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Metastatic neuroendocrine tumors mimicking as primary ocular disease

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ABSTRACT

Purpose: To report two cases of metastatic neuroendocrine tumors masquerading as primary ocular disease.
Observations: Case 1 is a 38-year-old man who was referred with subacute onset diplopia and fluctuating ptosis suggestive of myasthenia gravis. Case 2 is a 21-year-old man who presented with blurry vision and was found to have a pigmented ciliary body mass and retinal detachment suggestive of uveal melanoma. Both patients were ultimately diagnosed with metastatic neuroendocrine tumors.
Conclusions and Importance: Neuroendocrine tumors, though rare and infrequently metastatic to the eye and orbit, can initially present with ocular signs. A broad differential and careful consideration of ocular and systemic symptoms are critical in such challenging cases.

1. Introduction

Neuroendocrine tumors are rare neoplasms which arise from neuroendocrine cells in various organ systems, including the gastrointestinal (GI) tract, tracheobronchial tree, thymus, parotid, breast, ovary, and testis.[1,2] They have an incidence of 6.98 new cases/100,000/year. A majority of cases (50–75%) present with metastatic disease, most commonly to the liver, lymph nodes, or bone.[3,4] Metastases to the eye are rare but can involve the orbit or the uvea.[5,6] Neuroendocrine tumor metastases in the orbit and uvea can present atypically and mimic other diseases, making accurate and timely diagnosis challenging. We present two cases of neuroendocrine tumor metastases presenting with ocular signs suggestive of primary ocular diseases.

2. Findings

2.1. Case 1

A 38-year-old male presented with subacute onset diplopia and fluctuating ptosis of the right upper eyelid concerning for myasthenia gravis (MG). He endorsed generalized weakness, weight loss, and lower trunk pain. His visual acuity was 20/20 OU. Adnexal exam was notable for 2 mm ptosis of the right eye with normal levator function, negative lid fatigue, and absent Cogan lid twitch (Fig. 1A and B). No lateral flare or proptosis was noted. Sensorimotor exam revealed a large angle intermittent right exotropia and left hypertropia (Fig. 1C and D). Saccadic velocities, pupillary and funduscopic examination were normal. Orbital and adnexal exam revealed palpable mobile masses of the left orbit (Fig. 1E) as well as the scalp (Fig. 1F). Magnetic resonance imaging (MRI) of the brain/orbits revealed extraconal masses in the left orbit as well as involvement of right superior rectus/levator complex (Fig. 2). Due to concern for malignancy, a computed tomography (CT) scan of the chest abdomen and pelvis was obtained which showed multiple hypoattenuated liver lesions. A biopsy of both liver and scalp lesions revealed a low-grade carcinoid tumor. Whole body positron emission tomography scan demonstrated additional spinal and renal metastases. Systemic capecitabine/temozolomide for metastatic carcinoid with presumed GI origin was initiated. He was also started on intramuscular octreotide. Despite treatment, his disease burden continued to worsen, with increased size of his known metastases and new masses suggestive of spreading disease. His ocular exam remained stable. He developed multiple vertebral body compression fractures which resulted in severe cord compression of T5, T8, T10. The patient chose not to pursue additional aggressive treatment and was discharged to home hospice.

2.2. Case 2

A 21-year-old with no past medical history presented with two weeks of left eye pain and blurry vision. He denied flashes or floaters but

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reported acute loss of vision in the left eye 4 days prior to presentation. He additionally endorsed a cough for the last month. His best corrected visual acuity was 20/30 OD and 20/70 OS; intraocular pressure was 12 and 9. His left pupil was ovoid and nonreactive. Slit lamp exam of the left eye was notable for conjunctival injection, 3+ pigmented cell and 2+ flare, and a large pigmented ciliary body mass extending from approximately 6 o'clock to 10:30 with some internal vascularization (Fig. 3A). Dilated exam of that eye was notable for extensive subretinal fluid, hemorrhage, and exudates (Fig. 3A); the right eye was normal. Gonioscopy revealed erosion of the iris root with invasion of the angle. B-scan demonstrated a dome-shaped tumor arising from the ciliary body measuring 11.2mm × 12.77mm with low internal reflectivity and inferior retinal detachment (Fig. 3B). Due to the pigmented nature of the lesion and B-scan findings, initial concern was for uveal melanoma and imaging for staging was done.

Two weeks after initial presentation, he reported worsening vision and eye pain, as well as dyspnea and hoarseness. On repeat exam, his vision was light perception in the left eye and his intraocular pressure was 30. Slit lamp exam showed massive interval growth of the mass, which now appeared predominantly amelanotic and filled approximately 80% of his anterior chamber (Fig. 3C).

MRI of the brain/orbits showed enlarged retropharyngeal lymph nodes but no extension past the globe and no intracranial metastatic disease. CT scan of the chest, abdomen, and pelvis revealed a large left suprahilar mass, multiple pulmonary nodules, and multiple lesions in the pancreas (Fig. 3D). CT-guided biopsy of his mediastinal mass revealed a high-grade small cell neuroendocrine carcinoma (positive cytokeratin (CK AE1/AE3), synaptophysin on immunohistochemical staining) (Fig. 4). Chemotherapy with cisplatin/etoposide was initiated for metastatic neuroendocrine carcinoma of unknown primary.

Two weeks after his first round of chemotherapy, his mass had regressed but he had developed new neovascularization of his iris. One month later, he was seen with worsening left eye pain and found to have a diffuse hyphema and elevated intraocular pressure. He was offered enucleation or palliative radiation and chose to begin palliative radiation (20 Gy in 5 fractions) for pain and tumor control. His pain minimally improved with radiation and the patient eventually elected for enucleation. Histology of his left eye was consistent with metastasis of high-grade small cell neuroendocrine carcinoma (Fig. 5).

Approximately 6 months after his initial presentation, he developed an anterior uveitis in the previously unaffected right eye. He was found to have a new metastatic lesion to the inferior ciliary body in his right eye. Repeat imaging demonstrated multiple intracranial metastases. He completed whole brain radiation therapy and radiation to the right eye. He was also found to have lytic lesions to the left scapula, humerus, and sixth rib. He then developed bilateral leg weakness and was found to have metastatic lesion to his lumbar spine causing spinal canal compromise. He was started on palliative topotecan infusions and dexamethasone for his cord compression. Because he had continued progression on topotecan, he was switched to paclitaxel and enrolled in a clinical trial for nivolumab in the setting of relapsing small cell neuroendocrine tumor. He was hospitalized for worsening respiratory status due to increasing tumor burden and atypical pneumonia and expired due to respiratory failure.

3. Discussion

Here, we present two cases in which metastatic neuroendocrine tumors to the orbit and uvea led to atypical presentations mimicking primary ocular diseases. The lack of non-ocular symptoms in both cases may have caused a delay in diagnosis. In the first case, the patient presented with variable strabismus and ptosis, leading to suspicion for myasthenia gravis. Although he had no known history of malignancy, closer exam revealed a left inferior orbital mass as well as palpable scalp

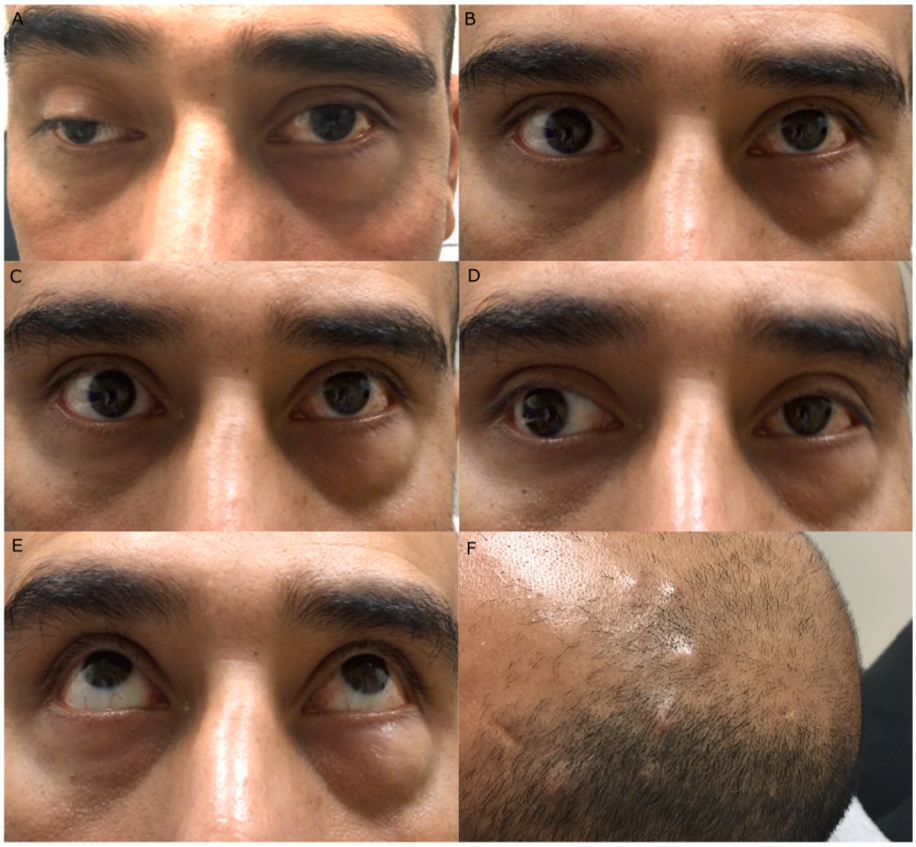

Fig. 1. Case 1 Clinical Photos. (A–B) Variable ptosis. (C–D) Variable strabismus. (E) Left inferior orbital mass. (F) Scalp lesions.

lesions which increased concern for metastatic lesions to the orbit. Neuroendocrine tumors metastasize to the orbit in 22% of patients and orbital mass is the presenting sign in 31% of patients.[1] Although orbital metastatic neuroendocrine tumors do typically present as a mass (80%) or diplopia (27%), they have not, to our knowledge, been previously reported to cause fluctuating ptosis and diplopia mimicking myasthenia gravis.[1] Notably, cutaneous metastases in the setting of neuroendocrine tumor, which was noted in our first case, are rare but have been previously reported and typically present as firm, tender papules.[7] This case emphasizes the importance of careful examination of the orbit and adnexa when evaluating patients complaining of fluctuating diplopia.

Recognition of symptoms as suspicious for metastatic disease allows initiation of workup for a primary tumor. For neuroendocrine tumors, the majority (85%) of metastatic disease to the orbit is of gastrointestinal origin.[1,8] While our patient did not present with any symptoms of carcinoid syndrome that would suggest neuroendocrine malignancy, patients who present with suspected neuroendocrine metastasis to the orbit likely warrant close imaging and examination of their GI system. Expedient identification of the source of the orbital metastasis is important so patients can be initiated on treatment, which can be life-saving and improve patient quality of life.

Similarly, Case 2 initially presented with signs masquerading as a different condition, in this case a ciliary body melanoma. The vast majority of uveal metastatic neuroendocrine lesions are nonpigmented, however, some lesions can present with significant pigmentation.[6,9,10] As in this case, when pigmented, these lesions can closely resemble primary malignant melanomas clinically as well as on ultrasound evaluation.[6] However, the patient quickly presented back to our clinic with very rapid progression which was not consistent with melanoma. In the two weeks since initial presentation, his tumor evolved from a heavily pigmented mass only visible on dilated exam to an amelanotic mass filling the majority of his anterior chamber, leading to his ultimate diagnosis of uveal metastasis. Primary neuroendocrine tumor is a rare cause of uveal metastases, comprising only 2.2% of uveal metastases.[10] Unlike orbital metastases, the majority of these are bronchopulmonary in origin. Similar to our patient, most patients (56%) have no prior diagnosis of neuroendocrine tumor at the time of their ocular presentation.[10]

This patient was found to have a large mediastinal mass that was biopsied to diagnose primary neuroendocrine tumor. If no other lesion is amenable to biopsy, fine-needle aspiration biopsy of the ocular lesion may provide a definitive diagnosis.[6,9,10] Immunohistochemical analysis for positive immunoreactivity for cytokeratin, synaptophysin, chromogranin, and calcitonin can establish the diagnosis of a neuroendocrine metastasis if routine light microscopic evaluation is atypical or non-diagnostic.[11] In our patient's case, histology did not reveal the specific etiology of the unusual pigmented appearance of his left eye tumor given the level of necrosis in his eye from prior palliative radiation at the time of enucleation. However, other cases of pigmented ciliary body neuroendocrine tumors have reported histology demonstrating RPE and pigmented ciliary epithelium hyperplasia which are likely responsible for the pigmented appearance of such lesions.[9] Beyond the atypical presentation with a pigmented mass that progressed rapidly, his case was also remarkable for the development of a late metastasis to his other ciliary body. His presentation with metachronous bilateral ciliary body metastases is notable because the ciliary body is not a common site of uveal metastases, with less than 7% of metastases to the eye involving the ciliary body.[9]

The treatment of metastatic ocular or orbital tumors depends on the status of the eye and the patient's systemic disease. Identifying cutaneous metastases such as the scalp lesions in Case 1, and orbital or ocular metastases is important in staging of disease. If there is widespread disease, chemotherapy is indicated. Treatment options also include surgery and radiation therapy.[9] In the case of our patients, both were initiated on systemic chemotherapy, although Case 2 ultimately underwent palliative radiation and eventual enucleation of the left eye. Neuroendocrine tumors can be part of familial syndromes and patients should be evaluated for multiple endocrine neoplasia syndrome 1 or 2 (10% of cases), von Hippel-Lindau syndrome, and neurofibromatosis 1.[1] Case 2 was referred to genetics and was undergoing evaluation.

In conclusion, we present two cases of atypical presentations of metastatic neuroendocrine tumors masquerading as other conditions. These cases demonstrate the importance of careful consideration of ocular and systemic symptoms and maintenance of a broad differential. Neuroendocrine tumors are rare tumors and rarely metastasize to the orbit or globe, but ocular symptoms can be the presenting sign of disease in up to one third of cases. These lesions can present atypically as pigmented lesions, and immunohistochemical stains can help confirm the diagnosis. The most common origin of orbital metastatic tumors is gastrointestinal, while intraocular metastatic tumors originate from

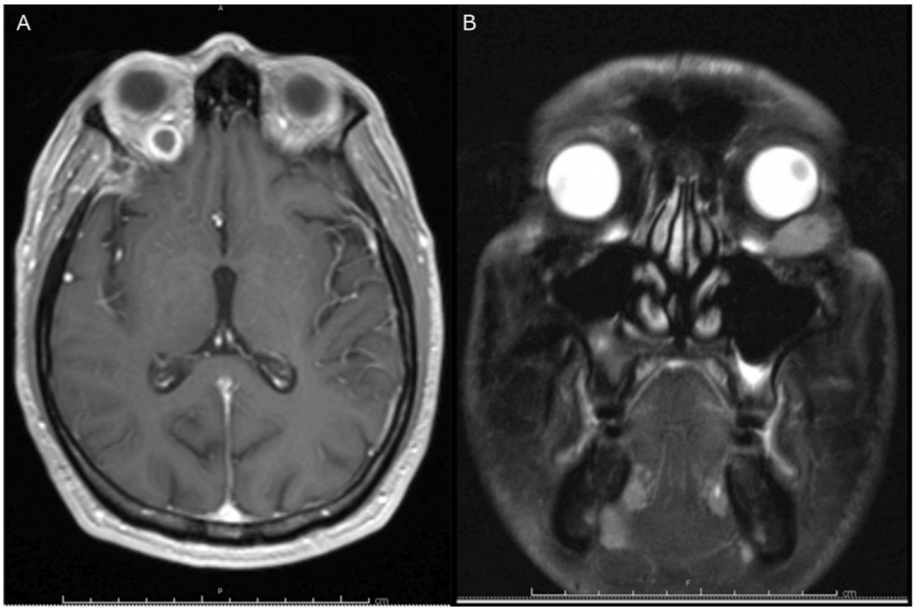

Fig. 2. Case 1 MRI Imaging. (A) T1 post-contrast axial magnetic resonance imaging (MRI) demonstrating an enhancing superior right orbital mass. (B) T2 axial MRI demonstrating left inferior orbital mass.

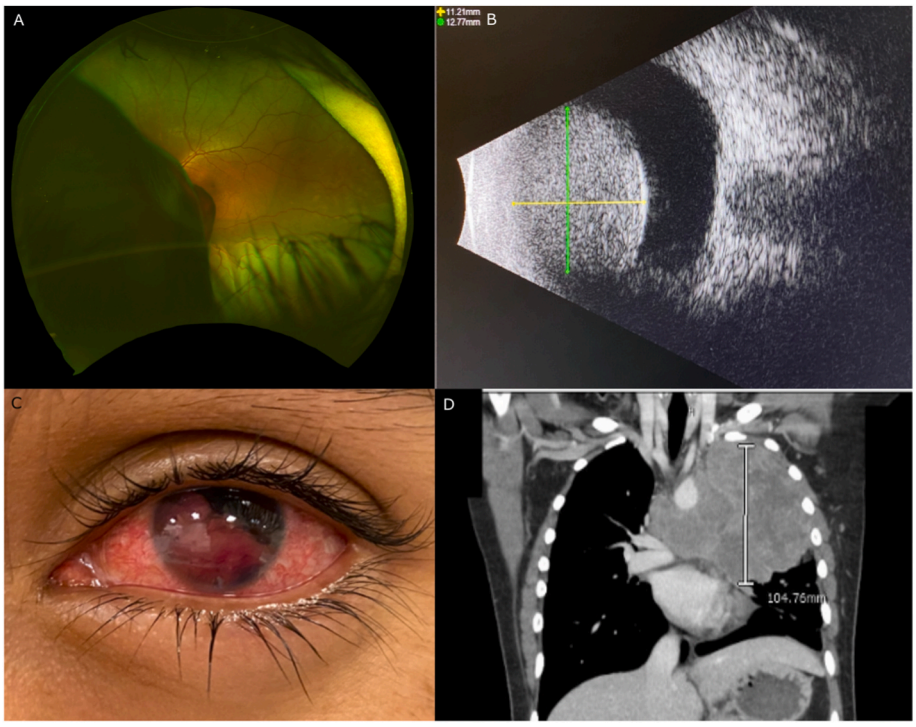

Fig. 3. Case 2 Clinical Photos and Imaging. (A) Left eye fundus photos demonstrating nasal pigmented ciliary body mass and inferior exudative retinal detachment. (B) B-scan of left eye demonstrating large ciliary body mass and inferior retinal detachment. (C) External photo of left eye two weeks after presentation with amelanotic tumor filling the anterior chamber. (D) Computed tomography scan of the chest, abdomen, and pelvis demonstrating large metastatic left suprahilar mass.

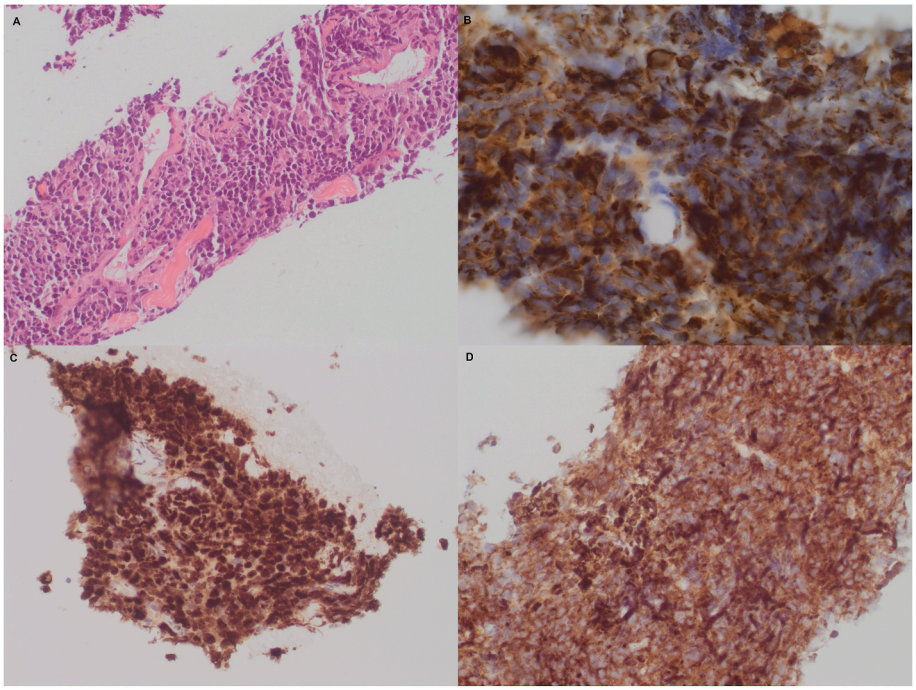

Fig. 4. Mediastinal Biopsy Histology. (A) Hematoxylin and eosin stain (200x) shows malignant small cells with scant cytoplasm, salt and pepper chromatin, nuclear molding, and frequent mitoses consistent with high grade small cell neuroendocrine carcinoma. (B) Cytokeratin AE1/AE3 (400x) is punctate positive in tumor. (C) Ki67 (200x) shows high proliferation index (>90% tumor cells in cycle). (D) Synaptophysin (200x) is positive in tumor.

tracheobronchial tissue. Chemotherapy and external beam radiation therapy are the mainstays of treatment, but surgical treatment can sometimes be appropriate depending on the location and extent of the metastasis.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

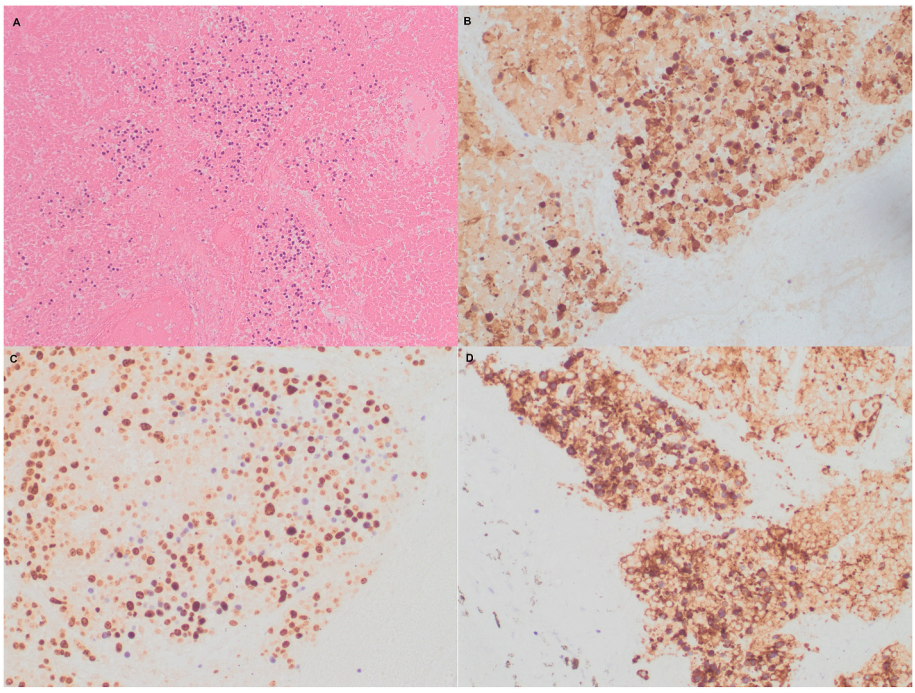

Fig. 5. Left Eye Metastasis Histology. (A) Hematoxylin and eosin stain (100x) shows small subsets of viable tumor cells in a background of extensive necrosis consistent with treatment effect. (B) Cytokeratin AE1/AE3 (200x) is punctate positive in tumor. (C) Ki67 (200x) shows high proliferation index (>90% tumor cells in cycle). (D) Synaptophysin (200x) is positive in tumor.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors have no financial disclosures.

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References

1. Mehta JS, Abou-Rayyah Y, Rose GE. Orbital carcinoid metastases. *Ophthalmology*. 2006;113(3):466–472. https://doi.org/10.1016/j.ophtha.2005.10.051.
2. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39(6):707–712. https://doi.org/10.1097/MPA.0b013e3181ec124e.
3. La Salvia A, Persano I, Trevisi E, et al. Ocular metastases from neuroendocrine tumors: a literature review. *Semin Oncol*. 2020;47(2-3):144–147. https://doi.org/10.1053/j.seminoncol.2020.04.003.
4. Jensen R, Norton J. Carcinoid tumours and the carcinoid syndrome. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer Principles and Practice of Oncology*. fifth ed. Lippincott- Raven Publishers; 1997:1704–1723.
5. Shetlar DJ, Font RL, Ordóñez N, El-Naggar A, Boniuk M. A clinicopathologic study of three carcinoid tumors metastatic to the orbit. *Ophthalmology*. 1990;97(2):257–264. https://doi.org/10.1016/S0161-6420(90)32617-9.
6. Fan JT, Buettner H, Bartley GB, Bolling JP. Clinical features and treatment of seven patients with carcinoid tumor metastatic to the eye and orbit. *Am J Ophthalmol*. 1995;119(2):211–218. https://doi.org/10.1016/S0002-9394(14)73875-9.
7. Dhingra R, Tse JY, Saif MW. Cutaneous metastasis of gastroenteropancreatic neuroendocrine tumors (GEP-Nets). *JOP*. 2018;19(5). http://www.ncbi.nlm.nih.gov/pubmed/30405324.
8. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003;97(4):934–959. https://doi.org/10.1002/cncr.11105.
9. Bardenstein DS, Char DH, Jones C, Crawford JB, Miller TR, Riekhof FT. Metastatic ciliary body carcinoid tumor. *Arch Ophthalmol*. 1990;108(11):1590–1594. https://doi.org/10.1001/archopht.1990.01070130092038.
10. Harbour JW, De Potter P, Shields CL, Shields JA. Uveal metastasis from carcinoid tumor: clinical observations in nine cases. *Ophthalmology*. 1994;101(6):1084–1090. https://doi.org/10.1016/S0161-6420(94)38030-4.
11. Eagle RC, Ehya H, Shields JA, Shields CL. Choroidal metastasis as the initial manifestation of a pigmented neuroendocrine tumor. *Arch Ophthalmol*. 2000;118(6):841–845. https://doi.org/10.1001/archopht.118.6.841.