Superior Division Third Nerve Palsy as the Presenting Sign of Metastatic Breast Cancer

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Abstract
The third cranial nerve divides into superior and inferior branches at the level of anterior carotid sinus and superior orbital fissure. In extremely rare scenarios, metastatic lesions at this location may present with divisional third nerve involvement. We here describe an 85-year-old woman who presented with superior division third nerve palsy due to breast cancer metastasis. Our case demonstrates the rare presentation of double vision and ptosis because of superior division third nerve palsy. The differential diagnosis for this examination finding should include metastatic disease even in the absence of a known cancer diagnosis. This case also reiterates that the “rule of the pupil” should not be applied to superior division third nerve palsy.

Introduction

The third nerve originates from the midbrain at the level of superior colliculus. It travels through the interpeduncular fossa and subarachnoid space and eventually pierces the dura to enter the cavernous sinus, where it receives sympathetic branches from the carotid plexus, and travels rostrally to enter the orbit at the superior orbital fissure. At the level of anterior cavernous sinus and superior orbital fissure, the third cranial nerve divides into superior and inferior branches. The superior branch supplies the superior rectus and levator palpebrae.
superioris, while the inferior branch supplies the medial rectus, inferior rectus, inferior oblique, and lower part of the ciliary ganglion, which innervates the ciliary muscle and pupillary sphincter [1].

Sudden onset divisional involvement of the third cranial nerve is most often caused by lesions in the vicinity of anterior cavernous sinus/superior orbital fissure and can be attributed to various etiologies, including infiltration from infectious sinusitis, meningiomas, and aneurysms [2–4]. In older patients, metastasis to the orbit may rarely present as superior division third nerve palsy. Of particular concern is metastasis from primary lung and breast tumors as these tend to most commonly metastasize to the orbit [5].

We here report an 85-year-old woman who presented with monocular ptosis and elevation deficit due to orbital apex infiltration from breast cancer metastasis. Our case demonstrates the importance of keeping metastasis as a differential diagnosis for divisional third nerve palsy and demonstrates that “rule of the pupil,” which states that compression of the third nerve typically presents with pupillary involvement, should not be applied to patients with superior division third nerve palsy.

**Case Report**

An 85-year-old woman was referred to neuro-ophthalmology for evaluation of right ptosis. Past medical history was remarkable for hypertension and dyslipidemia, which were being treated with candesartan and rosuvastatin. She reported right ptosis for 3 months and did not notice diplopia. Around this time, she also experienced back and hip pain, which made it difficult for her to sit comfortably. She had seen her family doctor for this symptom and had blood testing that showed a hemoglobin of 95 g/L, elevated erythrocyte sedimentation rate of 94 mm/h, and C-reactive protein of 106.6 mg/L. One week prior to presentation to ophthalmology, she had a fall, which prompted her to go to the emergency room. She had a CT scan of her head that showed an old right basal ganglia infarct. She had a lumbar spine and right clavicle X-ray that showed no acute fracture but degenerative changes in the spine. She was referred to ophthalmology for further evaluation.

Initial ophthalmology assessment revealed a best-corrected visual acuity of 20/70 in right (OD) and 20/30 left eye (OS). Pupils were equal and reactive with a mild relative afferent pupillary defect. There was right ptosis and complete limitation of elevation in the right eye (Fig. 1).

**Fig. 1.** Eye movements in 9 cardinal positions of gaze demonstrating right ptosis and a limitation of elevation in the right eye.
Ocular ductions were otherwise full. The anterior segment exam was remarkable for grade 2 nuclear sclerotic cataracts, while the posterior segment exam showed mild right optic disc edema. She was diagnosed with a superior division third nerve palsy in the right eye and was admitted to hospital for further evaluation.

She underwent an MRI of orbits and the brain with contrast which demonstrated diffuse heterogeneous osseous lesions scattered through the skull and a soft tissue mass in the right orbital apex involving the lesser wing of the right sphenoid bone and the right orbital apex/right orbital canal (Fig. 2). A CT chest/abdomen/pelvis was performed which revealed a lobulated soft tissue mass in the right breast and axillary lymphadenopathy, multiple hepatic lesions, and diffuse osseous lesions. A core biopsy confirmed metastatic invasive lobular carcinoma breast cancer (ER/PR positive, HER-2 negative), and she was subsequently placed on palliative radiotherapy and treated with letrozole and ribociclib. At 1-year follow-up, her ptosis and elevation deficit improved but continued to persist. This was not a bothersome symptom to her.

Discussion

We here described an extremely rare case of metastasis resulting in superior division third nerve palsy. To our knowledge, only two other cases have been reported in the literature. Khalili et al. [6] described a 40-year-old female who developed sudden onset ptosis and diplopia, without pain and proptosis, and normal pupillary findings. She was found to have an orbital apex lesion from breast cancer metastasis. Pecen et al. [7] reported a 59-year-old male who presented with 4 weeks of right eye pain, swelling, and diplopia. His exam demonstrated monocular ptosis and elevation deficit, with normal pupils. He was found to have metastatic lesions to the superior orbital apex from pancreatic cancer. The clinical presentation in our case was different as our patient did not complain of diplopia, which likely led to a delay in diagnosis prior to referral to our center. This emphasizes an important point regarding superior division third nerve palsy: patients may not always complain of diplopia as severe ptosis may prevent patients from recognizing misalignment, particularly when it only impacts up-gaze. Our patient also had mild right optic disc edema, which may have been due to optic nerve sheath involvement from the metastases.

The pupillary exam is commonly normal in patients with superior division third nerve palsy as the superior division does not carry any pupillomotor fibers [8]. Even though a mild
RAPD was present in our case, both pupils were reactive without anisocoria. Therefore, the “rule of the pupil,” which states that third nerve palsy from compressive lesions results in sluggish or dilated pupil, does not apply to superior division third nerve palsy and can only be applied when there is complete involvement of the third nerve.

Any type of lesion or inflammation in the anterior cavernous sinus and superior orbital fissure may cause divisional third nerve palsy. Previously reported cases include: cavernous meningioma [2], orbital lymphoma [9], aneurysm [3], and infectious causes including sphenoid sinusitis [2] and fronto-ethmoidal sinusitis [4]. While lesions in anterior cavernous sinus and superior orbital fissure are the most common site of divisional third nerve involvement, lesions before the bifurcation can also cause divisional involvement – as the third cranial nerve is topographically organized. Multiple reports of divisional third nerve palsy with subarachnoid pathologies have been reported: metastatic subarachnoid infiltration [10], cryptococcal meningitis [11], bacterial meningitis, basilar artery aneurysm, surgical damage during craniotomy, and malignant lymphoma [12]. Even earlier along the course of the third cranial nerve, posterior communicating artery aneurysm and lobectomy have been reported to cause superior divisional third nerve palsy due to involvement of the cisternal portion [13]. Rarely, lesions at the level of midbrain may result in superior division third nerve palsy by direct involvement of fascicles [14]. It is important to keep a broad differential as other etiologies, without directly pressing on the third nerve, can also rarely cause divisional third nerve palsy: unspecified viral infection [15], COVID-19 [16], post-traumatic [17], ophthalmoplegic migraine [18], and diabetes [19].

In conclusion, patients with metastasis may rarely present with isolated superior division third nerve palsy. It is therefore important metastasis is included in the differential of isolated divisional third nerve palsy to guide appropriate management and treatment. In addition, our case and previous reports demonstrate that “rule of the pupil” should not be applied to superior division third nerve palsy.

**Statement of Ethics**

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

We have no conflict of interest to disclose.

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**Author Contributions**

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and Jonathan A. Micieli; b. Revising it for intellectual content: Amir R. Vosoughi and Jonathan A. Micieli. Category 3: a. Final approval of the completed manuscript: Amir R. Vosoughi and Jonathan A. Micieli.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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