CLINICAL VIGNETTE

Tumor Progression Manifesting as Cavernous Sinus Syndrome

Kathleen Yip, MD and Brittany Mull, MD

Case

A 78-year-old male with right neck squamous cell carcinoma on cisplatin and filgrastim while receiving radiation therapy was referred to the emergency department with right-sided facial droop over 3 days. He reported initial numbness and tingling, then sinus pressure and gradual difficulty hearing on the right side. His vitals were within normal limits and on focused physical exam, he demonstrated complete ptosis of the right eye and his right pupil was 6mm and minimally reactive to light with lack of extraocular movements except for occasional weak downward gaze. He also had decreased sensation in the right V2 distribution, lower right facial droop with symmetric forehead raise and had decreased hearing loss, especially on the right.

His labs showed persistent leukocytosis to $17.8x10^9/\mu L$ as well as hyponatremia. MRIs with and without contrast were performed obtained showing expansion of the right cavernous sinus with irregular hypoenhancing tissue concerning for metastatic disease versus less likely cavernous sinus thrombosis (CST), though the right superior ophthalmic vein was not dilated as may be expected with CST. Magnetic resonance venography (MRV) was not able to definitively exclude a thrombus, and the patient was started on heparin, steroids, as well as broad spectrum antibiotics given his immunocompromised status with leukocytosis, and admitted with consultations from neurology, neurosurgery, otolaryngology, oncology, and infectious disease.

During his hospitalization the patient underwent multiple imaging tests and attempted biopsy to rule out an invasive fungal sinusitis, it was determined that the patient's tumor had extended to the cavernous sinus, leading to the patient's presentation of cavernous sinus syndrome. His hospitalization was complicated by an intracranial hemorrhage at the right cerebellopontine angle and pituitary microinfarcts, while on heparin. He died shortly after discharge due to several aspiration events.

Discussion

Clinical Anatomy

The cavernous sinus (CS) is one of the dural venous sinuses, receiving blood from several head and neck venous structures including the cerebral veins, ophthalmic veins, and emissary veins. These connections make it possible for extracranial infections to travel into intracranial locations.[1] Several critical cranial nerves (CN) and structures pass through the CS. The oculomotor (III), trochlear (IV) and ophthalmic (V_1) and maxillary (V_2) branches of the trigeminal nerve course superiorly to inferiorly within the lateral dural wall of each CS, while the abducens nerve (VI) passes through the medial wall and is the only cranial nerve to lie within the venous sinusoids of the CS. The internal carotid artery (ICA) is also the only artery that is surrounded entirely by venous blood and the ICA itself is surrounded by a sympathetic plexus.[2] The cavernous sinuses drain into the superior petrosal sinuses that then drain into the transverse sinuses.[1]

Thorough understanding of the anatomy is key as it influences signs and symptoms of CS pathology. Involvement of CN VI is the most common, as it has the longest intracranial course between the brainstem and the eye and is also the only nerve that passes entirely through the CS itself, presenting clinically as a lateral rectus palsy and horizontal diplopia.[3] Lesions of CN III and IV may result in ophthalmoplegia and fixed and dilated pupil. Injury to CN V_1 and V_2 may result in upper and mid-face sensory deficits. Damage to the sympathetic plexus around the ICA can lead to Horner's syndrome (myosis, ptosis and anhidrosis). Chemosis and proptosis may also be seen states of impaired venous drainage such as thrombosis or a carotid-cavernous fistula. Sudden onset of symptoms may be suggestive of an acute inflammatory or vascular cause, while a more insidious onset may be suggestive of a neoplastic or chronic inflammatory cause.

While non-contrast CT scan is often the first imaging study performed in a patient with new neurologic symptoms, it is not sensitive for cavernous sinus pathologies. MRI is the preferred imaging with superior soft tissue contrast resolution. Additionally, it also examines the patency of the dural venous sinuses and cerebral veins. Though CT venogram (CTV) can be performed more rapidly, use of iodinated contrast and ionizing radiation may be limiting factors. The differential for a cavernous sinus syndrome can be neoplastic, infectious, inflammatory, or vascular in nature.

Neoplastic Etiologies

Pituitary adenomas are the most common neoplasm to involve the cavernous sinus and by proximity, often grow laterally from the sella turcica into the CS. Other slow growing tumors known

to commonly affect the CS include meningiomas or schannomas. Lymphomas may impact the CS from direct extension from adjacent structures such as bone marrow or the nasopharynx, or via hematogenous dissemination. Nasopharyngeal carcinoma can directly invade the CS or spread perineurally. Involvement of the cavernous sinus typically occurs late in the course of the disease. Metastasis to the CS may occur by hematogenous, perineural or direct vascular means and is primarily associated with lung, breast, renal and gastric cancers.[4] These often result in unilateral CS symptoms with rapid growth.[2]

Infectious Etiologies

Invasive fungal infections, especially those of Aspergillus and Zygomycetes (Mucor) are found in immunocompromised patients. These can extend intracranially from the paranasal sinuses or hematogenous spread from the lungs. Administration of steroids in patients with invasive fungal disease may result in rapid worsening.

Inflammatory Etiologies

Sarcoidosis rarely involve the CS, and most patients will have intrathoracic involvement at the time of diagnosis.[2] Granulomatosis with polyangiitis (GPA), or formerly known as Wegener's granulomatosis, results in the formation of necrotizing granulomas in the paranasal sinuses, nasal cavities and orbits and may secondarily extend to CS.[2] Tolosa-Hunt syndrome is a diagnosis of exclusion, and is characterized by episodic, painful ophthalmoplegia with Horner syndrome and is caused by nonspecific inflammation of the superior orbital fissure-cavernous sinus. Other features include spontaneous remissions and dramatic improvement with corticosteroids.[4,5]

Vascular Etiologies

Cavernous carotid aneurysms can be caused by infectious, traumatic, or idiopathic etiologies. These account for 2-9% of all intracranial aneurysms.[6] Unruptured aneurysms may be found incidentally and are often asymptomatic. If symptomatic, diplopia and headache are most common due to mass effect. Ruptured aneurysms rarely cause subarachnoid hemorrhages, given that the CS is lined by dura. Most cavernous carotid aneurysms are considered benign with a low risk of rupture and if asymptomatic, are often managed conservatively with serial imaging. Ruptured aneurysms are emergently treated surgically.[6]

A carotid-cavernous fistula (CCF) may occur after trauma, aneurysm rupture or as a post-operative complication and may present clinically with chemosis and pulsatile exophthalmos.[2] More subtly, due to an inflammatory response within the dura, a CCF may present with visual disturbances and progressive chemosis.

Cavernous sinus thrombosis may complicate bacterial or fungal infection of the paranasal sinuses, face, orbit and skull base and clinically manifest as headache, orbital pain, ophthalmoplegia and vision loss.[4] Tributaries to the CS are valveless, predisposing the CS to infection. This is a life-threatening condition with 20-30% mortality rate, is seen more commonly in patients with diabetes or immunocompromised status and must be treated urgently with anticoagulation and antibiotics.[2]

Conclusion

We describe the extension of squamous cell carcinoma presenting as cavernous sinus syndrome. Cavernous sinus syndrome may manifest clinically as ophthalmoplegia, vision loss, Horner syndrome, facial pain, or headache. Pathologic conditions are broadly characterized by neoplastic, infectious, inflammatory, or vascular etiologies. Close physical examination and understanding of neuroanatomy are imperative in obtaining the diagnosis.

REFERENCES

1. **Drake RL, Vogl AW, Mitchell AWM**. Chapter 8: Head and Neck. In: Drake RL, Vogl AW, Mitchell AWM, eds. *Gray's Anatomy for Students*. 4th ed. Elsevier; 2020:823-1121.
2. **Munawar K, Nayak G, Fatterpekar GM, Sen C, Zagzag D, Zan E, Hagiwara M**. Cavernous sinus lesions. *Clin Imaging*. 2020 Dec;68:71-89. doi: 10.1016/j.clinimag.2020.06.029. Epub 2020 Jun 18. PMID: 32574933.
3. **Singh A, Sharma P, Pal H, Sharma S, Dixit A**. Isolated Sixth Nerve Palsy as the First Manifestation of Cavernous Sinus Metastasis From Primary Breast Cancer. *Cureus*. 2021 Dec 2;13(12):e20094. doi: 10.7759/cureus.20094. PMID: 35003950; PMCID: PMC8723733.
4. **Mahalingam HV, Mani SE, Patel B, Prabhu K, Alexander M, Fatterpekar GM, Chacko G**. Imaging Spectrum of Cavernous Sinus Lesions with Histopathologic Correlation. *Radiographics*. 2019 May-Jun;39(3):795-819. doi: 10.1148/rg.2019180122. Epub 2019 Apr 12. PMID: 30978149.
5. **Kim H, Oh SY**. The clinical features and outcomes of Tolosa-Hunt syndrome. *BMC Ophthalmol*. 2021 May 27;21(1):237. doi: 10.1186/s12886-021-02007-0. PMID: 34044807; PMCID: PMC8161661.
6. **Eddleman CS, Hurley MC, Bendok BR, Batjer HH**. Cavernous carotid aneurysms: to treat or not to treat? *Neurosurg Focus*. 2009 May;26(5):E4. doi: 10.3171/2009.2.FOCUS0920. PMID: 19409005.