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

A Case Report

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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.

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Glossary

AIE = autoimmune encephalitis; **AMPA-R** = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **AMPARE** = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis; **CDK** = cyclin-dependent kinase; **ICI** = immune checkpoint inhibitor; **irAE** = immune-related adverse event.

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).[1] 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.[2,3] 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).[2,3] 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. CSF showed a lymphocytic pleocytosis, and antibody evaluations (Mayo Clinic) revealed serum and CSF α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R) antibodies. She was switched from palbociclib to capecitabine and treated with steroids, IV immunoglobulin, and rituximab with marked improvement in her neurologic symptoms. At neurology follow-up, she had complete resolution of her nystagmus and ataxia and markedly improved cognitive (Montreal Cognitive Assessment was 8/30 during her admission, 27/30 at 2-month follow-up, and 29/30 at 6-month follow-up). Her cancer remains stable on capecitabine.

Discussion

AMPA-R encephalitis has been well described as a paraneoplastic syndrome associated with breast (among other) cancers.[4] However, it is increasingly recognized that paraneoplastic syndromes may be driven or unmasked by medications, notably ICIs.[5]

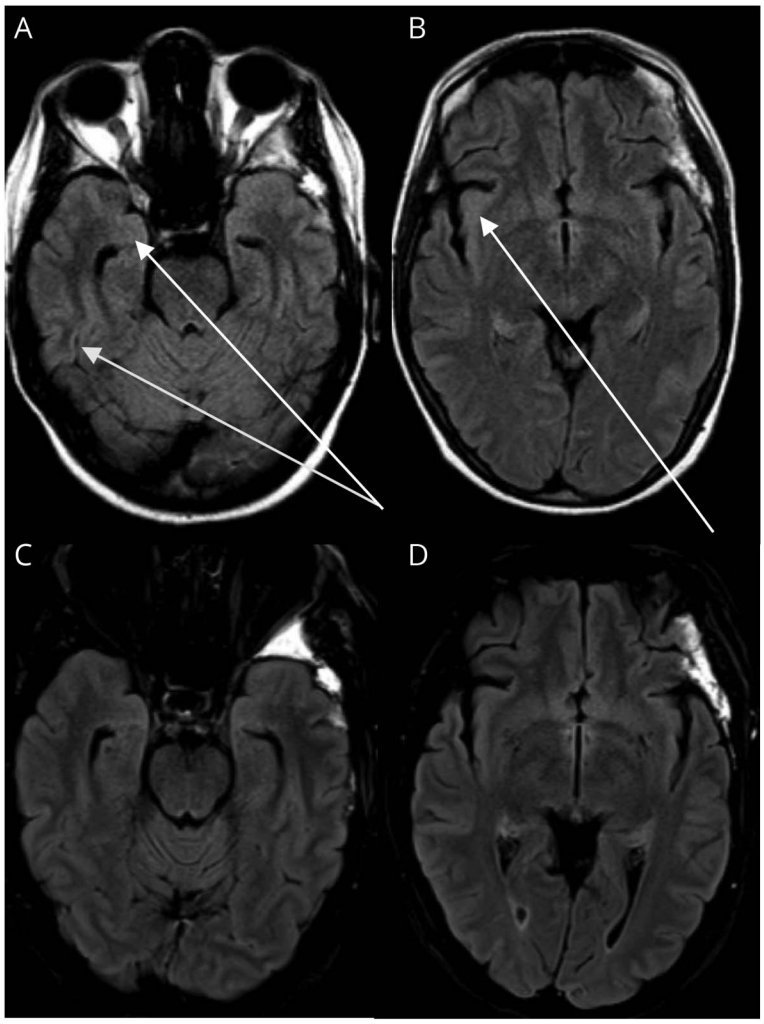
The mechanism behind ICI-associated encephalitis is quite logical. By inhibiting regulatory immune checkpoints, ICIs lead to increased antitumor immunity. However, this effect nonspecific, and unregulated immune activity can affect nearly every organ system, leading to a variety of irAEs. This can include exacerbation of underlying immunologic conditions unrelated to the cancer or can present as tumor antigen-driven paraneoplastic syndromes that are unmasked when exposed to ICIs—which has been demonstrated eloquently in mouse models.[1] When this unmasking occurs, the majority of cases occur within 3 months of ICI therapy.

Palbociclib has not historically been considered immunomodulatory. It is a CDK4/6 inhibitor, which primarily works by arresting tumor cells from entering the G1 cell cycle phase, thus preventing tumor proliferation. However, emerging data suggest that palbociclib may have significant immunomodulatory effects as well.[2,3] T regulatory cells are particularly dependent on CDK4/6 for proliferation and are disproportionately depleted compared with T effector cells, tipping the immune system balance toward autoimmunity.[3] Preclinical studies have shown that palbociclib also increases tumor antigen presentation and enhances cytotoxic T-cell activity.[6,7] A similar phenomenon has been described with cyclophosphamide; at low doses, it preferentially depletes T regulatory cells and increases cytotoxic T-cell activity, leading to enhanced antitumor immunity.[8]

In addition to preclinical studies, there is growing real-world evidence that palbociclib may have both beneficial and detrimental immunomodulatory effects. A combined analysis of 2 phase I clinical trials suggests that clinical response to palbociclib in combination with ICIs is driven by immune priming by palbociclib.[9] Palbociclib has also been associated with multiple systemic complications, a number of which are known to be immune mediated. Reports have included palbociclib-induced pneumonitis, hepatitis, nephritis, alopecia, vitiligo-like lesions, vasculitis, cutaneous lupus erythematosus, and Sweet syndrome.[10-14] Many of these cases improved with discontinuation of palbociclib plus corticosteroids.

Although it is possible that our patient's AMPA-R encephalitis was purely due to her underlying malignancy, her neurologic symptoms developed while her cancer was responding

Figure MRI Images



(A-B) T2/FLAIR images demonstrate subtle temporal and insular hyperintensities (arrows). (C-D) T2/FLAIR sequences six months posttreatment. Accounting for differences in technique, the subtle asymmetries on initial MRI are less apparent.

clinically and radiographically to treatment, whereas paraneoplastic syndromes are often described in the setting of tumor progression or recurrence.[15,16] Conversely, ICI-associated AIE is more likely to occur when cancer is responding to therapy.[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.

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