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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

Superior oblique myositis following targeted therapy for papillary thyroid carcinoma

Papillary carcinoma of the thyroid gland (PCTG) constitutes 80%–85% of thyroid cancers globally. Despite early lymphatic invasion, PCTG has a relatively indolent course and rarely metastasizes outside of the neck.[1] Metastasis to the brain from PCTG is even more uncommon and usually occurs in the context of widely disseminated disease. While the mainstay of treatment for intracranial metastasis from PCTG includes surgical excision and radiotherapy, recent advances into our understanding of the molecular pathways governing PCTG have facilitated development of novel targeted chemotherapeutics. We present a case of superior oblique myositis that was presumed secondary to treatment of widely metastatic PCTG with dabrafenib and trametinib therapy. To our knowledge this is the first such case in the English language ophthalmic literature.

Case

A 61-year-old man presented with subacute, progressive, right-sided peripheral vision loss preceded by a month of headaches, 2 episodes of right-sided scintillating scotomas, and a single episode of transient confusion. Past medical history was significant for PCTG treated with total thyroidectomy, bilateral paratracheal, and lateral compartment neck dissection, followed by radioactive iodine therapy. Initial evaluation revealed 20/20 visual acuity in both eyes (OU) and a right homonymous hemianopsia. Computed tomography (CT) scan of the brain showed vasogenic edema and a mass in the left parieto-occipital lobe. Magnetic resonance imaging (MRI) showed multifocal brain metastasis, including left parietal-occipital lesion. CT scan of the chest and abdomen revealed metastatic involvement of the lungs, hilar and mediastinal lymph nodes, kidneys, and liver. The patient was treated with oral prednisone and levetiracetam. After surgical resection the patient was treated with 10 rounds of whole brain radiotherapy followed by a single round of stereotactic radiosurgery to the residual left parietal-occipital lesion. BRAF V600E testing confirmed the mutation, and the patient was treated with 300 mg/day of dabrafenib and 2 mg/day of trametinib. The trametinib dosage was subsequently reduced to 150 mg/day owing to nausea and vomiting.

Eight months after his initial presentation, the patient endured 3 weeks of right frontal headache and new binocular vertical diplopia. On examination, visual acuity had decreased to 20/50 in the left eye (OS). There was a left hypertropia of 15 prism diopters OS. Cerebrospinal fluid analysis was unremarkable with normal glucose, protein, leukocyte count, and negative malignant cells on cytology. Repeat CT scan of the head showed stable intracranial lesions. MRI of the brain and orbits revealed enhancement of the left superior oblique muscle and surrounding soft tissue (Figs. 1A and 1B). Owing to concerns for a superior oblique myositis secondary to dabrafenib and trametinib therapy, the patient was treated with a reduced dosage of these medications and initiated on a 30-day oral prednisone taper, which resolved the symptoms.

At a subsequent 2-month follow-up, the patient reported interval resolution of his right frontal headache and vertical diplopia. Unfortunately, the vertical diplopia recurred 1 week before the follow-up examination, coinciding with weaning of his prednisone therapy. His prednisone was increased and reweaned without recurrence of symptoms. Repeat MRI of the brain and orbits revealed decreased enhancement of the left distal superior oblique muscle in comparison with prior imaging (Fig. 1C).

Discussion

Thyroid cancer accounts for 1% of malignancies globally. PCTG is classified as a form of differentiated cancer that arises from thyroid follicular cells. The standard therapeutic approach to PCTG involves surgical resection followed by radioactive iodine ablation. Owing to the indolent course of PCTG and a high response rate to treatment, the prognosis for PCTG is excellent, with a 95% 5-year survival rate. Unfortunately, between 4%–15% of PCTGs remain resistant to standard treatment and metastasize to distant sites.[1] These aggressive PCTGs have a comparatively poor prognosis, necessitating the development of effective salvage therapies. Several novel therapeutics have been recently approved for treatment of aggressive PCTGs and are generally classified into 2 categories: small molecule-kinase inhibitors and immunotherapy.[2] Small-molecule kinase inhibitors are directed against intracellular signalling pathways that control cellular survival, proliferation, and differentiation, whereas cancer immunotherapies enhance the body's immune response against malignant cells.

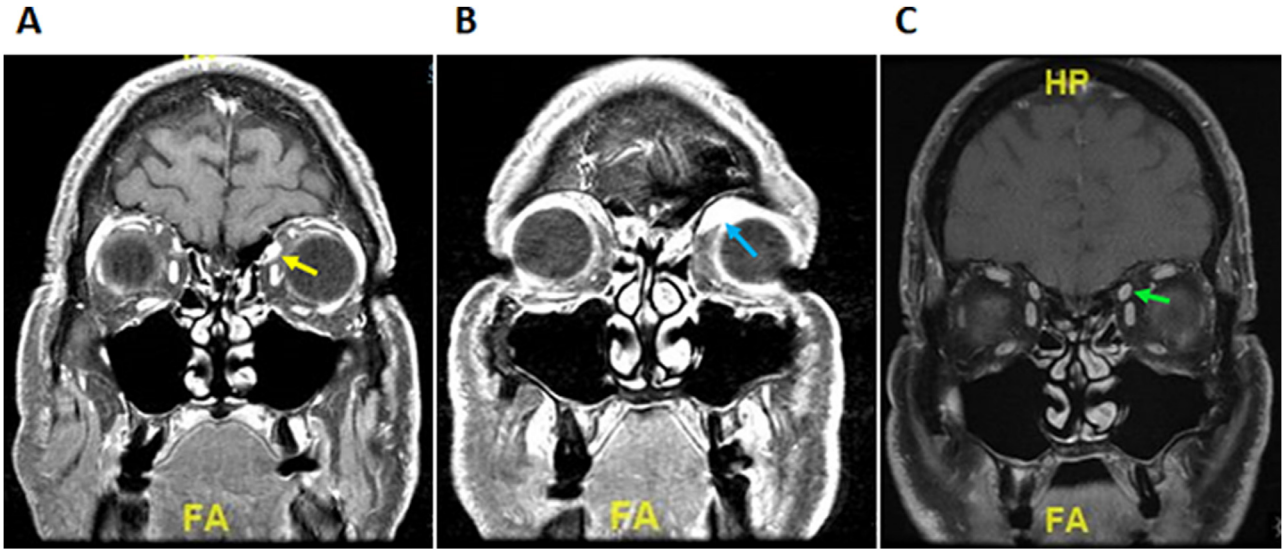

Fig. 1—Gadolinium-enhanced T1-weighted fat-suppressed coronal MRI images demonstrating enhancement of the left superior oblique muscle (A, yellow arrow) and anterior left superior orbital soft tissue (B, blue arrow). Repeat imaging at a 2-month interval demonstrated resolution of the left superior oblique muscle enhancement (C, green arrow).

Multitargeted kinase inhibitors (MKIs) are a class of small-molecular kinase inhibitors that target different components of the mitogen-activated protein kinase (MAPK) signalling pathway. One such MKI, dabrafenib, targets B-Raf and was initially developed for use in aggressive melanomas. Dabrafenib is often combined with an inhibitor of the downstream kinase MEK, trametinib. This combination therapy has recently been approved for advanced thyroid cancers, as 30%–70% of PCTGs contain activating BRAF mutations, most commonly V600E (a substitution of glutamic acid for valine at amino acid 600), leading to dysregulation of MAPK signaling.[2] Unfortunately, widespread use of MKI therapy is hampered by a high frequency of treatment-related adverse events (AEs).

The most common AEs associated with dabrafenib and trametinib combination therapy are dermatitis, pyrexia, arthralgia, fatigue, diarrhea, and vomiting. Several studies have also found high rates of ocular AEs with B-Raf and MEK inhibitors. B-Raf inhibitors, such as dabrafenib, are thought to disrupt ocular immune privilege, leading to uveitis, iritis, optic neuritis, and vitritis.[3] In contrast, MEK inhibitor–associated AEs arise through direct disruption MAPK signalling in various cellular compartments of the eye, leading to central serous chorioretinopathy, retinitis pigmentosa, and retinal venous occlusion.[3]

A review of the literature for MKIs causing myositis yielded only 3 previously reported cases, detailed further in Table 1.[4–6] Of these, only 1 case involved an extraocular muscle, with the patient developing an acute necrotizing lateral rectus myositis 4 weeks after being started on dabrafenib for Langerhans cell histiocytosis.

Furthermore, the systemic and ocular toxicities arising from MKIs and immunotherapy are managed similarly. Mild toxicities can be managed expectantly, whereas more severe effects require dose reduction or discontinuation with concomitant glucocorticoids therapy. Ultimately, clinicians

Table 1—Previously reported cases of MKIs causing myositis

Author	Journal	Year	Patient Details	Cancer Type	Targeted Therapy	Complication	Management of Complication	Outcome	Targeted Therapy Stopped?
Harrison et al.[4]	Rheumatology	2018	81 y/o F	Metastatic melanoma	Dabrafenib and trametinib	Dermatomyositis	Prednisone, IVIG	Declined further therapy for melanoma	Yes
van Landingham et al.[5]	Oncologist	2020	18 y/o M	Langerhans cell histiocytosis	Dabrafenib	Lateral rectus necrotizing myositis	Monitored	No recurrence	Yes
Karsan et al.[6]	Clinical medicine	2015	70 y/o M	Metastatic melanoma	Vemurafenib	Bell's palsy, rhabdomyolysis	Monitored	Abnormalities resolved after therapy cessation	Yes

MKI, multitargeted kinase inhibitors; M, male; IVIG, intravenous immunoglobulin.

should be aware of the pleomorphic presentations of MKI-associated AEs.

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Footnotes and Disclosure

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Junctional scotoma in moyamoya disease

A 66-year-old Hispanic woman presented to the eye clinic with chronic, progressively worsening vision in the right eye over 2 years associated with right-sided temporal headaches, cutaneous allodynia of the scalp, and jaw claudication. She denied fevers, chills, joint pains, nausea, photophobia, phonophobia, personal history of autoimmune disease, and family history of hereditary ophthalmological diseases. Her ocular history included pterygium removal from the OD. Seven years prior to presentation, she had an episode of light-headedness, blurry vision for 30 minutes, a severe headache, and mild weakness of the left hemiface and left body lasting 2 hours. She was evaluated by her primary care provider, the emergency department, and neurology; neuroimaging was recommended but never completed, and atypical migraine was considered.

At this presentation, her best corrected visual acuity was 20/400 OD and 20/20 OS. She had a 2+ relative afferent pupillary defect OD and optic disc pallor in the right eye with optic atrophy seen on magnetic resonance imaging of the brain and orbits. Fundoscopy of the left eye was normal. Automated perimetry showed visual field defects in each eye (Fig. 1). Erythrocyte sedimentation rate, C-reactive protein, and platelets were within normal limits. Computerized tomography angiography (CTA) was performed along with 3-dimensional volume-rendered CTA reformatting and angiography (Fig. 2), which demonstrated poor perfusion through the right supraclinoid segment of the internal carotid artery that was confirmed with angiography, leading to the diagnosis of moyamoya disease (MMD). Neurosurgery evaluated the patient and determined that the risks for undergoing an external carotid-internal carotid bypass outweighed the benefits at this time.

Discussion

MMD and moyamoya syndrome (MMS) are characterized by a diffuse narrowing of the internal carotid, middle cerebral, or anterior cerebral artery lumen.[1] The fine tangle of compensatory collateral vessels produces the distinctive cranial angiography. (*Moyamoya* is Japanese for "puff of smoke.") The classic patient is a young woman of Asian descent with a family history of medical issues similar to those demonstrated by our patient: temporal headache, jaw claudication, and progressive vision loss.

Etiologies for MMD and MMS include idiopathic, iatrogenic (i.e., radiation), atherosclerosis, and congenital. Twelve percent of cases are familial, and the disease has been associated with several polymorphisms of the RNF213 gene, which encodes a gene finger protein.[2] Although MMD and MMS are rare, this life-threatening disease is important to keep in the differential when a patient presents with ipsilateral optic atrophy.

Poor perfusion may result in optic nerve ischemia, which can result in the "morning glory disc" anomaly as the optic nerve develops. This finding is characterized by chorioretinal pigment changes surrounding the optic disc, an enlarged and funnel-shaped appearance of the optic disc, and central tuft of glia in the center of the optic disc.[3] Our patient is notable for the