Case Report

Ocular flutter as the presenting sign of lung adenocarcinoma

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Summary

Ocular flutter is a rare ophthalmic finding that could represent paraneoplastic phenomena. In adults it is most commonly associated with small cell lung cancer (SCLC). Most patients also present with other neurological defects. We report the case of a 75-year-old woman who presented with isolated ocular flutter. The ensuing workup was significant for an early lung adenocarcinoma that would not have been biopsied otherwise due to its small size. To our knowledge, this is the first reported case of isolated ocular flutter as the presenting symptom of non-SCLC.

Introduction

Nystagmus refers to eye movement abnormalities that are characterized by an abnormal slow phase followed by either a slow phase or a fast phase. Saccadic intrusions, on the other hand, are abnormal eye movements that have a pathologic fast saccade followed by a fast corrective saccade, with or without an intersaccadic interval. Ocular flutter, by contrast, is clinically characterized by intermittent bursts of conjugate, horizontal saccades without an intersaccadic interval.¹ The amplitude of the saccades varies and may be so small that the saccades can only be observed by means of an ophthalmoscope or slit-lamp.¹ The frequency tends to be 10–15 Hz, though it increases as the saccadic amplitude decreases.¹ Patients with ocular flutter often complain of oscillopsia.²

Ocular flutter is closely related to opsoclonus, where saccades are multidirectional. Importantly, the two conditions have the same localizing value and differential diagnosis.³ The most common etiologies are paraneoplastic syndrome, brainstem encephalitis, metabolic-toxic disturbance, and idiopathic.¹ In children, 50% of cases prove to be a paraneoplastic manifestation of neuroblastoma.³ In adults, paraneoplastic causes include malignancies, such as small cell lung cancer (SCLC)⁴ and breast cancer.⁵

Case Report

A 75-year-old woman presented to the Massachusetts Eye and Ear Infirmary with a 2-month history of intermittent, daily episodes characterized as “eyes were darting back and forth.” Her medical history was significant for breast ductal carcinoma in situ (status post bilateral mastectomy 1 year earlier), ulcerative colitis with partial colectomy, pulmonary embolus, toxic thyroid adenoma, asthma, uterine fibroid, and a peripheral neuropathy. Review of systems was significant for a 7-month history of increasing fatigue. Her family history was significant for a mother with Parkinson’s disease.

On examination, extraocular motility revealed isolated and intermittent episodes of low-amplitude, high-frequency horizontal saccades without an intersaccadic interval, consistent with ocular flutter (Video 1). Pursuit and saccadic function was normal. Ductions were full, and versions were comitant. The remainder of the examination was unremarkable.

A full-body CT scan revealed a small, right upper lobe lung mass. The consulting thoracic surgeon was hesitant to biopsy the lesion due to its small size, but given the concern that the ocular flutter was a manifestation of a paraneoplastic syndrome, he performed a fine needle aspiration of the lesion that yielded malignant cells. A

Published January 17, 2014.

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doi:10.5693/djo.02.2013.10.002

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right upper lobectomy was performed, and histopathology revealed a 2.4 cm, well-differentiated adenocarcinoma with bronchioalveolar and papillary features. Paraneoplastic autoantibody panels (Ri, Hu, Yo, Ma1, Ma2, LEMS, CAR, CV2, Zic4, and VGKC) were negative. Given that the ocular flutter was not symptomatic, no further treatment was provided. The patient has remained stable through 4.5 years of follow-up, without evidence of metastatic disease. Ocular findings remain unchanged.

Discussion

Ocular flutter is a concerning ophthalmic finding because its potential etiologies include life-threatening entities. In adults the most common etiology is a paraneoplastic syndrome. Tumors reported to be associated with this paraneoplastic syndrome include those of the lung and breast. Our case is unique because of its several atypical features. While there are numerous reports of opsoclonus associated with lung cancer, they are almost invariably the small cell type,⁶ which is highly associated with a paraneoplastic syndrome. The pathology in this case was consistent with non-SCLC. There are only a few reports of opsoclonus associated with non-SCLC,⁷⁻⁹ and to the best of our knowledge this is the first reported case of ocular flutter associated with a non-small cell carcinoma. Very early diagnosis of a small malignant lesion, which would not have otherwise been biopsied, was fortunately possible due to the high clinical suspicion for a paraneoplastic syndrome. The paraneoplastic ocular flutter was unlikely to be caused by the previous history of breast carcinoma because the breast cancer was definitely treated in the past without any associated ocular or cerebellar symptoms leading to or during the active disease period.

The exact etiology of ocular flutter and opsoclonus is unknown. It has been suggested that opsoclonus and flutter are due to dysfunction of omnipause neurons. There is also evidence to suggest that it is an autoimmune-mediated disorder, such as the finding of neuron-specific autoantibodies (eg, anti-Ri, anti-Hu) in some patients with the disorder and the finding that the disorder could respond to immunosuppressive therapy.⁹ The autoantibody screen performed in this case was negative, but this is not unusual. The majority of patients with opsoclonus, for example, are seronegative for autoantibodies.¹⁰

It is important for the clinician to differentiate ocular flutter from other saccadic motility disorders. Microsaccadic oscillations and square wave jerks can be distin-

guished from ocular flutter by the presence of an intersaccadic interval. Nystagmus can be differentiated by the presence of a slow and fast phase or two slow phases. Saccadic pulses can closely resemble ocular flutter, characterized by small-amplitude saccades away from fixation followed by a rapid drift back.¹ They can occur in normal subjects. Without eye-movement recording equipment, it is not always possible to distinguish the two. Thus we cannot rule out the possibility that the eye movement abnormality observed in our patient was saccadic pulses, although it would be extremely atypical that the workup was positive for a lung carcinoma. We believe that any eye movement abnormality that clinically resembles ocular flutter must be presumed to be ocular flutter until proven otherwise due to the grave implications of a missed diagnosis.

Management for opsoclonus and ocular flutter includes treatment of the underlying cause, but the motility defect often persists despite successful treatment of the tumor,⁹ as was the case with our patient. Further options include various immunosuppressive therapies, including prednisone, intravenous gammaglobulin, plasmapheresis and rituximab.¹¹ Anticonvulsants, such as clonazepam¹¹ and gabapentin,¹² have also proved effective. Our patient was not troubled by her symptoms; therefore, further interventions were deferred.

This case emphasizes the need for clinicians to carefully examine patients who present with saccadic anomalies and to perform an aggressive workup for malignancy when ocular flutter (or opsoclonus) is detected because it could potentially lead to early diagnoses of solid tumors still amenable to definitive treatment by surgical intervention.

Literature Search

The authors searched PubMed on January 17, 2014, for English-language articles (1950-present) using the following search terms: *ocular flutter*.

References

1. Leigh RJ, Zee DS. Diagnosis of nystagmus and saccadic intrusion. *The Neurology of Eye Movements*. 4th ed. New York: Oxford University Press, 2006:475-558.
2. Koh SH, Kim SH. Ocular flutter induced only by optokinetic stimulation. *J Clin Neurosci* 2006;13:479-81.
3. Liu GT, Volpe NJ, Galetta SL. Nystagmus and nystagmoid eye movements. In: *Neuro-Ophthalmology: Diagnosis and Management*. Philadelphia: Saunders, 2010:587-610.
4. Luque FA, Furneaux HM, Ferziger R, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. *Ann Neurol* 1991;29:241-51.

5. Luque FA, Furneaux HM, Ferziger R, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. *Ann Neurol* 1991;29:241-51.
6. Sahu JK, Prasad K. The opsoclonus–myoclonus syndrome. *Pract Neurol* 2011;11:160-6.
7. Hiasa Y, Kunishige M, Mitsui T, et al. Complicated paraneoplastic neurological syndromes: a report of two patients with small cell or non-small cell lung cancer. *Clin Neurol Neurosurg* 2003;106:47-9.
8. Bataller L, Graus F, Saiz A, Vilchez JJ, Spanish Opsoclonus-Myoclonus Study Group. Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. *Brain* 2001;124:437-43.
9. Pranzatelli MR. The immunopharmacology of the opsoclonus-myoclonus syndrome. *Clin Neuropharmacol* 1996;19:1-47.
10. Wong A. An update on opsoclonus. *Curr Opin Neurol* 2007;20:25-31.
11. Garg RK, Kar AM, Dixit V. Opsoclonus—myoclonus syndrome in an adult: a case report and response to clonazepam. *Indian J Ophthalmol* 1996;44:101-2.
12. Pistoia F, Conson M, Sarà M. Opsoclonus-myoclonus syndrome in patients with locked-in syndrome: a therapeutic porthole with gabapentin. *Mayo Clin Proc* 2010;85:527-31.

*Video 1 available at the journal website,
www.djo.harvard.edu.*