Complete Resolution of Sellar Metastasis in a Patient With NSCLC Treated With Osimertinib

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Non–small cell lung cancer with pituitary metastasis (NSCLC-PM) is a devastating disease; however, treatment is being revolutionized by a novel therapy targeting highly specific tumor signals, such as the mutation of epidermal growth factor receptors (EGFRs). Long-term management of hormonal defects in this population has become a unique neuroendocrine clinical challenge. We report the case of a 73-year-old female nonsmoker who was diagnosed with stage IV non–small cell lung cancer. The initial staging evaluation revealed a 7 × 11 × 21-mm sellar lesion abutting the optic chiasm and causing clinical hypopituitarism. The patient received three cycles of chemotherapy with carboplatin and pemetrexed, which was discontinued because of major cumulative side effects of myelosuppression and kidney disease. Eight months later, scans demonstrated evidence of disease progression. A repeated lung nodule biopsy revealed an *EGFR* exon 19 deletion mutation. EGFR-targeted therapy with osimertinib 80 mg daily was initiated. A complete resolution of the pituitary lesion was evident on a follow-up pituitary MRI 5 weeks later and was sustained 1 year after. However, the panhypopituitarism persisted. This is an illustrative case of NSCLC-PM with *EGFR* exon 19 deletion mutation, wherein osimertinib, a third-generation EGFR–tyrosine kinase inhibitor, eradicated the sellar metastasis and prevented the need for radiotherapy. However, the neuroendocrine deficits persisted despite anatomic improvement.

Freeform/Key Words: NSCLC, pituitary metastasis, neuroendocrine, EGFR mutation, osimertinib

Pituitary metastasis, a historically rare condition, is increasingly seen with improved detection and prolonged survival of patients with cancer. The condition is typically associated with an advanced stage of primary malignancy and has a median survival of only ~10 months [1, 2]; however, the recent development of a novel therapy targeting highly specific tumor signals has brought new hope for the successful treatment of this severe condition. Long-term management of hormonal abnormalities in this population has become a new neuroendocrine clinical challenge.

Non–small cell lung cancer with pituitary metastasis (NSCLC-PM), a subset of non–small cell lung cancer with brain metastasis (NSCLC-BrM), is a devastating and unique clinical entity in that patients often develop hypopituitarism with or without a visual field defect that typically requires special care by a neuroendocrinologist. Here, we report an illustrative case of NSCLC-PM with epidermal growth factor receptor *EGFR* exon 19 deletion mutation in which osimertinib, a third-generation EGFR–tyrosine kinase inhibitor (EGFR-TKI),

Abbreviations: EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitor; NSCLC, non–small cell lung cancer; NSCLC-BrM, non–small cell lung cancer with brain metastasis; NSCLC-PM, non–small cell lung cancer with pituitary metastasis.

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eradicated the sellar metastasis and prevented the need for radiotherapy. However, the neuroendocrine deficit persisted despite anatomic improvement.

1. Case Description

A 73-year-old female nonsmoker was diagnosed with stage IV non–small cell lung cancer (NSCLC). The initial staging evaluation revealed a 7 × 11 × 21-mm (anterior-posterior × transverse × superior-inferior) sellar lesion (Fig. 1A) abutting the optic chiasm and causing clinical hypopituitarism.

An initial hormonal assessment (Table 1) revealed the presence of diabetes insipidus, central hypothyroidism, hypogonadotropic hypogonadism, and mild hyperprolactinemia, which was believed to be a stalk effect. Adrenal insufficiency was clinically suspected, but testing was precluded at the time because the patient was being tapered from a supra-physiological dose of dexamethasone (part of chemotherapy). Her IGF1 level was at the low end of the normal range, suggesting a potential growth hormone deficiency. A neuro-ophthalmology evaluation revealed a predominantly right temporal field defect that was likely caused by her suprasellar mass lesion, which had imaging evidence of chiasmal/prechiasmal compression on the right.

The patient received three cycles of chemotherapy with carboplatin and pemetrexed. Her primary disease was stable overall on chemotherapy; however, because of major cumulative side effects, including fatigue, myelosuppression, and kidney disease, chemotherapy was discontinued. Eight months later, scans demonstrated evidence of disease progression, with enlarging bilateral lung nodules and progression of the sellar lesion. A repeated lung nodule biopsy revealed an *EGFR* exon 19 deletion mutation. EGFR-targeted therapy with osimertinib 80 mg daily was initiated. A follow-up pituitary MRI 5 weeks later showed complete resolution of the pituitary lesion (Fig. 1B). Repeated brain MRIs at 16 weeks, 29 weeks, 46 weeks, and 59 weeks (latest one; Fig. 1C) showed persistent resolution of the sellar or suprasellar lesion. Her thoracic lesions were also stable with no evidence of new/progressive disease (data not shown).

Radiation therapy, which was initially part of the multidisciplinary treatment plan, was deemed unnecessary given her great response to osimertinib.

Despite a seemingly complete and sustained resolution of the sellar metastasis on imaging studies, the patient's panhypopituitarism persisted even 1 year later. She has been stable

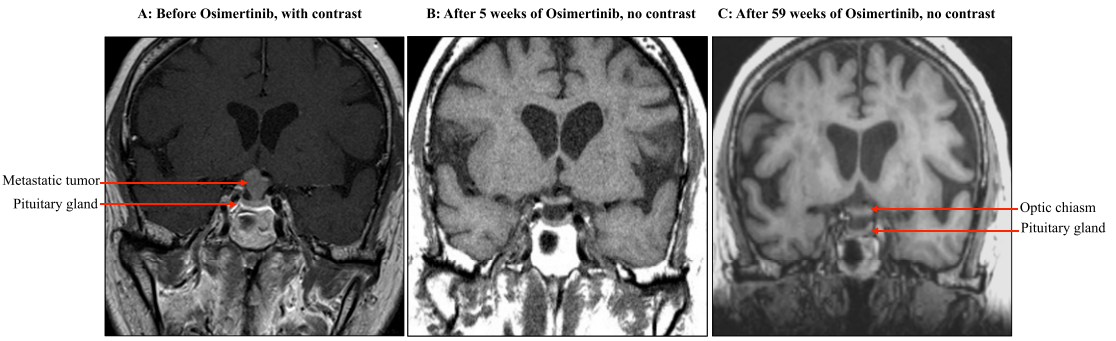

Figure 1. T1-weighted MRI coronal views of the sella. (A) Before osimertinib, a T1-weighted MRI coronal view with contrast material showed a 7 × 11 × 21-mm (anterior-posterior × transverse × superior-inferior) intrinsically T1-isointense, T2-hyperintense, enhancing lesion in the sella and suprasellar region involving the infundibulum, posterior pituitary gland, and hypothalamus. Sagittal view (data not shown) revealed that the normal T1 hyperintensity signal in the posterior pituitary gland disappeared. This lesion abutted the posterior aspect of the optic chiasm and displaced the postchiasmatic optic tracts superiorly and laterally. The cavernous sinuses appeared unremarkable. (B) T1-weighted MRI coronal view without contrast material (because of new renal dysfunction) 5 wk after initiation of osimertinib is shown. Note the resolution of the metastatic lesion and restoration of normal sellar structure. (C) T1-weighted MRI coronal view without contrast material 59 wk after initiation of osimertinib is shown. Note the persistent resolution of the metastatic lesion.

Table 1.

Item (Reference Range)	Result
Initial Hormonal Assessment	
Serum sodium (135–145 mmol/L)	147
Urine osmolality (150–1150 mOsm/kg water)	98
FSH (18.0–153.0 IU/L, postmenopause)	2.6
LH (16.0–64.0 IU/L, postmenopause)	<0.1
TSH (0.40–5.00 mIU/L)	0.4
Free T4 (0.9–1.8 ng/dL)	0.5
Prolactin (0.1–23.3 ng/mL)	108.3
IGF-1 (34–245 ng/mL)	41
Cosyntropin Stimulation Test at 56th Wk	
ACTH, basal (6–76 pg/mL)	<2
Cortisol, basal	<0.2
Cortisol, 30 min	0.7
Cortisol, 60 min	0.9
Hormonal Assessment at 70th Wk	
Morning cortisol (5–25 ug/dL)	0.4
TSH (0.40–5.00 mIU/L)	0.04
Free T4 (0.9–1.8 ng/dL)	1.3
Serum sodium (135–145 mmol/L)	144

The number of weeks shown reflects the time after initiation of osimertinib.

on a regimen of levothyroxine 75 μg daily for central hypothyroidism, dexamethasone 0.5 mg daily for central adrenal insufficiency, and 1-deamino-8-D-arginine vasopressin (DDAVP) 0.05 mg daily for diabetes insipidus. She continues to have regular hormonal assessments. A cosyntropin stimulation test performed at the 56th week after initiation and after 3 months of treatments with a physiological dose of dexamethasone showed persistent central adrenal insufficiency (Table 1). An early morning cortisol level tested at the 70th week remained low. Her levothyroxine dose requirement has increased slightly from 50 to 75 μg daily over the past year. Her free T4 levels have been stable, and her TSH levels have remained low. Her sodium levels were normal while she was taking DDAVP replacement (Table 1).

2. Discussion

Pituitary metastasis is a relatively rare condition with poor prognosis that is typically seen in patients with advanced primary malignancy. It was found in 1.9% of 3680 autopsied patients with cancer [3]. Breast and lung cancers are the two most common primary cancers [1, 3, 4]. Common direct clinical consequences include anterior pituitary hormonal deficits, diabetes insipidus, visual field involvement, and headache. The overall prognosis is poor, with a median survival time after diagnosis of ~10 to 12 months [1, 2]. As shown by a recent large series by Schill *et al.* [1], who examined 38 patients with pituitary metastasis from 1996 to 2018 in Sweden, only 50% and 26% of patients were alive 1 year and 2 years after the diagnosis, respectively.

Aside from hormonal replacement therapy, radiotherapy, surgery, and chemotherapy are the traditional primary treatments for a metastatic pituitary tumor. This combination of treatment modalities was recently revolutionized by identification of targetable oncogenic molecular mutations and development of novel therapy targeting highly specific tumor signals. The gain-of-function mutations in EGFR, namely deletions of exon 19 (exon19del) and point mutations of L858R, are identified in 20% to 40% of patients with NSCLC, and

small molecular tyrosine kinase inhibitors blocking mutant EGFR signal transduction have been superior to chemotherapy in the treatment of EGFR-mutant NSCLC. Although the first and second generations of EGFR-TKIs are associated with acquired resistance due to development of a gatekeeper mutation of T790M, osimertinib, a potent, irreversible third-generation EGFR inhibitor, blocks both sensitive (exon 19 deletion and L858R) and resistant EGFR mutations (T790M) with good brain-blood barrier penetrance. In comparison with standard EGFR-TKIs, osimertinib substantially prolonged progression-free survival among patients with NSCLC and NSCLC-BrM (FLAURA [5] and AURA3 [6]).

NSCLC-PM is a unique clinical entity in that patients often develop hypopituitarism with or without a visual field defect that typically requires special care by a neuroendocrinologist. Although studies such as FLAURA and AURA3 demonstrated encouraging clinical efficacy of osimertinib on tumor progression in NSCLC–BrM in general, so far, to the best of our knowledge, no case or cohort study has specifically addressed NSCLC-PM and its neuroendocrine aspects.

Although radiotherapy is typically considered the standard of care for progressive metastatic pituitary tumors, patients with primary NSCLC harboring an EGFR activating mutation may be effectively treated with the third-generation EGFR inhibitor osimertinib, which is known to have excellent activity in the central nervous system. As illustrated in this case, in which osimertinib eradicated the sellar metastasis, one may consider reserving the use of radiotherapy until after a tyrosine kinase inhibitor response can be evaluated in patients with mutant EGFR.

Of note, despite a sustained complete resolution of sellar metastasis on serial imaging studies, this patient's neuroendocrine hormonal defects persisted, with a mechanism that needs to be elucidated.

3. Conclusion

In this case of NSCLC with *EGFR* exon 19 deletion mutation, osimertinib eradicated a sellar metastasis and prevented the need for radiation therapy, which is consistent with the known clinical efficacy of the third generation of EGFR-TKIs. The case also illustrates persistent neuroendocrine deficiencies despite anatomic improvement and the need for continuous close hormonal monitoring and replacement.

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Additional Information

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