Regression of a nonfunctioning pituitary macroadenoma on the CDK4/6 inhibitor palbociclib: case report

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A 71-year-old female patient was referred in 2013 for evaluation of an asymptomatic nonsecreting pituitary adenoma. The adenoma, measuring 13 mm in height by 10 mm in width, was discovered incidentally on imaging in 2012. Biochemical testing demonstrated a nonfunctioning adenoma. Given the relatively small lesion size and the lack of symptoms, observation was preferred over surgical intervention. The patient was monitored with routine MRI, which until 2016 demonstrated minimal growth. In early 2016, the patient developed recurrence of metastatic breast cancer and was treated with palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor. This inhibitor acts on a pathway believed to be involved in pituitary adenoma tumorigenesis. One year after starting palbociclib, routine imaging demonstrated significant regression of her pituitary adenoma. The authors hypothesize that inhibition of the CDK4/6 pathway by palbociclib contributed to adenoma regression in this patient, and that palbociclib may represent a possible adjuvant therapy for the treatment of nonfunctioning pituitary adenomas.

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KEYWORDS pituitary adenoma; palbociclib; CDK4/6 inhibitor

PITUITARY adenomas are benign neoplasms that account for up to 15% of intracranial masses.²⁹ Autopsy and radiological studies suggest that the prevalence of pituitary adenomas may be as high as 20%.⁷ Common presentations of patients with adenomas include neurological symptoms of headache or vision loss related to local compression, endocrinological dysfunction, or incidental diagnosis through imaging studies.³⁶ Current treatment for pituitary adenomas is dependent on the secretory status of the tumor, size of the tumor, and patient symptoms. While a conservative approach consisting of serial MRI scans may be appropriate for nonfunctioning microadenomas (< 1 cm), a neurosurgical assessment is often warranted for patients with macroadenomas (≥ 1 cm) causing visual field deficits or neurological symptoms.^{10,21}

The most common subtype of pituitary adenomas are prolactinomas (46.2%–66.2%) followed by nonfunctioning adenomas (14.7%–37%).^{3,9,14,28} Up to 95% of tumors occur sporadically, although there are several hereditary disorders that increase the risk of pituitary adenoma formation, such as multiple endocrine neoplasia types 1 and 4, Carney's complex, McCune-Albright syndrome, *AIP* mutations, and succinate dehydrogenase-related syndromes.²³

There are many pathways implicated in sporadic pituitary adenoma formation, among which is the cyclin D/CDK/pRB axis.²⁵ In one study, mutations in components of this pathway were seen in 80% of pituitary adenomas.³³ In this report, we present the case of a 71-year-old woman with a history of nonsecreting pituitary adenomas who was treated with a CDK4/6 inhibitor for metastatic breast cancer in 2016 and was subsequently found to have reduction of her pituitary adenoma.

Case Report

A 71-year-old woman was referred in 2013 for evaluation of a nonsecreting pituitary adenoma. The adenoma was discovered incidentally on MRI in 2012 during a workup for arm pain secondary to initiation of hydroxychloroquine for spontaneous recurrent angioedema. Other significant medical history for the patient included a C2–3 meningioma that had been resected in 2003, hypothyroidism treated with a thyroidectomy in 1978, hypercalcemia treated with a parathyroidectomy, and breast cancer treated with mastectomy in 1993 and 2005. Following her MRI, the patient was initially seen by her endocrinologist

ABBREVIATIONS CDK4/6 = cyclin-dependent kinase 4 and 6 complex.

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and subsequently referred to Tufts with a diagnosis of a nonsecreting pituitary adenoma.

At the time of her initial appointment at Tufts, the patient was asymptomatic, and formal ophthalmological visual field testing found no deficits. On MRI, her pituitary adenoma measured 13 mm in height and 10 mm in width and was elevated to the level of the undersurface of the optic chiasm.

The patient was next seen in 2015 following episodes of right ear pain. At the time, she denied headaches, polyuria, polydipsia, and any changes in peripheral vision. MRI was performed and did not show any changes when compared to the 2013 study. Subsequent MRI in 2016 showed a slight increase in size of the adenoma with slight uplifting of the optic chiasm. Ophthalmological testing confirmed no visual field deficits, and therefore observation was continued with follow-up formal visual field testing and MRI.

In early 2016, the patient was diagnosed with recurrent breast cancer at the site of her prior tumor location and started on a regimen of palbociclib therapy. In October 2016, the patient had 2 episodes of spinning and unsteadiness. MRI showed restricted diffusion in the left inferior cerebellum in the territory of the posterior inferior cerebellar artery, consistent with an acute ischemic infarction. Following these events, she was seen by the neurosurgery service in November 2016. At the time of this visit, she continued to deny polyuria, polydipsia, or headache. The tumor remained stable in size, and, because the patient was asymptomatic and was being treated for breast cancer recurrence, the decision was made to follow up in 6 months.

Six months later, in 2017 repeat MRI showed that the patient's adenoma had significantly decreased in size, now measuring 8 mm in height by 8 mm in width (Fig. 1). The tumor was no longer touching the chiasm or optic nerves and did not extend more rostral than the diaphragma sellae. The patient denied any sudden severe headaches to suggest pituitary apoplexy. At the time of this MRI study, she had been on palbociclib for approximately 1 year.

Discussion

Pituitary adenomas are the most common cause of sellar masses in patients 30 years of age and older.^{11,16} Treatment is dependent on secretory status of the tumor, size of the tumor, and patient symptoms. Standard of care for symptomatic prolactinomas, the most common type of pituitary adenoma, is medical management, although resection remains an option in those patients unable to tolerate dopamine agonist therapy. Conversely, standard of care for larger and/or symptomatic nonsecreting adenomas is resection.

Although pathways involved in the pathogenesis of nonsecreting adenomas have been studied, medical management of nonfunctioning pituitary adenomas has been limited. Two classes of drugs that have been used in the treatment of pituitary adenomas are somatostatin analogs and dopamine agonists. These drugs take advantage of the presence of somatostatin and dopamine receptors on the surface of some nonfunctioning pituitary adenomas.^{15,27,34} Studies have shown that up to 67% of nonfunctioning pituitary

FIG. 1. Postgadolinium T1-weighted MR images in the coronal (left panels) and sagittal (right panels) planes. **A and B:** Images from 2015, demonstrating a pituitary macroadenoma contacting the undersurface of the optic chiasm with a cystic component. **C and D:** In 2016, shortly before the start of palbociclib therapy, the adenoma is stable in comparison to earlier. **E and F:** One year later in 2017, the macroadenoma has significantly reduced in size, with near resolution of the suprasellar component.

adenomas express D2 receptors and up to 100% may express one type of somatostatin receptor.^{13,24,26}

In vitro studies of somatostatin analogs and dopamine agonists have shown that both classes of drugs are effective in promoting cell death. In a study by Padova et al., somatostatin analogs specific for the somatostatin 2 (*Sst2*) receptor reduced cell viability by 20%–80% in nonfunctioning pituitary adenomas exhibiting *Sst2* expression.²⁶ Similarly, in vitro studies of bromocriptine, a D2 receptor antagonist, reduced cell viability in 60% of nonfunctioning pituitary adenoma cell cultures.¹⁵

In vivo effects of these drugs have been varied. Octreotide, a somatostatin receptor analog, improved visual fields in patients with pituitary adenomas, although it had no effect on tumor size.⁴ In a study by Bevan et al., treatment with bromocriptine for 1 year resulted in adenoma reduction in only 15% of patients.¹ The most effective of these drugs in vivo has been cabergoline, a D2 dopamine

agonist. In a study by Pivonello et al., treatment with cabergoline resulted in tumor shrinkage in 56% of patients. Unsurprisingly, cabergoline was more effective in tumors expressing D2 receptors.²⁷ These studies demonstrate that while medications can aid in tumor reduction, there are mixed responses and the response to treatment largely depends on receptor expression of the cell.

In the case presented herein, the patient had a history of an asymptomatic nonsecreting pituitary adenoma. After a year of treatment with palbociclib, a CDK4/6 inhibitor, for metastatic breast cancer, her pituitary tumor decreased in size. Although the pathways involved in the pathogenesis of this specific tumor are unknown, the pathway inhibited by palbociclib is frequently found to be involved in the pathogenesis of pituitary adenomas. Therefore, there is reason to believe that the medical therapy used for the treatment of the patient's breast cancer may have played a role in size reduction of the adenoma.

Palbociclib, in combination with letrozole, was granted FDA accelerated approval in 2015 for initial endocrine-based treatment of estrogen receptor–positive, HER2-negative advanced breast cancers in postmenopausal women.^{2,32} Palbociclib, like other CDK4/6 inhibitors, targets the cyclin D/CDK/retinoblastoma protein (pRB) pathway. In normally functioning mammalian cells, CDK 4 and 6 form a complex with cyclin D1 to initiate phosphorylation of retinoblastoma tumor suppressor protein (Rb). When Rb is phosphorylated, it is unable to suppress E2F, a protein required for progression from G₁ to S of the cell cycle, and thus the cell initiates cell division. However, when p16, a CDK inhibitor, is activated, the CDK4/6 and cyclin complex is inhibited, resulting in a hypophosphorylated pRB. When hypophosphorylated, pRB inhibits E2F, thus halting progression through the cell cycle. In malignancy, this pathway is frequently disrupted, leading to unregulated progression through the cell cycle.^{6,31}

In preclinical studies, palbociclib has shown activity against a variety of cell lines, including colon, breast, glioblastoma, and prostate cancer.¹² Given that mutations in the cyclin D/CDK/pRB pathways have been seen in up to 90% of all cancers, these results are encouraging.^{22,30} With respect to the cyclin/CDK/pRB pathway in pituitary adenoma formation, inactivation of Rb in murine models has been associated with an increased risk of developing pituitary adenomas.^{19,37}

Studies on human pituitary adenomas have confirmed the involvement of this pathway in pituitary tumorigenesis. In a study by Simpson et al., abnormal expression of pRB, p16, or cyclin D1 was seen in 80% of tumors.³³ Two additional studies by Jordan et al. and Hibberts et al. independently demonstrated overexpression of cyclin D1 in 67% of nonfunctioning pituitary adenomas.^{18,20} Furthermore, this pathway has been implicated in pituitary adenoma recurrence following resection.¹⁷ Given the tumor regression seen in the patient presented herein following treatment with a cyclin 4/6 inhibitor, we hypothesize that the medication contributed to the regression. It is notable that the adenoma contained a moderately sized cystic component prior to palbociclib therapy. Resolution of this cystic component likely contributed significantly to the reduced overall size of the adenoma. Whether palbociclib is

more effective against cystic versus solid components of tumors as well as the mechanism underlying this possibility remains uncertain and is an area of future research.

Although there is evidence to suggest that palbociclib might have affected tumor reduction in this case, there may have been other contributing factors. It is possible that pituitary apoplexy occurred in this patient, although it is unlikely given the lack of clinical findings to suggest the occurrence of apoplexy between 2016 and 2017. Additionally, the pituitary adenoma could have spontaneously regressed in this patient. Spontaneous regression of non-functioning pituitary macroadenomas has been reported in approximately 10% of tumors.⁵ It is also possible that this patient might have been particularly susceptible to a targeted therapy such as palbociclib. Given that she developed several separate primary tumors (breast, meningioma, and pituitary), this raises the possibility of a genetic predisposition to tumor development from a germline mutation in the CDK4/6 pathway.

The radiographic appearance of the lesion in the pituitary gland, the timeline of slow growth over several years, and the location of the lesion in the anterior pituitary gland suggest that this lesion is most likely a pituitary adenoma. As this patient did not undergo resection, pathologic confirmation was not obtained. However, metastases to the anterior pituitary gland without involvement of the bony sella would be unusual, with lesions in the pituitary stalk and median eminence being more common.⁸ Patients in this scenario generally present with diabetes insipidus, which was not present in our patient. It remains possible, yet unlikely, that this lesion was a slow-growing breast cancer metastasis rather than a pituitary adenoma, although the available evidence points toward the latter.

While this case suggests that CDK4/6 inhibitors may have a role in the treatment of pituitary adenomas by promoting tumor regression, it is also possible that these inhibitors could be beneficial as adjuvant treatment in prevention of tumor recurrence or as a means to prevent tumor growth following primary surgical treatment. Tumor recurrence within 5 years of resection has been observed in anywhere from 15% to 66% of patients.³⁵ As mentioned earlier, involvement of the cyclin/CDK/pRB pathway has been implicated in tumor recurrence.¹⁷ Thus, use of CD4/6 inhibitors may have a multifactorial role in medical management of nonfunctioning pituitary adenomas.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Heilman, Lechan. Acquisition of data: Anderson, Heller. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Heilman, Anderson, Lechan. Approved the final version of the manuscript on behalf of all authors: Heilman. Study supervision: Heilman, Lechan.

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