Acute Horner Syndrome From Supraclavicular Lymphadenopathy as the First Manifestation of Metastatic Lung Carcinoma

Kathryn Hohs, OD, FAAO
Assistant Professor
of Optometry,
Illinois College of Optometry,
Chicago

Christina Morettin, OD, FAAO
Private Practice,
Toronto

ABSTRACT

INTRODUCTION

Horner syndrome is a rare ocular condition classically consisting of pupil miosis, eyelid ptosis and facial anhidrosis. It occurs secondary to damage along the three-neuron sympathetic nerve pathway that travels a long course from the brain to the eye. If acute, the syndrome can be the presenting sign of life-threatening pathology in the head, chest, or neck. Thorough history, careful clinical exam, and proper imaging studies are essential to diagnose the syndrome, help localize the lesion, and determine proper treatment for the underlying etiology.

CASE REPORT

This case presents a 62-year-old female patient with an acute left-sided Horner syndrome confirmed by pharmacologic testing. She had an unremarkable medical history beyond arthritis, denied a history of trauma, and reported a tobacco smoking history. Further review of symptoms did not allow for definitive localization of the lesion, nor did she have a known underlying cause of Horner syndrome at presentation. Emergent imaging of the chest and neck revealed a preganglionic lesion caused by metastatic supraclavicular lymphadenopathy in the neck originating from primary lung carcinoma. Brain magnetic resonance imaging identified several areas of metastasis to the brain. She was treated with prompt chemotherapy and radiation.

CONCLUSION

An adult patient with acute Horner syndrome without significant localizing symptoms or pertinent findings during review of systems requires an emergent and thorough workup to rule out malignancy. Horner syndrome as the first presenting sign of undetected malignancy along the sympathetic chain is rare. An accurate diagnosis from an optometrist and subsequent timely referral is critical to uncover potentially life-threatening pathology that may be unknown to the patient at the time of presentation.

KEYWORDS: Carcinoma, Horner syndrome, lymphadenopathy, supraclavicular, sympathetic

INTRODUCTION

Horner syndrome is characterized by unilateral pupil miosis, minor eyelid ptosis, apparent enophthalmos, dilation lag of the affected eye, and facial anhidrosis on the affected side.[1] It occurs from an interruption to the oculosympathetic nerve pathway from the hypothalamus to the eye.[1] Etiologies of this rare condition are widespread, given the extensive course of the sympathetic fibers through the head, chest, and neck.[1,2] It can range from first-order neuron disorders (i.e. central lesions along the hypothalamospinal tract), second-order neuron disorders (i.e. preganglionic lesions), or third-order neuron lesions (i.e. postganglionic lesions at the level of the internal carotid artery).[1] Careful history, clinical exam, and proper imaging studies are essential to diagnose the syndrome and help localize

the lesion, given the potential for life threatening etiologies.[2] This case presents a patient with an acquired preganglionic Horner syndrome as the first sign of undetected metastatic lung carcinoma in the head and neck. Horner syndrome as the presenting sign of undetected malignancy to a site along the sympathetic chain is incredibly rare; it is more common for it to be caused by local extension of a tumor (i.e. Pancoast tumor).[3,4] This report discusses the important localizing case history questions to ask in patients presenting with acute Horner syndrome. It also highlights the essential role eye care providers play in ensuring accurate diagnosis of this subtle clinical entity, specifically in patients without known causes of Horner syndrome at presentation.

CASE REPORT

A local urgent care clinic referred a 62-year-old African American female for evaluation of a smaller-appearing left eye for two weeks. She denied any additional ocular symptoms. She reported an associated intermittent non-specific headache that was difficult to localize. Her ocular history was unremarkable. Her medical history was significant for rheumatoid arthritis and osteoarthritis, for which she was taking oral hydroxychloroquine and azathioprine. She was an everyday tobacco smoker, denied history of recent trauma, and denied arm or shoulder pain. There were no neurological deficits or other symptoms noted on review of systems. Her best corrected distance visual acuity with pinhole was 20/20 (6/6) in both eyes. Extraocular motility was full in both eyes and confrontation field testing was unremarkable. Both pupils were round and reactive to light without an afferent pupillary defect, but anisocoria was present, with the left pupil measuring smaller than the right pupil in both bright and dim illumination (Table 1).

Anterior segment evaluation was unremarkable in both eyes except for a 3 mm ptosis of the left eyelid as measured by a reduced marginal reflex distance-1 and an increased marginal crease distance when compared to the right eyelid (Table 1). Intraocular pressures were measured 19 mmHg in the right eye and 19 mmHg in the left eye by Goldmann applanation, and un-dilated posterior pole evaluation was unremarkable in both eyes. Apraclonidine ophthalmic solution 0.5% was instilled into both eyes and pupil measurements were repeated 30 minutes later. Her left eyelid ptosis improved and reverse anisocoria occurred, with the left pupil measuring larger than the right pupil in both bright and dim illumination (Table 2). The clinical appearance of the patient and the resultant pharmacologic testing supported damage to the sympathetic pathway, thus confirming the diagnosis of left-sided Horner syndrome. Emergent comprehensive head, neck, and chest imaging was recommended due to the acute onset, the complaints of non-specific head pain, and the reported tobacco use.

Table 1: *Entering pupil size measurements and eyelid measurements prior to instillation of 0.05% apraclonidine; anisocoria present (right eye larger than left eye) that is greater in dim illumination, with ptosis of the left eyelid.*

	OD	OS
Pupil size (bright illumination)	2 mm	1.5 mm
Pupil size (dim illumination)	4 mm	3 mm
Eyelid measurements	MRD1: 4 mm MRD2: 5 mm MCD: 7mm	MRD1: 1 mm MRD2: 5mm MCD: 9mm

MRD1=marginal reflex distance-1
MRD2=marginal reflex distance-2
MCD=marginal crease distance

Table 2: *Pupil size 30 minutes after apraclonidine 0.5% instillation in both eyes, demonstrating reverse anisocoria (left pupil measuring larger than right pupil).*

	OD	OS
Pupil size (bright illumination)	2 mm	3 mm
Pupil size (dim illumination)	4 mm	5 mm

Initial chest X-ray identified an indeterminate mass in the left midlung lobe. Further characterization by chest computed tomography (CT) revealed a left lung upper lobe nodule measuring 2.0 cm x 1.3 cm, consistent with primary lung carcinoma. Extensive metastatic disease in the superior mediastinum, left axillary, and left supraclavicular lymph nodes

was visualized on chest CT and neck computed tomography angiography (CTA), with the largest supraclavicular node measuring 4.3 cm (Figure 1). Significant pericardial effusion was also seen. The supraclavicular lymphadenopathy was the presumed etiology of the patient's clinical preganglionic Horner syndrome. Brain magnetic resonance imaging (MRI) showed several enhancing intracranial lesions indicative of metastasis to the brain (Figure 2). The patient received chemotherapy every 21 days and 10 sessions of radiation therapy for initial treatment. Treatment efficacy was then to be assessed at the end of the initial therapy cycle.

Figure 1: *Chest and neck computed tomography (CT) scans with (A and B) coronal and (C) axial views confirming the presence of large left supraclavicular lymphadenopathy (blue arrows) compressing on the sympathetic chain at the level of the cervical ganglion. The nodal masses vary in size from 2.6 cm to 4.3 cm. Superior mediastinal lymphadenopathy measuring 3.3 cm x 4.5 cm (orange arrow) is also highlighted.*

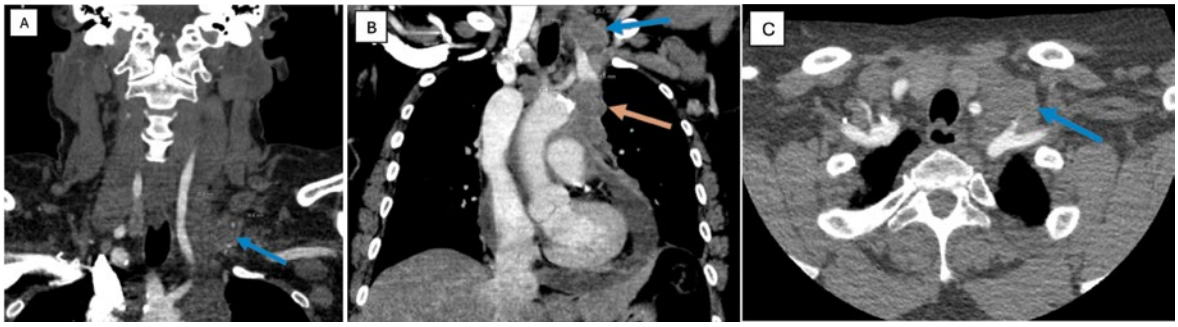
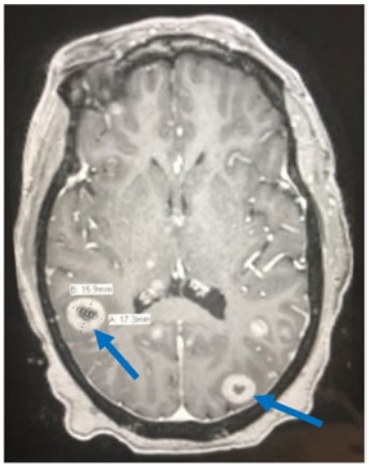


Figure 2: *Magnetic resonance imaging of the brain with areas of hyperintensity (blue arrows) indicating metastasis of primary lung carcinoma.*



DISCUSSION

Among the large published reports studying the causes of Horner syndrome, tumors or tumor-related causes have been variably reported between 5% and 36% as the underlying cause.[3-5] The exact incidence of metastatic lymphadenopathy as the underlying cause is not known, as most studies include metastasis as a tumor or tumor-related cause.[3,4] Supraclavicular lymphadenopathy, compared to adenopathy in other areas of the head and neck, has a high association with malignancy, specifically in the abdominal or thoracic cavity.[6] Clinicians may consider external evaluation of the supraclavicular region for visualization or palpation of large adenopathy in patients with Horner syndrome, especially in those without significant findings on a review of symptoms.

The association between preganglionic Horner syndrome and pulmonary malignancy, specifically Pancoast tumors, is well known. Pancoast syndrome is a preganglionic Horner syndrome from an apical lung tumor with associated arm or shoulder pain, limb paresthesia, and finger paresthesia or paresis.[7] While the preganglionic Horner syndrome of our patient was related to pulmonary malignancy, she was unique in that the tumor location was not consistent with Pancoast tumor, and she had no complaints consistent with Pancoast syndrome. Also of note, she denied systemic complaints consistent with lung malignancy, including chest pain, shortness of breath, weight loss, or progressive fatigue.[7]

It is imperative to distinguish Horner syndrome caused by local extension of a tumor (i.e. Pancoast tumor) versus a true metastasis to a site along the sympathetic chain, as was detected in our patient. Horner syndrome as the first sign of such a metastasis is exceedingly rare. Based on a review of 450 patients with Horner syndrome conducted by Maloney et al, less than 3% of patients presented with Horner syndrome as their initial sign of malignancy.[3] Of these 3%, 77% had tumors involving the apex of the lung, and 69% had an associated complaint of arm pain consistent with Pancoast syndrome, which, as discussed above, our patient did not have.[3] Another more recent retrospective analysis by Sabbagh et al of 318 patients with Horner syndrome supported the rarity of Horner syndrome as the first sign of undetected disease.[4] Only 9% of patients had Horner syndrome that preceded the known cause, and of these 9%, five patients (1.6%) were diagnosed with either carotid artery dissection or malignancy.[4] Additionally, 3.8% of this subset of patients had no localizing symptoms, similar to our patient.[4] Both studies, as well as our case, highlight the importance of thorough imaging from the sternum to the head to investigate potentially malignant etiologies in patients who present with acute Horner syndrome without a known underlying etiology. While the overall yield may be low, specifically for patients without localizing symptoms, the risk of life-threatening pathology warrants emergent evaluation.

The clinical findings associated with Horner syndrome can be subtle to detect. If Horner syndrome is suspected, pharmacologic testing should be used to confirm the diagnosis. Topical apraclonidine 0.5%, as used in our patient, has become the preferred solution in adult patients for confirmatory diagnosis since it is more readily available in the clinical setting and has similar sensitivity compared to traditional 5% to 10% cocaine solution.[2,8] After topical apraclonidine administration into both eyes, a pupil with Horner syndrome will dilate and a normal pupil will not change size. This is due to the upregulation of alpha-1 postsynaptic receptors at the iris dilator muscle, a phenomenon known as denervation super sensitivity.[8] It should be noted that apraclonidine testing does have limitations. It should not be used in young children, and the test may produce a false negative if used in the acute phase of the Horner presentation due to the time it takes for super sensitivity to develop at the nerve ending.[8] Once Horner syndrome is confirmed, hydroxyamphetamine 1% or dilute phenylephrine 1% could be used to localize the lesion along the sympathetic chain.[2,8] Hydroxyamphetamine can differentiate a third-order neuron lesion from first- or second-order, as it will dilate all pupils except for those with a third-order neuron lesion.[8] Similarly, dilute phenylephrine can identify a third-order neuron lesion by causing mydriasis of only a third-order neuron Horner pupil.[2] Both drops, however, require a delay of at least 24-48 hours after initial confirmatory testing is completed.[2] Given the urgent need for imaging in patients with acute Horner syndrome, pharmacologic localization is not frequently done or recommended.

A thorough review of systems and symptoms can help localize the lesion and direct imaging strategies in patients with acute Horner syndrome. Pain is a concerning symptom for potentially fatal pathology and thus increases clinician concern for emergent workup. Head, orbital, or neck pain is often associated with carotid artery dissection,[9] and arm or shoulder pain is a reliable sign associated with malignancy.[3,7] As seen with our case, Horner syndrome may represent metastatic disease; therefore, patients must be questioned on previous or current malignancy.[10,11] Given the association between smoking and lung malignancy, confirmation of smoking history is important. A history of trauma or recent neck surgery must be investigated as both are common causes of preganglionic Horner syndrome.[8,9] Central neuron Horner syndrome is rarely an isolated clinical entity as it often presents with neurologic symptoms, including, but not limited to, ataxic hemiparesis, nystagmus, vertigo, or cranial nerve palsies.[8] The history of our patient did not allow for definitive localization of the lesion, but her non-specific symptoms of head pain were concerning for carotid artery dissection. This symptom, along with the acute onset, warranted an urgent workup with initial radiographic imaging targeting the chest and neck, including angiography.[2]

There is not a clear consensus for standardized imaging protocol for all patients with acute Horner syndrome. Chest X-ray and carotid ultrasonography, while easily accessible in emergency room settings, are not often specific enough to rule out apical lung carcinoma and carotid artery dissection, with most patients requiring further imaging.[2] CT, CTA, and MRI are more specific and preferred in a diagnosis of Horner syndrome. Imaging is directed first to areas where the clinician suspects the oculosympathetic pathway is compromised. Patients with suspected central neuron Horner syndrome require MRI of the head with and without contrast and magnetic resonance angiography (MRA).[8,9] If there

are no associated brain or brainstem localizing symptoms, MRI of the upper thoracic cavity should also be included.[9] In suspected second-order Horner syndrome, CT or MRI of the neck spanning from C2 to T2 vertebrae, including the apex of the lung, is recommended.[9] MRI offers better contrast of the cervical cord and the brachial plexus,[8] though CT may be easier to obtain in the emergency room setting. Third-order Horner syndrome requires angiography of the head and neck (MRA or CTA) to rule out carotid artery dissection in addition to brain imaging similar to a suspected central neuron lesion.[9] If directed studies are negative, then it is recommended the remaining portion of the sympathetic pathway not yet imaged should be addressed.[8] See Table 3 for a summary of recommended imaging strategies for acute Horner syndrome.

Table 3: *Recommended imaging strategies for acute Horner Syndrome*[8,9]

Area of Suspected Lesion (based on localizing signs or symptoms)	Recommended Imaging Strategy
First-order (central)	Brain MRI with and without contrast MRA +/– Cervical MRI
Second-order (preganglionic)	Chest CT or Chest MRI including lung apex and brachial plexus +/– CTA (or MRA) of head and neck
Third-order (postganglionic)	CTA (or MRA) of head and neck + Brain MRI with and without contrast

MRI=magnetic resonance imaging
MRA= magnetic resonance angiography
CT= computed tomography
CTA= computed tomography angiography

Prognosis for this patient was poor given the presence of pericardial effusion[12] and the significant amount of metastasis. Depending on the extent of sympathetic nerve damage, the Horner syndrome may not resolve even with treatment of the malignancy.[10] Compression of the sympathetic chain and subsequent permanent damage to the nerve plexus is thought to be the reason for this.[10,13] Early diagnosis of the syndrome may prevent long-term nerve damage and therefore higher likelihood of it resolving with treatment, as well as the obvious benefits of earlier intervention and treatment for systemic malignancy.

In conclusion, an adult patient with an acute Horner syndrome without a known history of Horner-causing disease and limited localizing symptoms requires a complete workup to rule out malignancy. Metastatic lymphadenopathy should be included in the differential diagnosis. While it is rare for undetected malignancy to be identified as the underlying cause, these are the patients where an accurate diagnosis and prompt referral from an eye care provider matters most. ●

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CORRESPONDING AUTHOR: Kathryn Hohs—KaHohs@ico.edu

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