

## Unilateral Ptosis with Bilateral Incomplete Ophthalmoplegia as the Initial Presentation in Metastatic Cancer

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Orbital metastases are rare and predominantly unilateral occurrences. Bilateral metastases affecting the extraocular muscles are extremely rare. A few case reports of bilateral metastases to extraocular muscles described binocular diplopia with conspicuous bilateral external ophthalmoplegia as an initial symptom. We report a case in which unilateral ptosis was an initial symptom and bilateral incomplete ophthalmoplegia was found on initial neurologic examination in invasive ductal carcinoma of the breast. The patient had hormone receptor-positive breast cancer, and so was treated by hormonal therapies and closely monitored. The presence of a secondary orbital lesion presents many difficulties of differential diagnosis and treatment. A thorough neurologic examination to detect ocular manifestations is most important for localization and broad differential diagnosis including mechanical orbital metastatic lesion. (**Ewha Med J 2017;40(3):136-139**)

Received June 7, 2017

Revised July 7, 2017

Accepted July 10, 2017

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### Key Words

Orbital neoplasms; Neoplasm metastasis; Neurologic examination; Carcinoma, ductal, breast

### Introduction

Orbital metastases are rare, representing 1%–13% of all orbital tumors [1]. When occurring, they are predominantly unilateral occurrences [2]. Bilateral metastases affecting the extraocular muscles are extremely rare. A few case reports of bilateral metastases to extraocular muscles have been presented [3–7]; they featured binocular diplopia with conspicuous bilateral external ophthalmoplegia as an initial symptom. Herein we report a case in which unilateral ptosis was an initial symptom and bilateral incomplete ophthalmoplegia was found on initial neurologic examination in invasive ductal carcinoma of the breast. The case highlights the need for a thorough neurologic examination for the localization and differential diagnosis of ocular manifesta-

tions. If the ophthalmoplegia is not compatible with neural presentation, more broad differential diagnostic considerations including mechanical orbital metastatic lesion should be considered.

### Case

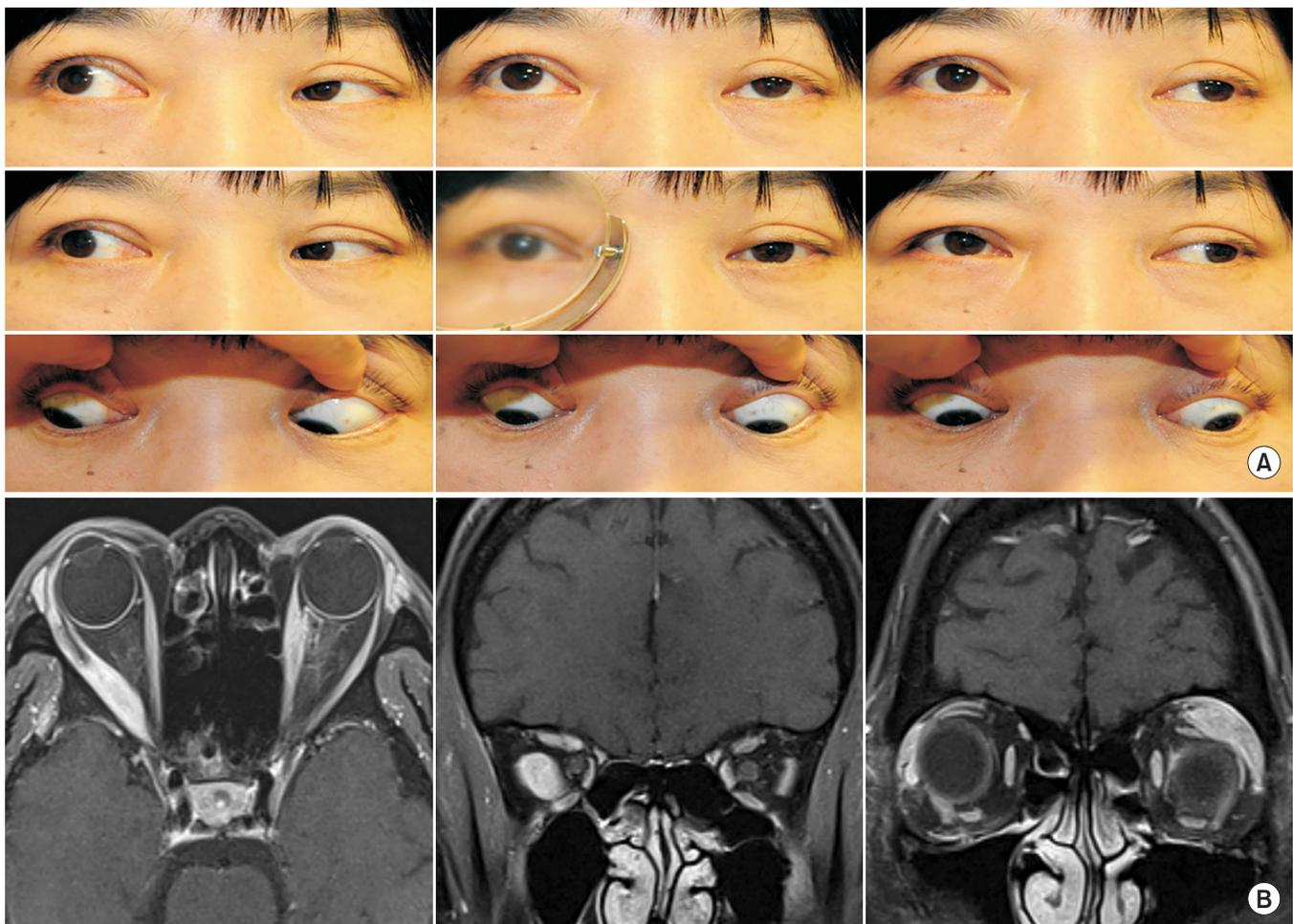
A 47-year-old woman presented with a 1-month history of gradually worsening ptosis in her left eye. She had no significant past medical history. Aside from the ptosis, she had experienced some difficulty seeing at a distance several times when driving during the prior 2 months. She reported her sight was not failing and she had not experienced double vision. The ptosis seemed to have diurnal variation, and worsened at the end

of the day. Before visiting our hospital, she visited a local hospital where she was recommended to visit a neurologic clinic for possible ocular myasthenia gravis.

External eye inspection revealed normal head posture and left eye ptosis with margin reflex distance 1 (MRD1) of 3 mm while right eye with MRD1 of 4 mm, which was characterized as non-fatigable ptosis on extended upward gazing. There was no palpable mass of the left lid. There were no signs of proptosis, periorbital erythema, tenderness, and bruit around the orbit on auscultation. An examination of the extraocular muscles revealed slightly limited adduction and abduction in the right eye, and slightly limited elevation and abduction in the left eye (Fig.

1A). Convergence and divergence were also slightly insufficient with movement of the extraocular muscles. The pupils were equal, round, and reactive to light, with no afferent pupillary defect. Confrontation visual fields were full to finger counting in all quadrants. Optical coherence tomography (OCT) and ocular pressure were within normal limits. Neurologic examination on the other cranial nerves, motor system, sensory system, and reflexes were normal.

She presented unilateral ptosis with MRD1 of 3 mm which had been gradually progressive for 1-month by history and incomplete bilateral ophthalmoplegia at initial presentation. The differential diagnosis included thyroid ophthalmopathy, orbital



**Fig. 1.** Extraocular muscles examination (A) and orbit magnetic resonance imaging (MRI) findings (B). Extraocular movement examination reveals slightly limited abduction and adduction in the right eye, and slightly limited elevation and abduction in the left eye. Left eye ptosis is evident with margin reflex distance 1 of 3 mm. Axial and coronal section of the orbit MRI shows enhancing mass (0.9×1.2×2.1 cm) in the right lateral rectus muscle of the right eye. There are enhancing masses in left medial rectus muscle of the left eye and intraconal lesion around left medial rectus muscle. Coronal section of the orbit MRI shows enhancing mass (6.7×2.5×1.5 cm sized) in left superior lateral extraconal area, which suggests the high probability of metastasis.

inflammatory responses, ocular myasthenia gravis, and neoplasm. Laboratory findings concerning thyroid function test and thyroid antibodies were normal and negative. Autoimmune antibody tests associated with vasculitis were negative. Repetitive nerve stimulation test and neostigmine test indicated no evidence of neuromuscular junction disorder. Chest computed tomography (CT) evaluation for possible hidden cancer showed enhancing masses in both breasts with enlarged lymph nodes in bilateral axillary areas, and multiple osteolytic bony lesions, which indicated a high probability of breast cancer. Abdominal and pelvic CT showed diffuse wall thickening of gastric body, which suggested the possibility of gastric cancer, although breast cancer with stomach metastasis was most likely. Magnetic resonance imaging (MRI) of the orbit indicated enhancing masses in right lateral rectus muscle, left medial rectus muscle, and left superior lateral extraconal area, which suggested a high probability of metastasis (Fig. 1B). There was no abnormal enhancing mass in brain parenchyma including cavernous portions.

We decided to take breast and stomach biopsies. Ultrasound guided biopsy of her left breast mass confirmed the presence of invasive ductal carcinoma of the breast. Immunohistochemical studies of the breast tissue demonstrated estrogen receptor (ER) and progesterone receptor (PR) were positive with Allred scoring [8] of 8 (the proportion score was 5 and intensity score was 3) in ER and 6 in PR (the proportion score was 4 and intensity score was 2). Gastric tissue biopsy results determined by endoscope examination were consistent with metastatic ductal adenocarcinoma from the breast. Immunohistochemical studies of the gastric tissue demonstrated ER and PR were positive with highest Allred scoring [8] of 8 in ER and 8 in PR. The oncoprotein human epidermal growth factor receptor 2 (HER2) was positive, as shown in the breast tissue. Whole body positron emission tomography (PET) imaging for evaluation of metastasis suggested multifocal bilateral breast cancer with bone and lymph nodes metastasis, and possible diffuse gastric cancer. Following the discovery of hormone receptor-positive breast cancer, she has been treated by hormonal therapies including the anti-estrogen drug and the luteinizing hormone-releasing hormone agonist with chemotherapy. After 6 months of treatment, cytological evaluation of cerebrospinal fluid (CSF) revealed metastatic carcinoma with the presence of malignant cells.

## Discussion

We describe a case of progressively worsening unilateral ptosis as an initial symptom and bilateral incomplete ophthalmoplegia found on initial neurologic examination. Bilateral ophthalmoplegia may be localized to the brainstem, cavernous sinus and orbit, neuromuscular junction and muscle, and nerves [9]. Our patient revealed pupil sparing bilateral ophthalmoplegia with no signs of altered level of consciousness and motor or sensory deficits, which seemingly excluded involvement of regions of the brainstem. In case of bilateral incomplete ophthalmoplegia, regions of the subarachnoid space and cavernous sinus are not likely causes. The absence of signs of ataxia, and hyporeflexia or areflexia likely excluded polyneuropathies including Fisher and Guillain-Barré syndromes. By this process of localization, regions in the orbit space including neuromuscular junction and extraocular muscles could be possible causes. In addition, according to the mechanisms that cause ptosis, unilateral ptosis could be less likely caused by aponeurotic or myogenic etiology, and neurogenic or mechanical etiology could be possible causes [10]. Based on laboratory and electrophysiologic findings, and the findings of a physical examination, thyroid ophthalmopathy, vasculitic inflammatory responses, and ocular myasthenia gravis could be unlikely causes.

The prevalence of orbital metastasis in cancer patients ranges from 2% to 4.7% [11]. Like our patient, orbital metastasis can be discovered before the primary cancer is detected. Breast cancer accounts for the most cases of orbital metastasis accounting for 28.5%–58.8% [12]. In metastatic breast cancer the most prevalent symptom of ocular manifestation is diplopia, due to a preferential involvement of extraocular muscle and surrounding orbital fat, which mechanically cause motility deficits [1,11]. And orbital metastases are predominantly unilateral occurrences [2] and bilateral metastases affecting the extraocular muscles are extremely rare. Only five cases of bilateral metastases to extraocular muscles have been reported; three cases were metastatic breast carcinoma with one case each of metastatic renal cell carcinoma and metastatic hepatocellular carcinoma [3–7]. All five patients presented with binocular diplopia and conspicuous bilateral external ophthalmoplegia as an initial symptom with or without previously diagnosed cancer, with metastasis to extraocular muscles occurring. Contrarily, our patient presented with unilateral ptosis as an initial symptom and was not accompanied

with diplopia and previously diagnosed cancer, and bilateral incomplete ophthalmoplegia was found on initial examination. Experiencing a difficulty of seeing at a distance was thought to be a symptom of ophthalmoplegia as visual acuity test and OCT were within normal limits.

The definitive diagnosis of an orbital lesion requires tissue diagnosis. Although fine-needle aspiration biopsy has been advocated, reports have described inaccuracy, complications of dissemination of tumor cells with the procedure, and a risk of globe injury [13]. In this case, there was a strong clinical, imaging, and pathological suspicion for orbital metastasis from breast cancer. And the orbit was not the only site of suspected metastasis, so tissue was obtained from the breast and stomach. In addition, CSF cytology confirmed the presence of metastatic carcinoma with malignant cells.

Treatment for metastatic breast cancer is usually palliative in intent [1]. Prognosis of patients with metastatic orbital tumors is rather poor, with a median survival ranging from 22 to 31 months for breast cancer [11,12]. In patients with hormone receptor-positive and HER2-negative tumors, hormonal therapy should be the first therapeutic choice [14]. In cases featuring both hormone receptor and HER2 receptor positive tumors, like the presented case, the optimal treatment is less clear. Tumors rich in ER as this presented case with the highest Allred scoring [8] are considered to be less responsive to chemotherapy, and hormonal therapy has the benefit of being less toxic than chemotherapy [15]. However, preclinical evidence suggests that HER2 overexpression may confer resistance to hormonal therapy, even in the presence of hormone receptors, due to crosstalk between the two pathways [15].

In summary, we report the case in which unilateral ptosis was an initial symptom and bilateral incomplete ophthalmoplegia was found on initial neurologic examination in invasive ductal carcinoma of the breast. The presence of a secondary orbital lesion presents many difficulties for differential diagnosis and treatment. Thorough neurologic examination to find ocular manifestations is most important for localization and differential

diagnosis. In addition, if the ophthalmoplegia is not compatible with neural presentation, more broad differential diagnostic consideration including mechanical orbital metastatic lesion should be considered and breast cancer should be considered as one of the possible sources.

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