Clinical Reasoning: A 48-year-old Woman With 6 Months of Vivid Visual Hallucinations

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ABSTRACT

Visual hallucinations are frequently encountered in clinical practice. It is critical for neurologists, particularly those in training, to develop a systematic approach for evaluating patients presenting with such unique and often perplexing symptoms. Here, we present the case of a 48-year-old woman who developed vivid visual hallucinations after receiving nivolumab for melanoma. We discuss the broad differential diagnosis for visual hallucinations and how the history and examination can guide one’s evaluation.

SECTION 1

A 48-year-old woman with melanoma, anxiety, and depression presented to the neurology clinic with the chief complaint of vision loss and hallucinations.

The patient reported six months of gradually progressive, symmetric, central vision loss in each eye (OU) accompanied by visual hallucinations. There was no associated headache. The described hallucinations were silent, immobile, non-threatening, and entailed several semiologies including cartoon-like teddy bears and spiders, text on blank paper, faces with elaborate hair, wavy lines, and splotches of color. The hallucinations occurred intermittently throughout the day without clear provoking factors.

The ophthalmologic history was notable only for refractive error. The past medical history included anxiety, depression, and stage IIIb melanoma locally metastatic to lymph nodes diagnosed nine months prior, for which she underwent local excision and nine cycles of nivolumab. Current medications included fluoxetine and atomoxetine. Nivolumab had been held approximately two months prior to neurology evaluation due to adrenal insufficiency. The family history was notable for melanoma in both parents. The social history was relevant for no recreational drug use or alcohol consumption.

Examination of afferent visual function revealed best-corrected distance visual acuities of 20/50 in the right eye (OD) and 20/25 in the left eye (OS), dyschromatopsia OD, and concentric constriction of the visual filed OU (affecting the central field OD) on automated perimetry (Figure, A, B). The funduscopic examination revealed bilateral optic disc edema, obscuring most vessels on the disc OD and at the disc margin OS (Figure C, D). The general neurologic examination was unremarkable.

Questions for Consideration:
1) What is the differential diagnosis for visual hallucinations?
2) What are the key features relevant in the characterization of visual hallucinations?

SECTION 2

The broad differential diagnosis for visual hallucinations is presented in the Table below.

In this patient, Charles Bonnet Syndrome (CBS) was thought to be the most likely diagnosis given the silent, non-threatening, mostly formed visual hallucinations in the presence of afferent vision loss and preserved insight. Evaluation included normal complete blood count, electrolytes, creatinine, liver function tests, serum and urine toxicology screens.

Questions for Consideration:

1) What additional diagnostic testing can help clarify the underlying etiology?
MRI orbit with gadolinium revealed restricted diffusion along the bilateral optic nerves as well as abnormal contrast enhancement extending from the globe to the optic chiasm (Figure E and F, respectively). MRI of the brain and cervical spine with contrast were normal. EEG revealed no focal abnormalities, epileptiform changes, or seizures.

Lumbar puncture revealed an opening pressure of 15 cm H$_2$O and a lymphocytic pleocytosis (53 WBC, 94-98% lymphocytes, 2-5% monocytes, 0-1% PMNs), with 213 RBC, 60 mg/dL protein, and 54 mg/dL glucose. No oligoclonal bands were noted and IgG index was within normal limits (0.6 mg/dL). Serum myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP-4) antibodies were negative and flow cytometry was unremarkable. Serial lumbar punctures revealed no evidence of malignant cells on cytopathology.

Questions for Consideration:

1) What is the differential diagnosis for optic neuritis?
2) What aspects of this patient’s history and physical exam are pertinent in evaluating optic neuritis?
SECTION 4

Typical optic neuritis is clinically characterized by a unilateral optic neuropathy associated with ipsilateral eye pain, which is provoked or worsened by eye movement. The term optic neuritis generally implies an inflammatory, non-infectious, mechanism. Optic neuritis may be a manifestation of multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD), or sarcoidosis. Infectious, neoplastic, vasculitic, toxic, and para-inflammatory (e.g., from immune checkpoint inhibitor therapy) etiologies should also be considered. Many cases remain idiopathic with a presumed autoimmune mechanism but no ascertainable disorder to account for its presence. Features including nadir visual acuity, bilaterality, presence of optic disc edema, length of optic nerve enhancement, and clinical course provide clues to the underlying cause of optic neuritis. (5-8)

This patient’s presentation was felt to be atypical due to the bilateral optic nerve involvement, lack of pain, and long segment optic nerve enhancement on MRI. While bilateral disc edema may also raise concern for elevated intracranial pressure, the color vision loss out of proportion to the degree of edema and lack of headache further supported an optic neuropathy.

Treatment of this patient’s melanoma included immune checkpoint inhibitor (ICI) therapy. She received nine cycles of nivolumab prior to presentation. The associated vision loss developed after several cycles. Immune checkpoint inhibitors enhance T-lymphocyte activity by binding antigens with facilitate for T-lymphocyte inhibition. Nivolumab inhibits programmed cell death protein 1, increasing T-cell reactivity against tumor cells. Optic neuritis as an adverse event associated with ICI use may involve direct T-cell-mediated optic neuritis or unmasking of a previously-quiescent neuroinflammatory disease with the potential to cause optic neuritis. (9, 10)

This patient’s evaluation included negative anti-MOG and anti-AQP4 antibodies, a CSF examination without evidence of oligoclonal bands, and an MRI brain and cervical spine without characteristic lesions of MS or NMOSD. There were no malignant cells on serial lumbar punctures to support the diagnosis of leptomeningeal melanomatosis. Features supportive of nivolumab-associated optic neuritis include the slow tempo of progression, painlessness, bilaterality, and longitudinally-extensive enhancement of the optic nerves – all of which developed after receiving nivolumab. (11)
DISCUSSION

Common causes of visual hallucinations include CBS, migraine with aura, occipital lobe seizures, peduncular hallucinosis, neurodegenerative disease, hallucinogen use, alcoholic hallucinosis, delirium, and psychiatric disease. The formed, stereotyped, silent nature of the hallucinations in the setting of vision loss, preserved insight, and an otherwise-negative evaluation is consistent with CBS. Notably, while this syndrome is typically described in patients with loss of central vision (e.g., from macular degeneration), this case demonstrates that CBS hallucinations can occur in any form of visual loss, whether it is central or peripheral.

The cause of afferent visual dysfunction in this patient was checkpoint inhibitor-associated optic neuritis. Discontinuation of nivolumab and initiation of corticosteroids with plasma exchange lead to improvement in this patient’s vision and cessation of her visual hallucinations over the next few months. During this time, the visual field abnormalities returned to normal in the left eye and improved significantly in the right eye.

The patient provided informed consent (see supplemental file).
References

Table: Differential Diagnosis for Visual Hallucinations

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<tr>
<th>Differential Diagnosis</th>
<th>Hallucination Types</th>
<th>Associated Features</th>
<th>Tailored Workup</th>
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</table>
| Charles Bonnet Syndrome      | Formed or unformed. Typical semiologies include detailed images of people, faces, animals, flowers, trees, plants, and miniature images of people and objects (“Lilliputian hallucinations”).  
(3) Typically static and silent. Typically non-threatening. (4) | Preserved insight into hallucinations, central or peripheral afferent vision loss (e.g. optic neuritis, macular degeneration)  
(1,2) | Ophthalmological evaluation, lumbar puncture, MRI orbits, MRI brain |
| Occipital lobe seizure       | Unformed, mobile, silent, usually including small, brightly colored spots or shapes that flash. With visual association cortex involvement, may have more complex hallucinations.  
| |  | May occur as focal seizure with impairment of consciousness or evolution to bilateral convulsions. Tumors, vascular malformations, and developmental abnormalities are most commonly identified | EEG, MRI seizure protocol |
| Migraine with visual aura    | Unformed, silent, typically fortification spectra, scintillating scotoma, “C” shapes, or “heat waves.” Slow evolution in character, size, or position within the visual field, generally lasting 20 - 60 minutes.  
| |  | Unilateral headache, May be preceded by prodromal symptoms including yawning, depression, euphoria, irritability, food cravings, neck stiffness, and constipation | Detailed neurologic history and exam |
| Dementia with lewy bodies    | Silent, formed or unformed, may be mobile and potentially threatening  
<p>| |  | Neurodegenerative disease with cognitive fluctuations, REM sleep behavior disorder, Parkinsonism | EEG, MRI brain, dopamine transporter imaging, polysomnography |</p>
<table>
<thead>
<tr>
<th><strong>Advanced idiopathic Parkinson’s disease</strong></th>
<th>Silent, formed or unformed, may be mobile and threatening</th>
<th>Neurodegenerative disease with tremor, bradykinesia, rigidity, postural instability</th>
<th>EEG, MRI brain, dopamine transporter imaging</th>
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<td><strong>Delirium</strong></td>
<td>Formed or unformed, threatening or nonthreatening, silent or not. May have auditory component.</td>
<td>Acute onset fluctuating mental status</td>
<td>Serum electrolytes, creatinine, glucose, calcium, complete blood count, liver function tests, and urinalysis</td>
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<td><strong>Hallucinogenic substances</strong></td>
<td>Formed or unformed, threatening or nonthreatening. Typically acute-onset following drug exposure.</td>
<td>Heightened perception of sensory input, a distorted sense of time, euphoria, and a sense of well-being. May also present with hallucinogen persisting perception disorder, a chronic disorder in which patients experience recurrent visual hallucinations or perceptual distortions long after initial drug exposure.</td>
<td>Fingerstick glucose, electrocardiogram, serum and urine toxicology screen (although hallucinogens are typically not assayed)</td>
</tr>
<tr>
<td><strong>Psychiatric illnesses</strong></td>
<td>Most typically auditory (schizophrenia, depression with psychotic features may include visual)</td>
<td>Delusions, psychiatric instability</td>
<td>Detailed history</td>
</tr>
<tr>
<td><strong>Hypnopompic and hypnagogic hallucinations</strong></td>
<td>Dream-like, complex Narcolepsy, experienced during transitions between sleep and wakefulness</td>
<td>Polysomnogram, CSF measurement of orexin-A (hypocretin-1)</td>
<td></td>
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<tr>
<td><strong>Peduncular hallucinosis</strong></td>
<td>Vivid, formed, mobile, threatening, silent</td>
<td>Majority of associated structural lesions found in the diencephalon and mesencephalon</td>
<td>MRI</td>
</tr>
<tr>
<td><strong>Alcoholic hallucinosis</strong></td>
<td>Vivid, possibly threatening. May be accompanied by tactile (formication) or auditory</td>
<td>Follows decrease in or cessation of alcohol intake in patients with chronic alcohol overuse</td>
<td>Blood alcohol level (12-24 hours prior to hallucination onset)</td>
</tr>
</tbody>
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**Figure Title:** Automated Perimetry, Fundoscopy, and MRI Findings

**Figure Legend:**

**Figure:** Automated perimetry demonstrates primarily concentric vision loss in the left (A) less than right (B) eye with bilateral disc edema (C, D). Axial diffusion weighted (E) and post-contrast coronal (F) MRI demonstrates mild enlargement of the bilateral, right greater than left, optic nerves with slowed diffusion (arrows, E) and bilateral central enhancement (arrows, F). These findings are consistent with bilateral optic neuritis.
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