SMALL CASE SERIES

Association Between Uveal Melanoma and Myotonic Dystrophy: A Series of 3 Cases

Myotonic dystrophy is the most common type of adult muscular dystrophy. It is an autosomal dominant multisystem neuromuscular disorder. Type 1 myotonic dystrophy is caused by unstable trinucleotide (CTG) expansion in the dystrophia myotonica-protein kinase (DMPK) gene. Type 2 myotonic dystrophy is caused by unstable tetranucleotide (CCTG) expansion in the zinc finger protein 9 (ZNF9) gene. Both subtypes are characterized by progressive skeletal muscle weakness and myotonia. Other clinical features include insulin resistance, cardiac conduction defects, testicular atrophy, respiratory insufficiency, early-onset cataracts, and varying degrees of cognitive impairment. Patients with myotonic dystrophy have been recognized as having an increased risk of various malignancies.1,2

Uveal melanoma is the most common primary intraocular malignant tumor in adults, and it is not until recently that patients with myotonic dystrophy have been encountered with an increased risk of developing uveal melanoma.3 In our study, we report 3 cases with the association between uveal melanoma and myotonic dystrophy.

Patients were evaluated at the Ocular Oncology Clinic of the Princess Margaret Hospital in Toronto, Canada, between April 1997 and April 2012. Patients underwent a comprehensive ophthalmologic evaluation, and the clinical appearance and ancillary testing of the intraocular tumor were compatible with choroidal melanoma. All cases had diagnosis of type 1 myotonic dystrophy confirmed by genetic testing and a positive family history of myotonic dystrophy.

Report of Cases. Case 1. A 55-year-old woman presented with a peripheral choroidal melanocytic lesion associated with orange pigment and subretinal fluid in the left eye. She had a previous diagnosis of juvenile-onset type 1 myotonic dystrophy, which was characterized by severe distal muscle weakness and myotonia, accompanied by cognitive impairment, Crohn disease, diabetes mellitus, osteoporosis, fatty liver, and rosacea. She also had a history of long recovery times and complications from general anesthetic. Her ocular history was relevant for bilateral blepharoptosis repair. Visual acuity was 20/400 in both eyes, secondary to cataract. Extraocular movements were restricted in all directions of gaze bilaterally. The lesion in the left eye measured 12.5 mm in largest base diameter. An ultrasonographic examination revealed an apical height of 3.5 mm with a medium to low internal reflectivity. The systemic status of this patient is severely deteriorated secondary to the multisystem involvement, and treatment has been deferred because she has a high anesthetic risk and, also, probably because any intervention would not prolong the survival of this patient. On her last visit, 6 months after the initial diagnosis, the apical height increased to 3.8 mm, and her visual acuity remained stable.

Case 2. A 49-year-old man presented with a choroidal melanocytic lesion with overlying orange pigment and subretinal fluid in the left eye (Figure 1). He had a history of adult-onset type 1 myotonic dystrophy that started in the third decade of life with moderate distal muscle weakness and myotonia, accompanied by polycystic kidney disease, renal insufficiency, deep vein thrombosis, and varying degrees of cognitive impairment. Both eyes had medium to low reflectivity. The systemic status of this patient is severely deteriorated secondary to the multisystem involvement, and treatment has been deferred because she has a high anesthetic risk and, also, probably because any intervention would not prolong the survival of this patient. Her ocular history was relevant for bilateral blepharoptosis repair. Visual acuity was 20/400 in both eyes, secondary to cataract. Extraocular movements were restricted in all directions of gaze bilaterally. The lesion in the left eye measured 12.5 mm in largest base diameter. An ultrasonographic examination revealed an apical height of 3.5 mm with a medium to low internal reflectivity. The systemic status of this patient is severely deteriorated secondary to the multisystem involvement, and treatment has been deferred because she has a high anesthetic risk and, also, probably because any intervention would not prolong the survival of this patient. On her last visit, 6 months after the initial diagnosis, the apical height increased to 3.8 mm, and her visual acuity remained stable.

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Case 3. A 38-year-old man presented with a choroidal melanocytic lesion with overlying orange pigment and subretinal fluid in the left eye (Figure 1). He had a history of adult-onset type 1 myotonic dystrophy that started in the third decade of life with moderate distal muscle weakness and myotonia, accompanied by polycystic kidney disease, renal insufficiency, deep vein thrombosis, and varying degrees of cognitive impairment. Both eyes had medium to low reflectivity. The systemic status of this patient is severely deteriorated secondary to the multisystem involvement, and treatment has been deferred because she has a high anesthetic risk and, also, probably because any intervention would not prolong the survival of this patient. Her ocular history was relevant for bilateral blepharoptosis repair. Visual acuity was 20/400 in both eyes, secondary to cataract. Extraocular movements were restricted in all directions of gaze bilaterally. The lesion in the left eye measured 12.5 mm in largest base diameter. An ultrasonographic examination revealed an apical height of 3.5 mm with a medium to low internal reflectivity. The systemic status of this patient is severely deteriorated secondary to the multisystem involvement, and treatment has been deferred because she has a high anesthetic risk and, also, probably because any intervention would not prolong the survival of this patient. On her last visit, 6 months after the initial diagnosis, the apical height increased to 3.8 mm, and her visual acuity remained stable.

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Figure 1. Funduscopic photograph of the left eye of a 49-year-old man (case 2) that reveals a slightly elevated choroidal melanocytic mass associated with orange pigment and subretinal fluid involving the macular area.
bosis in the left leg, myocardial infarction, and an amputated right leg secondary to vasculitis. He was pseudophakic in both eyes, with a visual acuity of 20/30 in the right eye and of 20/800 in the left eye. The lesion measured 2.1 mm in apical height and had medium to low reflectivity. Given the patient's systemic status and the size of the melanoma, transpupillary thermotherapy was performed, resulting in satisfactory tumor control. The apical height decreased to 1.6 mm, and visual acuity improved to 20/300 at the last visit, 30 months after the transpupillary thermotherapy. Unfortunately, the patient died secondary to multisystem complications 6 months later, without any evidence of systemic metastasis from the uveal melanoma.

Case 3. A 31-year-old man presented with a choroidal juxtapapillary melanocytic lesion in the right eye. The patient's condition was diagnosed previously as type 1 myotonic dystrophy when the patient was 25 years of age and subsequently with diabetes mellitus and fatty liver disease. Myotonic dystrophy was characterized by mild distal muscle weakness and myotonia. A dome-shaped lesion with medium to low internal reflectivity and a maximum height of 3.9 mm was found using ultrasonography. Stereotactic radiotherapy with 7500 cGy was delivered in 25 fractions. Subsequently, radiation retinopathy and optic neuropathy developed, and his visual acuity decreased to counting fingers (Figure 2). Eleven years after the initial lesion was treated, a new lesion was found in the contralateral eye. His visual acuity was 20/25 in the left eye. The lesion was juxtapapillary, associated with orange pigment and subretinal fluid (Figure 3). Ultrasonography revealed a maximum thickness of 1.25 mm and medium to low internal reflectivity. The clinical diagnosis was compatible with choroidal melanoma. Because of the poor residual vision in the contralateral eye and the possible visual consequences of any intervention, it was decided to closely observe this lesion. After 2 years, the tumor increased in size (Figure 4) to 2.66 mm, and treatment with iodine-125 brachytherapy was performed. Local tumor control in both eyes and sight preservation (20/25) in the left eye have been achieved to date (1 year).

Comment. Patients with myotonic dystrophy have an increased overall cancer risk, with a demonstrated higher risk of endometrial, brain, ovarian, colon, and thyroid cancer.2,3 Thymoma, insulinoma, leukemia, lymphoma, and stomach cancer have also been reported.2,3 In a recent study3 of 307 patients with myotonic dystrophy, 2 cases of uveal melanoma were found. This was estimated to be a 28 times greater probability of developing uveal melanoma compared with the general population.3 We report 3 cases that support the association between uveal melanoma and myotonic dystrophy. The 31-year-old man (case 3) presented with uveal melanoma in the
right eye and was found with a second primary uveal melanoma in the contralateral eye 11 years after the initial diagnosis. The lifetime probability of bilateral uveal melanoma has been estimated to be 1.35 per billion. Within the population of Canada (34 million), the number of patients expected to develop bilateral uveal melanoma in their lifetimes would therefore be only 0.046 ($1.35 \times 10^{-9} \times 34 \times 10^6$). The joint probability of the occurrence of both bilateral uveal melanoma and myotonic dystrophy (estimated incidence of 1.25 in 10,000 in the same individual would be 0.16 per trillion ($1.35 \times 10^{-9} \times 1.25 \times 10^{-9}$), which is too remote to be compatible with the assumption that both entities arise independently in random fashion. The fact that 1 of our 3 cases is bilateral would seem to support the association between the 2 entities.

Despite well-known genetic defects, the pathophysiology of the tumorigenesis in these patients remains unknown. Recently, type 1 myotonic dystrophy and female sex, but not nucleotide repeat expansion size, were associated with increased risk of developing tumors. Interestingly, the nucleotide expansion in both type 1 myotonic dystrophy and type 2 myotonic dystrophy occur in the noncoding region of the DMPK and ZNF9 genes, respectively. This indicates that they are transcribed but do not alter the protein-coding portion of the gene. The mutant messenger RNA is sequestered in the nucleus and alters the normal function of RNA splicing factors, subsequently affecting numerous downstream targets. The proposed association for the increased risk of uveal melanoma in patients with myotonic dystrophy relates to the dysregulation of the Wnt/β-catenin signaling pathway. This pathway is involved in the inhibition of apoptosis and the promotion of cellular proliferation and migration, and it has been demonstrated to be altered in a wide spectrum of neoplasms present in patients with myotonic dystrophy, including uveal melanoma. β-Catenin is a cell membrane protein of normal cells, but it can also be expressed in the cytoplasm and nucleus of malignant cells. The inhibitor of DNA binding 2 (IκBα), a transcriptional target of β-catenin, is highly expressed in normal uveal melanocytes. It encodes a downstream regulator of the Wnt/β-catenin pathway, and its downregulation has been associated with epithelioid cell differentiation and metastatic death in patients with uveal melanoma. Another study demonstrated immunofluorescent staining for β-catenin in 22 of 82 samples (26.8%) of primary uveal melanoma. A statistically significant correlation was found between strong immunoreactivity to β-catenin and absence of metastasis, with no patient dying from metastasis in that subgroup. Conversely, increased expression of β-catenin was determined in the plasma membranes of class 2 (aggressive-epithelioid type) uveal melanoma and related to poor prognosis. These contradictory results demonstrate that evidence is controversial regarding β-catenin expression as being implicated in the relationship between myotonic dystrophy and uveal melanoma in the same individual.

In conclusion, this case series contributes to the recently reported association between myotonic dystrophy and uveal melanoma. We propose that all patients with both type 1 and type 2 myotonic dystrophy be periodically evaluated by an ophthalmologist given their higher incidence of cataract and their somewhat increased propensity to harbor uveal melanoma compared with the general population.

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A previously unrecognized adverse effect of the osteoporosis drug risedronate sodium (Actonel; Warner Chilcott Co, LLC) was observed in 2 unrelated patients who developed squamous metaplasia (epidermidalization) of their conjunctival epithelium, a vision-threatening condition, which resolved after discontinuation of the drug.

**Report of Cases. Case 1** An 80-year-old white woman from Philadelphia, Pennsylvania presented with conjunctival plaques (Figure 1A and B). Both eyes were affected with white plaques or deposits in the inferior fornix, without symblepharon. Her medication history showed the current use of the osteoporosis drug risedronate sodium for osteopenia. Additional medications included diuretics. A biopsy disclosed an acanthotic conjunctival epithelium, resembling epidermis with a thick layer of surface keratin, a prominent granular cell layer, and the absence of goblet cells with subepithelial chronic inflammation (Figure 1C and D). The results of an immunofluorescence study were negative for IgA, IgG, and C3. This, together with the results of a histopathologic examination, eliminated ocular cicatricial pemphigoid as a diagnosis. The histopathologic diagnosis was conjunctival epidermidalization, which resolved completely after 1 month following discontinuation of risedronate sodium.

**Case 2.** A 62-year-old African American woman from Syracuse, New York, presented with a conjunctival mass in the inferior cul-de-sac of both eyes (Figure 2A and B). The lesion rapidly increased in size, was not in a sun-exposed area, and was pearly gray in color. Other mucosal surfaces were not in...