AMPA Receptor Encephalitis in a Patient With Metastatic Breast Cancer Receiving Palbociclib

A Case Report

Elizabeth Matthews, MD, Barrie Schmitt, MD, Michlene Passeri, MD, Christopher Mizenko, MS, Karen Orjuela, MD, and Amanda Piquet, MD

Neurol Neuroimmunol Neuroinflamm 2022;9:e200012. doi:10.1212/NXI.0000000000200012

Abstract

Objective
To report a case of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis (AMPARE) as a potential immune-mediated complication of palbociclib (a cyclin-dependent kinase 4/6 inhibitor).

Background
Medication-induced autoimmune encephalitis is an increasingly recognized entity. To date, cases have been reported with immune checkpoint inhibitors (ICIs), typically within 3 months and while cancer is responding to immunotherapy.

Results
A 55-year-old woman with metastatic breast cancer presented with new-onset neurologic symptoms. After diagnosis and treatment in 2008, she was in remission from 2010 to 2021. In April 2021, she developed metastatic recurrence. She started palbociclib in June 2021. PET scan in August 2021 showed improved metastases without new lesions. In September 2021, she developed encephalopathy, vertical nystagmus, and ataxia. Workup revealed AMPA-R antibodies. Palbociclib was stopped, and she received steroids, IVIg, and rituximab with marked improvement in her neurologic symptoms.

Discussion
AMPARE is a well-described paraneoplastic syndrome. However, it is now understood that paraneoplastic syndromes can be driven by immunomodulatory medications, namely ICIs. Although palbociclib primarily prevents tumor proliferation, emerging data suggest that it may also be immunomodulatory. Given that our patient’s AMPARE developed shortly after initiation of palbociclib while her cancer was responding to therapy, we postulate that it may have been unmasked by palbociclib, similarly to what has been reported with ICIs.
It is increasingly recognized that autoimmune encephalitis (AIE) may be induced or unmasked by immunomodulatory medications. To date, cases have been reported with immune checkpoint inhibitors (ICIs). Palbociclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, which primarily works by arresting tumor cells from entering the G1 cell cycle phase, as opposed to through immune system activation. However, there is growing evidence that palbociclib may have previously unrecognized immunomodulatory effects and thus may also carry the risk of immune-related adverse events (irAEs). We present a case of possible palbociclib-mediated AIE.

Case Report

A 55-year-old woman with metastatic breast cancer presented with new-onset neurologic symptoms. She initially developed breast cancer in 2008 (ER+/PR+/HER2−, treated with lumpectomy, radiation, and tamoxifen), followed by contralateral breast cancer in 2009 (ER+/PR+/HER2+, treated with lumpectomy, chemotherapy [docetaxel/carboplatin/cyclophosphamide/trastuzumab], and hormonal therapy). She had no evidence of disease from 2010 until April 2021, when she developed facial swelling and was found to have bone and lymph node metastases. She received radiation from April 2021 to June 2021 and started palbociclib in June 2021. A PET scan in August 2021 showed improvement in her metastases without new lesions. In September 2021, she developed confusion, blurry vision, vertical nystagmus, ataxia, constipation, and urinary retention. MRIs are shown in the Figure. 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clinically and radiographically to treatment, whereas para-neoplastic syndromes are often described in the setting of tumor progression or recurrence.\textsuperscript{15,16} Conversely, ICI-associated AIE is more likely to occur when cancer is responding to therapy.\textsuperscript{1,5} Given that palbociclib has a distinct mechanism to ICIs, it is difficult to directly compare their complications. However, it does make plausible sense that successful antitumor activity and detrimental autoimmunity would be likely to co-occur due to an overall robust immune response to palbociclib. Based on this biologic plausibility, the timing of our patient’s presentation, the state of her cancer, and her rapid recovery after discontinuation of palbociclib and initiation of immunotherapy, we postulate that palbociclib may have induced or unmasked her AMPA-R encephalitis.

Acknowledgment
The authors acknowledge the patient and her family for consenting to the publication of this case report, as well as the University of Colorado oncology team for their collaboration in this patient’s care.

Study Funding
No targeted funding reported.

Disclosure
A.L. Piquet has received research funding from the University of Colorado and Rocky Mountain MS Center, consulting fees from Genentech/Roche and Alexion, honorarium from MedLink, and publication royalties from Springer. E.A. Matthews, B. Schmitt, M.R. Passeri, C. Mizenko, and K.D. Orjuela report no disclosures. Go to Neurology.org/NN for full disclosures.

Publication History
Received by Neurology: Neuroimmunology & Neuroinflammation January 28, 2022. Accepted in final form May 17, 2022.
Appendix Authors

| Name                  | Location                                      | Contribution                                                                 |
|-----------------------|-----------------------------------------------|-------------------------------------------------------------------------------|
| Elizabeth Matthews, MD| Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data |
| Barrie Schmitt, MD    | Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora | Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data |
| Michlene Passeri, MD  | Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora | Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data |
| Christopher Mizenko, MS| Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora | Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data |
| Karen Orjuela, MD     | Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora | Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data |
| Amanda Piquet, MD     | Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data |

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