

# Clinical Reasoning: New-Onset Diplopia and Headache in a Patient With Metastatic Breast Cancer

Skylar A. Rizzo, BS, Eoin P. Flanagan, MBBCh, Jorge A. Trejo-Lopez, MD, Michel Toledano, MD,\* and Nicholas H. Chia, MBBS\*

## Correspondence

Dr. Toledano  
toledano.michel@mayo.edu

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## Section 1

A 54-year-old woman presented with progressively worsening headache and diplopia. Five months earlier, she began to experience imbalance and nonspecific dizziness, followed by intermittent tingling and numbness over her right eyebrow, eyelid, and cheekbone. For the next 2 months, she suffered intermittent severe right frontal headaches, subsequently transforming to an unremitting dull bifrontal headache without classical migrainous features or positional exacerbation. She then noticed horizontal binocular diplopia with a mild vertical component. She was referred to neurology by her oncologist.

Notably, she had ER+, PR+, HER2–, and BRCA– invasive lobular breast cancer diagnosed 3 years prior and managed with bilateral mastectomy, adjuvant radiation therapy, and tamoxifen. She received leuprolide but changed to letrozole after total abdominal hysterectomy with bilateral salpingo-oophorectomy (for postmenopausal bleeding with a family history of endometrial cancer). One year earlier, lumbar spinal bony metastases were confirmed by biopsy. PET scan 4 months before hospitalization showed no evidence of disease progression. At presentation, her medications included palbociclib, fulvestrant, and denosumab. Crohn disease had been diagnosed 30 years earlier and treated with azathioprine, which had been stopped over a year before her current presentation without disease flares since.

On examination, she was unable to fully abduct either eye, more severe on the right. There was subtle right hypertropia only detectable with alternating cover testing, not clearly worse in any direction of gaze or with head tilt. There was no ptosis, proptosis, or chemosis. She had right optic disc swelling with normal visual acuity and fields. The pupils were equal and reactive to light without relative afferent pupillary defect. Temperature sensation was reduced over the right forehead. The remainder of the examination was unremarkable.

## Questions for Consideration:

1. Where do you localize the lesion?
2. What follow-up tests should you consider?

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\*These authors contributed equally to this work as senior authors.

From the Mayo Clinic Medical Scientist Training Program (S.A.R.); Department of Neurology (E.P.F., M.T., N.H.C.) and Department of Laboratory Medicine and Pathology (E.P.F., J.A.T.-L.), Mayo Clinic, Rochester, MN.

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## Section 2

The presentation is concerning for a secondary cause of headache due to her history of neoplasm, neurologic deficit, older age, and progressive atypical headache, all red flags in the SNNOP10 criteria.<sup>1</sup> She had multiple cranial neuropathies including bilateral cranial nerve [CN] VI, right VI, and suspected right IV. Cranial neuropathy may localize to the brainstem, subarachnoid space, dura, or extracranial soft tissues, and localization of multiple cranial neuropathies requires consideration of the anatomic locations shared by those nerves. Classic syndromes of patterned cranial nerve involvement have been well described; relevant considerations in this patient include orbital apex syndrome (involving cranial nerves II, III, IV, V<sub>1</sub>, and VI), superior orbital fissure syndrome (CN III, IV, V<sub>1</sub>, and VI), and cavernous sinus syndrome (CN III, IV, V<sub>1</sub>, V<sub>2</sub>, VI, and carotid sympathetic fibers).

Although the patient had right-sided deficits affecting CN IV, VI, and VI, there was no evidence of oculomotor palsy or Horner syndrome. The presence of unilateral disc swelling suggests a process affecting the optic nerve or sheath within the orbit or at the orbital apex, although normal visual acuity and lack of afferent pupillary defect argue against optic neuropathy. The patient's findings do not adhere to a specific cranial nerve syndrome but suggest an approximate localization. However, a unilateral lesion is insufficient to explain the contralateral CN VI palsy that may indicate a second lesion (multifocal disease) or a generalized asymmetric process affecting the meninges or CSF. Brainstem involvement is unlikely in the absence of long-tract signs

affecting the limbs. Intracranial hypertension may cause bilateral CN VI palsies and can be falsely localizing because of the prolonged subarachnoid course of CN VI. However, this would be unexpected to cause unilateral optic disc swelling, although unilateral optic disc edema and bilateral CN VI palsies may be seen in the setting of mass lesions (Foster Kennedy syndrome).

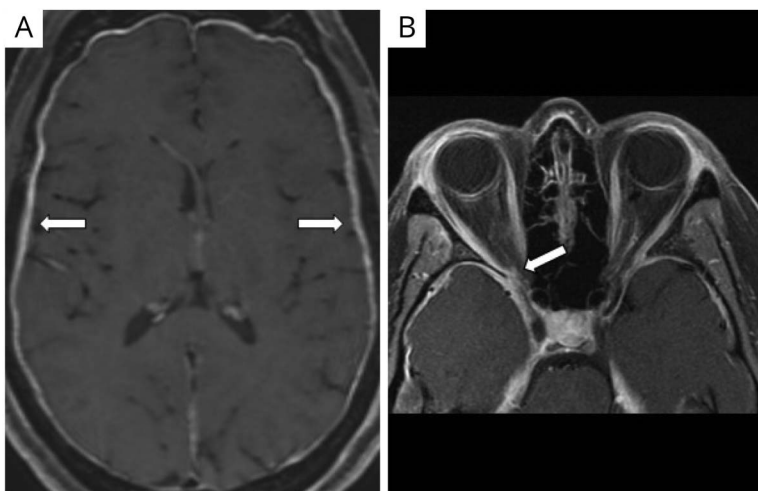
Contrast brain MRI and whole-body PET were performed to assess for new metastatic disease. MRI demonstrated widespread smooth dural thickening and enhancement with emphasis at the right orbital apex, possibly involving the optic sheath but not the nerve (Figure 1). PET scan showed fluorodeoxyglucose (FDG)-avid lesions in the left cervical lymph nodes, sternum, lumbar spine, and sacrum. Contrast MRI of the entire spine showed previously known spinal metastases.

CSF analysis showed 2 nucleated cells/ $\mu$ L (normal 0–5), protein 41 mg/dL (normal 0–35 mg/dL), glucose 63 mg/dL with plasma glucose 92 mg/dL (normal CSF glucose is 60% of plasma/serum glucose), and opening pressure 20 cm H<sub>2</sub>O (normal 5–25 cm H<sub>2</sub>O). No malignant cells were detected, and all cultures were negative. Rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, QuantiFERON-TB Gold Plus, and serum IgG4 were negative. Serum C-reactive protein (CRP) was increased at 37.8 mg/L (normal <8).

### Questions for Consideration:

1. What differential diagnoses would you consider?
2. What testing is necessary to confirm a diagnosis?

**Figure 1** Diagnostic Imaging



Post-gadolinium MRI: global pachymeningeal thickening and enhancement axial (A) and with asymmetric enhancement at the right orbital apex in axial (B).

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## Section 3

Dural (pachymeningeal) enhancement may be due to neoplasia, inflammation, infection, or secondary to intracranial hypotension. Although intracranial hypotension is associated almost exclusively with smooth global pachymeningeal enhancement, other causes of duropathy can display smooth, irregular, or nodular patterns. Neoplastic causes include lymphoma or metastatic carcinomatosis, most commonly because of breast or lung cancer.<sup>2,3</sup> Meningiomas can also result in pachymeningeal thickening and enhancement around the dural tail.<sup>4</sup> Inflammatory and autoimmune disorders associated with pachymeningeal disease include IgG4-related disease, granulomatosis with polyangiitis, sarcoidosis, rheumatoid arthritis, relapsing polychondritis, Behcet disease, and Vogt-Koyanagi-Harada syndrome.<sup>2,3</sup> Infection may cause isolated pachymeningitis but more commonly is associated with leptomeningitis or a combination of the two.<sup>4</sup> Bacterial causes include tuberculosis, *Treponema*, *Borrelia*, and contiguous spread from the sinuses or ears (especially *Pseudomonas*), whereas fungal causes include *Aspergillus*, *Coccidioides*, *Histoplasma*, and *Cryptococcus*.<sup>2,5,6</sup> Finally, intracranial hypotension may be iatrogenic, after lumbar puncture, neurosurgery, or overshunting.<sup>4</sup> Spontaneous intracranial hypotension (SIH) occurs in the context of a spinal CSF leak because

of ventral dural tear, meningeal nerve root diverticulum, or CSF-venous fistula.<sup>7</sup>

Metastatic disease was strongly considered because of her known history. CSF cytology can be falsely negative, especially early in disease course,<sup>8</sup> although sensitivity improves with repeat testing. Inflammatory causes remained a consideration, given the patient's history of autoimmune disease with cessation of immunosuppression and elevated CRP, although autoimmune serologies were negative. Orthostatic headache is typical in SIH rather than the constant headache seen in our patient; however, there is marked variability in headache phenotype, and positional exacerbation may attenuate in chronic cases.<sup>7</sup> The patient's CSF opening pressure was not low, but a normal pressure is found in two-thirds of patients with SIH.<sup>7</sup> Other imaging findings typical of SIH, such as brain sag or venous sinus and pituitary enlargement, were absent on MRI.<sup>7</sup>

Fine-needle aspiration of the FDG-avid submandibular lymph node revealed lymphocytes with abundant granulomatous inflammation. There was no evidence of malignancy, and mycobacterial and fungal stains were negative.

### Question for Consideration:

1. What further testing should be performed?

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## Section 4

Given the non-neoplastic lymph node biopsy, a dural biopsy was performed to definitively evaluate the etiology of the pachymeningeal enhancement. Biopsy showed non-necrotizing granulomatous and histiocytic inflammation without evidence of malignancy or infection (Figure 1). With reasonable exclusion of other causes of granulomatous inflammation and a compatible clinical syndrome of multiple cranial neuropathies due to pachymeningitis and probable optic perineuritis, diagnostic criteria for neurosarcoidosis were met.<sup>9</sup> The patient was treated with IV methylprednisolone 1 g daily for 5 days followed by 3 months of oral prednisone 60 mg daily. Oncologic treatments were continued.

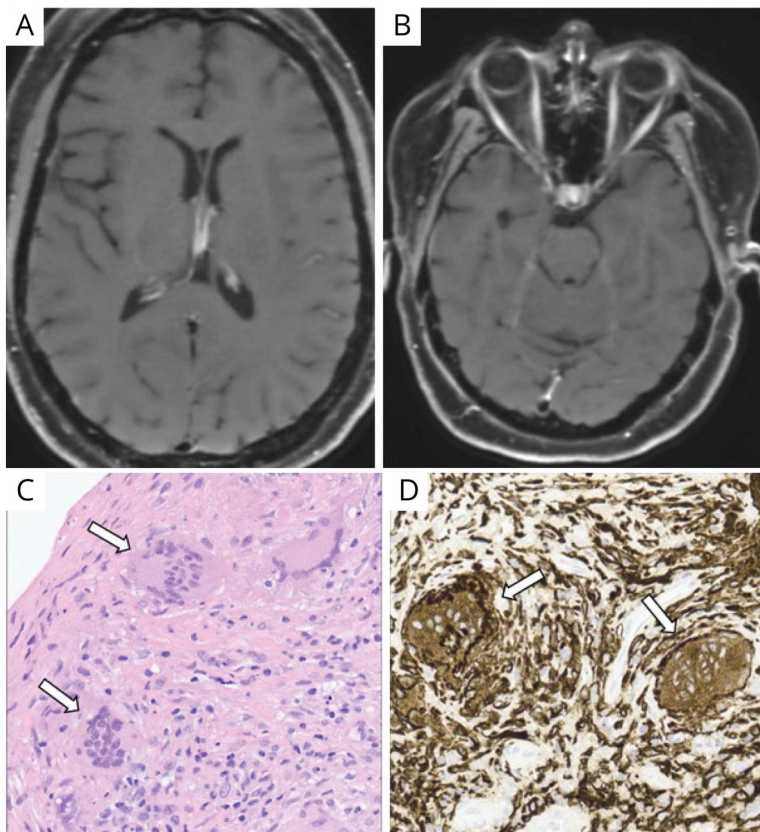
At 3-month follow-up, her oculomotor abnormalities and right optic disc swelling had resolved, although dull headache remained. Repeat contrast brain MRI showed near-complete resolution of the prior gadolinium enhancement (Figure 2).

## Discussion

This case demonstrates the importance of systematically confirming a diagnosis even when the diagnosis appears obvious. Despite the presence of metastatic disease, the underlying cause of her symptoms was not neoplastic. Misdiagnosis of malignancy in this case may have had significant management and prognostic implications.

Non-necrotizing granulomatous inflammation of the dura is not specific for neurosarcoidosis, and clinical judgment is required to rule out other possible causes.<sup>9</sup> Malignancy and infectious causes were ruled out by histopathology and microbiological testing. The patient's history raises the possibility of granulomatous inflammation because of extraintestinal Crohn disease. Although the patient did not have active gastrointestinal disease, it is recognized that extraintestinal manifestations often do not parallel intestinal disease; furthermore, the patient's long-term immunosuppression had been ceased. However, reports of

**Figure 2** Histology and Posttreatment Imaging



Post-gadolinium axial MRI: resolution of global pachymeningeal thickening and enhancement (A) and remaining asymmetric enhancement at the right orbital apex (B). Dura with non-necrotizing granulomatous and histiocytic inflammation at  $\times 400$  magnification: H&E-stained sections (C) show segments of dura involved by a patchy distribution of histiocytic inflammation, coalescent into non-necrotizing granulomas (arrows). Histiocytic and granulomatous inflammation is highlighted by CD68 immunohistochemistry (D) and is negative for evidence of fungal or acid-fast organisms by Grocott methenamine silver and acid-fast bacilli studies (studies not shown).

direct CNS involvement in Crohn disease are rare and involve cerebral lesions with a single case of pachymeningitis reported in a patient with coexisting relapsing polychondritis.<sup>10,11</sup>

This case also raises the potential association between malignancy and granulomatous inflammation. The term “sarcoid-like reaction” (SLR) is sometimes used in the literature to designate the presence of noncaseating granuloma pathologically indistinguishable from sarcoidosis but hypothesized to be triggered by an antigen, commonly in the setting of malignancy or medication.<sup>12</sup> In the case of malignancy, SLRs are usually asymptomatic and most often affect lymph nodes draining the tumor or the involved organ itself.<sup>13</sup> However, overt sarcoidosis (and neurosarcoidosis) may occur with malignancy, including breast cancer, which usually—but not always—precedes the sarcoidosis diagnosis.<sup>14</sup>

Drug-related SLRs are clinically identical to sarcoidosis but usually remit with cessation of the offending drug.<sup>12</sup> There is a preponderance of pulmonary and dermatologic involvement. SLRs are most frequently reported with immune checkpoint inhibitors, interferons, highly active antiretroviral therapy, and, paradoxically, tumor necrosis factor-alpha inhibitors.<sup>12</sup> There is a single case report of a palbociclib SLR that presented with hilar and mediastinal lymphadenopathy.<sup>15</sup> Our patient’s disease onset was not clearly linked to commencement of palbociclib, making drug-induced SLR less likely.

In summary, this patient’s clinical syndrome and diagnostic testing were typical for systemic neurosarcoidosis. Given the extent of involvement and asynchronous onset in relation to palbociclib, it remains unclear whether this represented the sort of secondary granulomatous inflammation that has been described as SLR—if indeed this diagnosis represents a pathophysiologically and clinically distinct entity. Regardless of the diagnostic label, such pathologies are steroid responsive, and treatment should be offered to those with significant symptoms, as exemplified by our patient’s excellent clinical and radiologic response.

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## Appendix Authors

Name	Location	Contribution
<b>Skylar A. Rizzo, BS</b>	Mayo Clinic Medical Scientist Training Program, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and study concept or design
<b>Eoin P. Flanagan, MBBCh</b>	Department of Neurology, Mayo Clinic, Rochester, MN; Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
<b>Jorge A. Trejo-Lopez, MD</b>	Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
<b>Michel Toledano, MD</b>	Department of Neurology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and co-senior author
<b>Nicholas H. Chia, MBBB</b>	Department of Neurology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and study concept or design

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