Clinical Reasoning: A 59-year-old man with multifocal strokes, then subsequent painful eye movements and diplopia

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SECTION 1

A 59-year-old man, who was a nonsmoker, with persistent hematuria and history of multifocal strokes was admitted for progressive painful right eye movements and binocular vertical diplopia.

He initially presented 2 months prior with acute-onset left-sided numbness and hemiparesis. He denied any weight loss or constitutional symptoms, but did report persistent hematuria several weeks prior to presentation. His general examination did

not reveal any abnormal skin findings, organomegaly, lymphadenopathy, or palpable masses. His MRI showed extensive embolic-appearing infarcts in multiple vascular territories most concentrated in the right middle cerebral artery region (figure, A).

Questions for consideration:

1. What are the potential stroke mechanisms for multifocal infarcts on MRI?
2. What stroke workup is recommended?

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(A) Initial MRI. Axial fluid-attenuated inversion recovery sequence image shows multifocal strokes in the right greater than left middle cerebral artery territories. (B) Follow-up MRI 2 months later. Axial T1 postcontrast MRI demonstrates a new area of enhancement in the left occipital lobe without mass effect, favoring subacute late ischemia over metastasis. (C) Coronal CT of the orbits with contrast shows marked thickening of right inferior rectus muscle and adjacent soft tissue (*) and enlargement of the left superior rectus (longer white arrow) and slightly enlarged left inferior rectus (shorter white arrow) muscles. (D) Biopsy of proximal thigh mass. Hematoxylin & eosin, 20 $\times$. The neoplastic cells diffusely infiltrate the skeletal muscle in a discohesive fashion. The cells are plasmacytoid, with irregular, eccentrically placed nuclei. Mitotic figures—including atypical forms—are prominent (arrowheads), and occasional cells demonstrate intracellular mucin (arrows).

SECTION 2

Potential mechanisms for multifocal, embolic-appearing infarcts in different vascular territories include cardioembolism, hypercoagulability of malignancy or inherited hypercoagulability, paradoxical venous thromboembolism, diffuse intracranial atherosclerosis, or vasculitis.

The patient had basic stroke workup, including a normal magnetic resonance angiogram of the head and neck, and transthoracic and trans-esophageal echocardiograms, which were unremarkable except for a patent foramen ovale. Given the appearance of his strokes and hematuria, he also had extensive malignancy workup. He had markedly elevated d-dimer and carcinoembryonic antigen (CEA), and his urine cytology showed atypical cells, though recent catheter instrumentation confounded these findings. He had a cystoscopy, with visibly normal mucosa, so biopsies were not performed. His hematuria was attributed to his benign prostatic hyperplasia. He had a CT chest, abdomen, pelvis, and MRI abdomen, which were all normal. Hypercoagulable workup (antiphospholipid antibody, homocysteine, factor V Leiden, prothrombin gene mutation, antithrombin III, protein C and S) was also negative. He was ultimately discharged on empiric enoxaparin for presumed hypercoagulability of occult malignancy and arranged for outpatient colonoscopy.

Two months later, the patient developed pressure-like pain with right eye movements in all directions and binocular vertical diplopia. He was evaluated by ophthalmology as an outpatient. Best-corrected visual acuity was 20/60 right eye and 20/40+1 left eye. Intraocular pressure was 24 (normal < 22) right eye and 15 (normal) left eye. There was no afferent pupillary defect and color vision in both eyes was normal. He had complete right eye elevation and moderately severe abduction deficits. A large angle left hypertropia in primary, down, and left gazes with a mild esotropia on downgaze were found. There was no ptosis, but there was superotemporal chemosis and injection in the right eye. The fundi were normal without pathologic optic disc cupping. Other than his previously noted left face, arm, and leg hemiparesis and sensory loss, the remainder of his neurologic examination was unremarkable. Two days later, his outpatient colonoscopy was performed. He had 3 sessile polyps, which were biopsied, but otherwise normal mucosa.

Questions for consideration:

1. Given the history and new examination findings, what is the differential diagnosis at this time for diffuse ophthalmoparesis?
2. What additional diagnostic tests would be most helpful?

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SECTION 3

Diffuse ophthalmoplegia can be caused by a diffuse brainstem process, combined ocular motor palsies, neuromuscular junction dysfunction, or an abnormality affecting multiple extraocular muscles. Given the right eye superior temporal chemosis, injection, elevated intraocular pressure, restricted motility, and pressure-like orbital pain with eye movements, there was concern for an orbital process causing mechanical or neuropathic restriction of eye movements. Considerations in this context include thyroid-associated orbitopathy, idiopathic orbital inflammatory syndrome, neoplasm, or vasculitis such as granulomatosis with polyangiitis (GPA). Other processes outside of the orbit, such as cavernous sinus thrombosis, can present with orbital signs and symptoms if severe enough. Myasthenia gravis is painless and is not associated with any orbital findings.

We recommended an MRI brain/orbits with and without contrast to assess for a possible orbital process and a magnetic resonance venogram (MRV) to assess for cavernous sinus thrombosis. However, before the patient was able to obtain these scans, he presented to the emergency department with worsening right ocular pain, blurry vision, and continued hematuria. Visual acuity was stable, but intraocular pressures had increased to 33 mm Hg in the right and

22 mm Hg in the left eye. He had near complete ophthalmoplegia of the right eye with new elevation and depression deficits in the left eye. The right orbit was full and tense and the eye was difficult to open with resistance to retropulsion. A hard ropelike mass under the right eye was palpated, and flesh-colored tissue superotemporal to the right eye was seen, suggestive of an orbital process affecting motility.

MRI and MRV were obtained in the emergency department. The MRV ruled out cavernous sinus thrombosis. The MRI brain/orbits with and without contrast showed new acute and subacute scattered infarcts and a new larger right occipital enhancing lesion consistent with subacute ischemia. Most notably, the patient had new asymmetric enlargement and enhancement of multiple bilateral rectus muscles (right inferior, right medial, to a lesser extent right lateral and superior rectus muscles, also with prominence of left superior rectus/levator muscle complex) (figure, B–C). He was admitted for further workup.

Questions for consideration:

1. Given these radiographic findings, what is the differential for infiltration and enhancement of the extraocular muscles?
2. What additional diagnostic tests would you send?

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SECTION 4

The differential diagnosis for enlargement and enhancement of the extraocular muscles includes thyroid-associated orbitopathy, idiopathic orbital inflammatory syndrome, lymphoma, histiocytosis, metastasis, trichinosis, cavernous sinus fistula, sarcoidosis, GPA, and amyloidosis. Imaging of the extraocular muscles showed enlargement and enhancement of the right medial, inferior, and superior rectus with prominence of the left levator complex. In contrast, thyroid-associated orbitopathy more commonly involves the inferior and medial rectus muscles. Idiopathic orbital inflammatory syndrome would not be expected to be associated with the intracranial strokes. GPA, polyarteritis nodosa, histiocytic disorders, and sarcoidosis can rarely cause vasculopathy, which could also cause ischemia of the brain's parenchyma. Finally, extraocular muscle metastasis or lymphoma could be considered. While the clinical presentation of orbital metastasis is variable, it often has an abrupt presentation with decreased vision, diplopia, proptosis, and a palpable mass, as in our patient. Therefore, in our case the most likely unifying diagnosis for the multiple strokes and extraocular muscle enlargement and enhancement was an underlying systemic neoplasm leading to (1) strokes due to either marantic endocarditis with emboli to the brain or hypercoagulable state and (2) extraocular muscle infiltration by metastatic tumor.

The patient reported no known family or personal history of malignancy including skin cancers.

Further studies including thyroid function tests, rheumatologic panel, and serum protein electrophoresis/urine protein electrophoresis were unremarkable. The patient had a lumbar puncture, with elevated protein (84 mg/dL), but was otherwise unremarkable with normal cytology. His CEA remained elevated (1,401 ng/mL), and his CA-19-9 was highly elevated (35,217 units/mL).¹ The biopsies from his outpatient colonoscopy revealed metastatic poorly differentiated carcinoma involving the colonic mucosa. The malignant cells were plasmacytoid and infiltrated the lamina propria in a discohesive manner. Immunohistochemical stains were positive for PAN-CK, CK7, CK20, and GATA3. He had a full body PET scan, which showed metastatic disease including the bilateral extraocular muscles, right thigh, left forearm, and retroperitoneal/inguinal lymph nodes. A biopsy of the patient's right thigh lesion was performed. This demonstrated similarly discohesive plasmacytoid cells that demonstrated marked mitotic activity. The immunohistochemical studies and morphology suggested a diagnosis of plasmacytoid variant of urothelial (bladder) carcinoma (figure, D).

Questions for consideration:

1. What was his treatment and final course?
2. What makes this case unique?

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SECTION 5

The patient was treated with 10 days of palliative radiation to his right orbit, but he subsequently began to lose vision in his left eye. His course was then complicated by disseminated intravascular coagulation. In this setting, anticoagulation was discontinued. Given the aggressiveness of his malignancy as well as his progressive thrombocytopenia and coagulopathy, it was felt that chemotherapy would provide more harm than benefit. After discussion and thought, the family opted for home hospice.

Metastasis to the orbit, although an unusual location, generally seeds through hematogenous spread. In most studies, 1%–13% of all orbital tumors are metastatic.² Although breast (39%), kidney (11%), and lung (9%) are the more frequent primary sites, a gastrointestinal source is often strongly investigated regardless of the patient's age.³ Generally, the clinical presentation of orbital metastasis with orbital signs is often rapid and progressive, presenting as blurry vision (43%), diplopia (30%), proptosis (73%), pain (12%), and increased intraocular pressure (12%).⁴ There are fewer than 25 cases of urothelial carcinoma metastatic to the orbit reported in the literature; they usually present with a known cancer history that has been treated with chemotherapy or radiation.^{5–8}

This case of urothelial carcinoma with orbital metastasis presenting with an unknown primary neoplasm is very rare. In most published cases, the longest duration of time between diagnosis and urothelial orbital metastasis was 4 years, and those patients died within 6 months.⁸ To our knowledge, this is the first published case of urothelial orbital metastasis as the initial presenting symptom with associated symptoms of a stroke. This case raises awareness of this cancer's ability to metastasize to

the orbit and confirms the aggressive nature and poor prognosis associated with this metastatic disease.

AUTHOR CONTRIBUTIONS

Jessica L. Weinstein: case design and conceptualization, general case history (excluding ophthalmology findings), MRI figure collection. Ahmara G. Ross: neuro-ophthalmology discussion. Nicole M. Fuerst: ophthalmology history. Daniel Lubin: pathology discussion and figures. Grant T. Liu: critical revision of manuscript for intellectual content.

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