recently found to be effective in controlling radiation-induced maculopathy and optic neuropathy.

This study investigates intravitreous ranibizumab (Lucentis) to treat radiation vasculopathy in the macula. The primary objective was to test the safety and tolerability of anti-VEGF intravitreous ranibizumab in the treatment of radiation retinopathy. The secondary objectives were to observe for changes in visual acuity, regression of retinopathy, and changes in tumor size.

Methods. US Food and Drug Administration, Investigational New Drug, and The New York Eye Cancer Center Institutional Review Board approvals were obtained. We describe the first 5 consecutive patients enrolled in a phase 1, open-label, Genentech-sponsored (Genentech, Inc, South San Francisco, California), single-center clinical trial.

Study Entry Criteria. In this study, all patients had been treated with palladium 103 for 7 consecutive days. Patients received a mean tumor apex dose of 75.3 Gy (range, 58.8-82.3 Gy) and a mean foveal dose of 61.9 Gy (range, 17.4-138.5 Gy) (to convert gray to rad, multiply by 100)

(Table 1). Our methods of radiation dosimetry, plaque placement, and follow-up have been described.

Inclusion criteria were as follows: (1) radiation treatment must have been given at least 6 months prior to enrollment; (2) initial visual acuity of 20/400 or better; (3) a subjective or objective loss of vision; and (4) no intraocular surgery within 60 days. In this series, no subjects had previously received intravitreous anti-VEGF or triamcinolone.

Radiation maculopathy was defined by intraretinal hemorrhage, intraretinal microangiopathy, neovascularization, cotton-wool spots, vascular sheathing, and/or cystoid macular edema.

Intravitreous Injections. Intravitreous injections of 0.5 mg of ranibizumab were required each month for 4 cycles, then modulated depending on the presence and persistence of radiation maculopathy. Treatments were deferred when examination revealed no radiation maculopathy and optical coherence tomography/scanning laser ophthalmoscopy (OPKO-OT1, Toronto, Ontario, Canada) showed no persistent macular edema.

Eyes were prepared with topical proparacaine hydrochloride and then povidone-iodine, followed by subconjunctival injection of lidocaine hydrochloride, 2%. While the anesthetic took effect, ranibizumab was drawn from the bottle into a 1-mL syringe, and a 30-gauge needle was then placed for injection. After a second application of anesthetic and antibiotic eyedrops, an eyelid speculum was placed; this was followed by transconjunctival injection through the pars plana. Optic nerve perfusion was checked by indirect ophthalmoscopy. After 30 minutes (±10 minutes), intraocular pressures were checked by Goldmann tonometry. Patients were prescribed antibiotic steroid eyedrops to be used 4 times a day for 7 days.

Main Outcome Measures. Outcome measures recorded at baseline and then monthly were best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study charts in Col...