Clinical Reasoning: Monocular vision loss, ophthalmoplegia, and strokes in a 61-year-old man with diabetes mellitus

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SECTION 1

A 61-year-old man presented with rapidly progressive right eye vision loss, swelling, and pain, ptosis, and numbness of his right forehead that started 4 days prior to admission. His medical history included coronary artery disease, type 2 diabetes mellitus with hospitalization a week prior to admission for diabetic ketoacidosis (DKA), hypertension, and hyperlipidemia. He denied any tobacco, alcohol, or drug use, and there was no history of head trauma or recent travel.

On physical examination, the patient was afebrile with mental status and higher cortical functions intact. There was a right ptosis and swelling of the right upper and lower eyelids with proptosis and chemosis. The right pupil was fixed, mydriatic, and non-reactive to light. There was no light perception in the right eye and in the left eye visual acuity was 20/20.

Complete ophthalmoplegia of the right eye was noted with normal extraocular motility of the left eye. The fundoscopic examination was normal in the left eye and revealed pallor of the optic disc and necrotic changes of the retina in the right eye. There was diminished sensation to all modalities on the right side of the patient's forehead. The rest of the cranial nerve examination was normal. Strength and sensation to all modalities were preserved in all extremities. Plantar responses were flexor. The gait was normal and there were no cerebellar abnormalities. The rest of the physical examination did not reveal any abnormalities.

Questions for consideration:

1. Where would you localize the lesion?
2. What is your differential diagnosis?

[GO TO SECTION 2](#)

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SECTION 2

The combination of unilateral impairment of cranial nerves III, IV, VI, and V (ophthalmic branch), proptosis, ptosis, and loss of vision defines orbital apex syndrome (OAS), which is secondary to a pathologic process occurring near the apex of the orbit.¹ Impairment of cranial nerves III, IV, and VI results in ophthalmoplegia. Loss of function of the levator palpebrae (innervated by a branch of the oculomotor nerve) or damage to the superior tarsal muscle sympathetic innervation cause ptosis. Impaired parasympathetic innervation (III) causes mydriasis and the loss of vision is secondary to damage to the optic nerve. The engorgement of the retinal and orbital vessels caused by impaired venous drainage or an orbital inflammatory or infectious process with mass effect on the eye explain the pain, chemosis, and proptosis. Etiologies to consider include infectious, vascular, inflammatory, neoplastic, and traumatic/iatrogenic processes (table).

Infections. Fungal infection was a primary concern and the major risk factor was the uncontrolled diabetes mellitus with DKA. Opportunistic fungal infection can have an insidious presentation and rapidly progressive symptoms, and the history and findings on physical examination were highly suspicious for mucormycosis infection.¹ The most common bacteria involved in orbital infections are *Staphylococcus aureus*, *Streptococcus*, and anaerobic gram-negative bacilli.¹ There were no signs of cellulitis or bacterial sinusitis. Herpesviruses or *Mycobacterium tuberculosis* have been associated with OAS.^{2,3} However, the patient did not exhibit any rashes and there were no risk factors or signs of tuberculosis infection.

Vascular. The subacute nature of the symptoms raised concern for a vascular process. Direct carotid-cavernous fistulas often occur secondary to trauma when the internal carotid artery communicates into the cavernous sinus. The patient denied any trauma and the physical examination was negative for pulsatile exophthalmos and bruit. Indirect carotid-cavernous fistulas occur when a branch of the internal or external carotid arteries communicates with the cavernous sinus and the onset of symptoms is often insidious. It was unlikely in this case given the fulminant presentation and the severity of symptoms. There was no history of a hypercoagulable state or coagulopathies, which could result in cavernous sinus thrombosis. The combination of acute blindness, orbital pain, and total ophthalmoplegia in a patient with vascular risk factors also raised concern for an orbital infarction syndrome (ischemia of all

Table Orbital apex syndrome: Differential diagnoses

Infectious
Bacteria (<i>Staphylococcus aureus</i> , <i>Streptococcus</i> , anaerobic gram-negative bacilli, <i>Mycobacterium</i> , <i>Treponema pallidum</i>)
Fungus (<i>Mucormycosis</i> , <i>Aspergillus</i> , <i>Cryptococcus</i>)
Virus (herpes zoster)
Parasite (helminths)
Vascular
Carotid-cavernous fistulas
Aseptic cavernous sinus thrombosis
Cavernous carotid aneurysms
Orbital infarction syndrome
Inflammatory
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Polyarteritis nodosa
Giant cell arteritis
Sarcoidosis
Immunoglobulin G4-related disease
Thyroid-associated orbitopathy
Neoplastic
Primary neural tumors: neurofibroma, schwannoma, malignant peripheral nerve sheath tumor, pituitary adenoma, glioma, meningioma
Sinus carcinoma
Lymphoma
Metastases
Rhabdomyosarcoma
Traumatic/iatrogenic

intraorbital and intraocular structures). Finally, a carotid cavernous aneurysm can result in OAS secondary to compression, and occasionally rupture or ischemic events.¹

Inflammatory disorders. OAS has been associated with a variety of inflammatory disorders (table).¹ However, the patient did not exhibit any extra-neurologic or systemic symptoms (i.e., weight loss, fever). Tolosa-Hunt syndrome is a nonspecific granulomatous disease that can present with ophthalmoplegia, ptosis, and cavernous sinus inflammation.¹ However, it is typically painful, with headaches, and optic neuropathy is rare. Myositis of the extraocular muscles (idiopathic or secondary to Graves disease) can cause ophthalmoplegia but optic neuropathy is rare and symptoms are often bilateral.

Neoplastic. Benign or malignant primary neural or extraneural tumors have been described with

OAS (table).¹ However, the rate of progression of the symptoms made a neoplastic etiology unlikely.

Traumatic/iatrogenic. Direct and indirect injuries as well as orbital compartment syndrome secondary to retrobulbar hemorrhage or edema can present with

OAS.¹ However, there was no history of trauma or recent craniofacial surgery.

Question for consideration:

1. What initial tests (imaging and laboratory testing) would you consider to help narrow your differential diagnosis?

[GO TO SECTION 3](#)

SECTION 3

Pertinent imaging studies include a brain MRI with orbital sequences or fine-cut CT imaging of the head and vascular imaging such as magnetic resonance angiography (MRA) or CT angiography. A brain MRI and MRA showed opacification of bilateral ethmoid and sphenoid air cells with abnormal enhancement and punctate infarctions in the right middle cerebral artery territory and watershed regions, a right midbrain infarct, and diffusion restriction of the right optic nerve suggestive of infarction (figure). The right cavernous sinus and right superior ophthalmic vein were thrombosed and there was mild diffuse narrowing of the right cavernous internal carotid artery and a focal stenosis of a right M2 branch (figure). The T1-weighted

contrast-enhanced sequence demonstrated lack of enhancement of the right turbinates.

The capillary glucose was 194 mg/dL and the hemoglobin A1c was 16. Basic biochemistry was otherwise unremarkable. Basic hematology showed leukocytosis with a white blood cell count of 17.7 k/ μ L (80% of neutrophils), hemoglobin was 13.0 g/dL, and platelet count was 287,000/mm³. Thyroid-stimulating hormone was normal and initial blood cultures were negative (aerobic and anaerobic blood cultures as well as fungal cultures and acid-fast stains).

Questions for consideration:

1. What is the most likely diagnosis?
2. What treatment do you want to start on admission?

Figure Brain MRI and pathology from the right infratemporal fossa

Brain MRI sagittal T1 (A) reveals foci of signal hypointensity in the right sphenoid sinus and the clivus; axial fluid-attenuated inversion recovery (B) and T1 (C) reveal abnormal opacification of bilateral sphenoid air cells (right > left); axial diffusion-weighted imaging reveals foci of restricted diffusion in the right midbrain (D), right watershed regions (E), and right optic nerve (F). Brain magnetic resonance angiography time of flight (G) reveals narrowing of the right cavernous internal carotid artery. Pathology from the right infratemporal fossa, Grocott methenamine silver stain (H) and hematoxylin & eosin stain (I), reveal focal necrosis and angioinvasion of mucormycosis (arrows).

[GO TO SECTION 4](#)

SECTION 4

The clinical presentation, laboratory findings, and brain MRI and MRA were concerning for a necrotizing rhino-orbital-cerebral infection such as mucormycosis complicated by ischemic strokes.

IV liposomal amphotericin B (5 mg/kg) was started as well as IV vancomycin and meropenem. Euglycemia was maintained with insulin. Endoscopic debridement of the right skull base and right maxillary, ethmoid, and sphenoid sinuses was performed within 24 hours of admission and pathology of the sinuses content showed necrotizing sinusitis associated with fungal elements characteristic of invasive mucormycosis (figure). Aspirin 81 mg daily was started for secondary prevention of ischemic stroke.

Two weeks later, the patient presented with left hemiplegia and was found to have new ischemic strokes in the right anterior choroidal artery territory. He underwent another debridement surgery with right orbital exenteration. Despite surgery and adding posaconazole, new ischemic strokes were found on follow-up MRI. After a family meeting and given a likely poor outcome, the patient was transitioned to comfort care and died.

DISCUSSION Mucormycosis represents a group of life-threatening infections caused by fungi of the order *Mucorales*.⁴ The rhino-orbital-cerebral form of the disease is characterized by angioinvasion and tissue necrosis involving the sinuses, the orbits, and the brain.⁴ Risk factors include immunosuppression, uncontrolled hyperglycemia or DKA, and iron overload states.⁴ In DKA, the acidosis promotes fungal survival and virulence by facilitating iron dissociation from sequestering proteins in serum. Hyperglycemia contributes to mucormycosis infections through hyperglycation of iron-sequestering proteins, expression of proteins promoting tissue penetration of the fungi, and defects in phagocytic function.⁴

Invasion of the brain may develop by venous spreading of the infection into the cavernous sinuses, by invasion along the optic nerve, and by direct extension from the sinuses.^{4,5} The first symptoms are often nonspecific and include fever, lethargy, headache, facial pain, and blurry vision.^{5,6} Spreading of the infection can cause OAS, seizures, brain abscesses, coma, and death.^{4,5} Mucormycosis has been associated with ischemic strokes and the pathophysiology involves a combination of growth of the hyphae into the arterial lumen, direct endothelial injury, and vasculitis.⁶ Intracranial hemorrhages have also been reported, possibly secondary to venous congestion or rupture of mycotic aneurysms.⁷ MRI of the face can be helpful in the diagnosis and classically reveals lack of enhancement of the nasal and sinus mucosa secondary to necrosis.⁸

Definitive diagnosis requires biopsy with identification of characteristic hyphae or recovery of the organism in culture.⁴ Administration of parenteral amphotericin B is the recommended treatment for mucormycosis, with posaconazole and isavuconazole representing alternative therapeutic options.⁹ Antifungal therapy should be continued until resolution of symptoms and underlying immunosuppression.⁹ Defects in host defense should be reversed (e.g., by restoring euglycemia) and aggressive surgical debridement should be performed to eradicate the disease.⁹ There are no data supporting the role of antiplatelet therapy for secondary prevention of stroke in patients with invasive mucormycosis. Retrospective studies found a potential benefit of anticoagulation in cavernous sinus thrombosis in reducing the incidence of septic emboli but one must consider the risk of hemorrhages from intracranial mycotic aneurysm.¹⁰ Limited data indicate a possible role for iron chelating agents and hyperbaric oxygen as adjunct therapies.⁹ Early diagnosis is key and survival rate has been reported to be 70% when amphotericin B and an aggressive surgical approach are combined.⁵ However, delayed diagnosis and treatment lead to poor prognosis.

AUTHOR CONTRIBUTIONS

G.L.: conceptualization, writing and preparation of the manuscript, review and critique of the manuscript. Z.F., W.D.Z., S.H., P.d.B., D.M.: writing contribution and review of the manuscript.

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