Case Report

Genetic characterization of a case of sellar metastasis from bronchial carcinoid neuroendocrine tumor

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INTRODUCTION

Metastases to the region of the sella remain uncommon, representing approximately 1% of all sellar tumors. However, with increased frequency of surveillance imaging of the central nervous system in tandem with prolonged overall survival of patients with a previously known diagnosis of cancer, metastasis must remain among the differential diagnosis for newly diagnosed lesions within the sellar region. While the various clinico-pathologic characteristics pertaining to the presentation of patients with metastases to the sella continues to amount, including pituitary dysfunction, no studies have reported the underlying genetic alterations that may promote such spread.
While surgery and radiation remain front-line therapies for most sellar lesions, effective medical treatment, such as targeted therapies for hormonally active pituitary adenomas, is limited for other sellar pathologies. However, the recent success of small molecule inhibitors in BRAF-mutated craniopharyngioma has demonstrated the utility of comprehensive genetic analysis of challenging sellar pathologies.\textsuperscript{[6,16]} In this report, we describe the clinical course of a patient who underwent surgery for a sellar metastasis from a systemic pulmonary neuroendocrine tumor and the results from whole-exome sequencing (WES) of her resected tumor. WES revealed oncogenic somatic mutations, previously reported in neuroendocrine tumors and primary pituitary tumors, garnering further insight into the biology of both neuroendocrine origin and spread to the sellar region, as well as potentially actionable therapeutic targets.

**CASE DESCRIPTION**

**Clinical presentation**

The patient is a 68-year-old female who was first diagnosed with a carcinoid tumor of the left lower lobe of the lung, diagnosed after lobectomy with 7/9 lymph nodes positive for tumor spread, consistent with pT2, N2 Grade 2 staging. She was treated with adjuvant etoposide and cisplatin, as well as concurrent fractionated radiation therapy (50 Gy in 25 fractions). Her clinical course remained uneventful, but due to rising surveillance chromogranin levels, she underwent a surveillance PET-CT 6 years later, which showed increased metabolic activity in the sellar region, despite being on octreotide therapy. This prompted brain magnetic resonance imaging, which demonstrated a 2.6 × 2.5 × 2 cm suprasellar mass, extending into the right cavernous sinus, with mass effect on the optic chiasm [Figure 1a and b]. Clinically, she described progressive headaches and blurred vision, most pronounced while reading. Formal neuro-ophthalmology evaluation showed very mild temporal field deficits. A comprehensive endocrine evaluation revealed minimally depressed cortisol and FSH/LH levels and mildly elevated prolactin levels from stalk effect [Table 1], but clinically she was without symptoms of endocrine dysfunction.

Although a diagnosis of pituitary adenoma was suspected, given her cancer history, PET-CT findings, and rising chromogranin levels, metastasis remained in the differential diagnosis, and as such, she underwent endoscopic endonasal resection of her sellar tumor. Intraoperatively, the tumor was resected piecemeal and noted to have a separate plane from the normal appearing pituitary gland, which was kept intact. Intraoperative imaging showed gross total resection of the tumor [Figure 1c and d]. The patient recovered from surgery uneventfully without immediate new endocrine abnormalities or visual deficits. Final pathology demonstrated findings, consistent with neuroendocrine tumor metastasis, including positive immunohistochemistry for synaptophysin, CK7, TTF-1, and CAM5.2, while negative for endocrine stains, including prolactin, hGH, ACTH, TSH, FSH, and LH. The Ki-67 index was estimated at 8–12%. Histopathologically, the tumor exhibited enlarged nuclei, focal necrosis, and stromal fibrosis, together supporting a diagnosis of neuroendocrine tumor metastasis. Immunohistochemistry from initial lung and recurrent sellar specimens is shown in [Figure 2].

Given the high proliferative index of the tumor, the patient underwent adjuvant stereotactic radiosurgery 2 months after resection. Late postoperative endocrine evaluation demonstrated central hypothyroidism, for which she was started on levothyroxine therapy. She continues to be monitored for signs of hypoadrenalism.

### Table 1: Endocrine evaluation at time of diagnosis.

| Hormones  | Value | Range         |
|-----------|-------|---------------|
| fT4       | 0.69  | 0.58–1.64 ng/dL |
| TSH       | 3.4   | 0.45–5.33 uIU/mL |
| FSH       | 4.5   | 16.7–113.6 mIU/mL |
| LH        | 1.3   | 10.9–58.6 mIU/mL |
| Cortisol 8 AM | 5.7 | 6.7–22.6 ug/dL |
| GH        | 0.31  | 0.01–3.61 ng/mL |
| PRL       | 47.57 | 2.74–19.64 ng/mL |
| IGF-1     | 68    | 34–194 ng/mL |
| ACTH      | 18    | 7.2–63 pg/mL |

![Figure 1: Magnetic resonance imaging preoperatively and postoperatively. Representative (a) sagittal and (b) coronal images of T1-weighted postcontrast magnetic resonance imaging (MRI) are shown at time of presentation. Intraoperative MRI was obtained, demonstrating gross total resection of the sellar tumor, as seen on representative (c) sagittal and (d) coronal images of T-weighted postcontrast MRI.](image)
Genomic analysis

WES was performed on the resected sellar tumor and the matching blood sample [Figure 3]. There was not enough tissue from the original lung specimen for similar analysis. There were a total of 91 somatic alterations identified, only 7 of which were previously reported to be implicated in oncogenesis (MYO18A, PTCH1, BCOR, CLIC6, TLL2, COL1A1, and PTPRK). Notably, mutations in BCOR and PTCH1 have been previously implicated in both systemic neuroendocrine tumors and primary tumors of the pituitary gland.\cite{1,13,14,25,27,29,34,35} Mutational signatures of all somatic alterations revealed an abundance of C>T transitions followed by C>A transversions. Further, analysis of the mutational signatures in relation to the well-established COSMIC signatures identified an interesting pattern for enrichment of Signature 4, which is seen in lung adenocarcinoma, lung squamous cell carcinoma, and small cell lung carcinoma.\cite{10} The other dominant signatures were signatures 16 and 23, for which the etiology remains unknown. Copy number variation (CNV) analysis revealed increased rate of genomic instability with 18.7% of the genome being deleted. Identified CNV events included large-scale deletions of chromosomes 3, 6, and 9 and focal deletions on chromosomes 1, 2, 11, 15, and 16 [Table 2]. Interestingly, acquisition of increased CNV events in nonsmall cell lung cancer metastases to the brain has been reported before with both amplifications and deletions.\cite{19}

DISCUSSION

As patients continue to live longer with advances in systemic therapy, metastases to the sellar region, while still rare, must remain in the differential of new sellar lesions in patients with a known oncologic history. The most common origins of sellar metastases in women originate from the breast and lung in men.\cite{15,18,30} Within neuroendocrine neoplasms, only a handful of reports have been previously published describing metastases to the sella. These studies were most recently reviewed by Goglia et al.\cite{12} and Moshkin et al.\cite{22} whose review of the literature totaled 28 cases of metastatic neuroendocrine
Table 2: Disease-associated somatic SNV/INDELs identified with WES.

| Gene       | HGVS cDNA         | HGVS protein | Variant type | dbSNP   | Tumor MAF (%) |
|------------|-------------------|--------------|--------------|---------|---------------|
| MYO18A     | NM_001346767:c.G1674T | p.Q558H      | Missense     | -       | 5.2           |
| PTCH1      | NM_000264:c.4148delC  | p.P1383fs    | Frameshift   | -       | 31            |
| BCOR       | NM_001123383:c.G2572T | p.E885X      | Stop gain    | -       | 8.1           |
| CLIC6      | NM_001317009:c.G641T  | p.G214V      | Missense     | -       | 28.3          |
| TLL2       | NC_000010.11:g.96420955C>A | Splice donor | rs754850293  | 42.7    |
| COL1A1     | NM_000088: c.G2902T  | p.G968X      | Stop gain    | -       | 31.6          |
| PTPRK      | NM_001291983: c.A1409G | p.Y470C     | Missense     | -       | 51.5          |

The majority of cases originated from small cell carcinoma pathology with diabetes insipidus a common clinical presentation, typically due to a propensity for sellar metastases to affect the posterior lobe of the pituitary gland, as well as visual deficits related to mass effect on the optic apparatus. Hormonal abnormalities related to anterior pituitary gland dysfunction were not as frequent but when present, most frequently manifested as Cushing’s disease secondary to ACTH secretion, followed by rarer cases of acromegaly, hyperprolactinemia, hypogonadism, and hypothyroidism. Within previous reports of metastatic bronchial carcinoid tumors to the sellar region, clinical presentations remained as heterogeneous, highlighting the need to perform thorough endocrine and ophthalmologic evaluations at time of presentation. While some have suggested that the presence of diabetes insipidus may distinguish metastases from primary pituitary adenoma at time of presentation, surgical management remains essential to achieve pathologic diagnosis, as well as relief of symptoms related to visual dysfunction or endocrine disturbances.

The genetic changes underlying sellar metastases from systemic cancer remain poorly characterized with no prior reports in the literature to our knowledge. We performed WES of the sellar metastasis in our patient, which revealed various genetic alterations, supporting initial neuroendocrine origin. We found a deleterious mutation of PTCH1, which encodes patched-1 protein, a receptor for sonic hedgehog (SHH) signaling that suppresses the release of SMO (smoothened)-mediated cell proliferation, thus acting as a tumor suppressor. Deleterious PTCH1 mutations have been previously reported in neuroendocrine carcinomas of the gastrointestinal system, leading to upregulation of the SHH pathway. We also identified a deleterious loss-of-function mutation in BCOR gene, which encodes a corepressor of the apoptotic protein, BCL6. BCOR acts as an epigenetic regulator through polycomb repressor complex-1. Somatic mutations in BCOR have been previously reported in neuroendocrine tumors such as small cell lung cancer, gastroenteropancreatic tumors, and pulmonary carcinoid, the latter case in which a single report of Cushing’s syndrome secondary to ectopic ACTH production from a BCOR-mutated pulmonary carcinoid tumor was reported. Likewise, we also found a mutation in PTPRK, which encodes receptor-type tyrosine-protein phosphatase kappa, a protein tyrosine phosphatase with broad downstream signaling implications that may affect tumor cell migration and survival. Although the mechanisms remain unclear, its downregulation or absence has been reported in numerous cancers, including melanoma, lymphoma, colorectal cancer, breast cancer, and glioma. However, mutations of PTPRK have not been reported in primary or metastatic neuroendocrine tumors and may warrant further mechanistic studies.

Interestingly, some of the mutations detected in the sellar metastasis have been previously implicated in normal pituitary development and pathology. PTCH1 has been shown to be important in pituitary embryogenesis, giving rise to normal pituitary development through proliferation of normal Rathke’s pouch progenitors and differentiation of pituitary cell types. Downstream consequences of PTCH1 inactivation have been implicated in the pathogenesis of adamantinomatous craniopharyngiomas and pituitary adenomas. We found other mutations in the sellar metastasis specimen, predicted to be deleterious based on prior genomic databases, but with otherwise limited preclinical study in the literature. These included MYO18A (myosin XVIIIa), shown as a part of a panel of genes to predict clinical prognosis for nonfunctioning pituitary adenomas. The previous studies on the genomics of brain metastasis of various primary tumor types identified common patterns of evolution where the metastatic specimens shared a common ancestor with the primary site but later evolved diverging significantly from the primary tumor. The case presented here, suggests a similar evolution pattern with mutations indicating a neuroendocrine ancestor, such as the BCOR alteration and also with a mutational signature commonly shared by other neoplasms originating from lung tissue.

While the genetic findings of this study are unique, the clinical implications remain unclear, as there is a paucity...
of data in the literature regarding systemic therapies that target specific mutations in sellar tumors and are limited to preliminary clinical studies, most notably the use of BRAF inhibitors in BRAF-mutated craniopharyngiomas. We detected a deleterious mutation of PTCH1, which can lead to aberrant SHH signaling, the latter of which is frequently seen in basal cell carcinoma and medulloblastoma, and other systemic cancers. Vismodegib and sonidegib are SHH pathway inhibitors, approved for the use of treating advanced basal cell carcinoma and are being tested in Phase 2 clinical trials for medulloblastoma. They have also been proposed as novel therapies for PTCH1-staining neuroendocrine cancers. We also found a deleterious mutation of BCOR, whose dysregulation has significant downstream consequences for epigenetic regulation of cellular differentiation. While targeted therapies for BCOR-mutated cancers have not been tested clinically, several preclinical studies have demonstrated abrogation of tumor growth through selective targeting with small molecule inhibitors of upregulated oncogenic signaling pathways, such as SHH, WNT, and JAK-STAT. Taken together, the aforementioned studies demonstrate the value of comprehensive genomic analysis that may lead to direct clinical therapeutic intervention and indicate areas for further preclinical study. As sellar tumors are complex pathologies, often surgically limited due to involvement of nearby vital structures, increased genetic characterization of these tumors is needed to develop novel therapies that address disease burden which surgery and radiation cannot treat alone.

This study was limited by the ability to perform comparable genomic analysis of the original pulmonary carcinoid specimen, which was not possible due to lack of available tissue. As such, we were not able to map the genetic evolution of the tumor from initial origin to distant recurrence in the sellar region. However, WES from the resected tumor did provide novel genetic insights into the pathophysiology of sellar metastasis from systemic tumors and may guide further avenues for research.

CONCLUSION

Sellar metastases from primary systemic tumors represent a small but growing pathology that arise as patients continue to live longer with modern oncologic therapies. While clinical features exist that may help differentiate patients with metastases from primary pituitary adenomas at time of presentation, such as the presence of diabetes insipidus, surgical intervention remains critical for definitive diagnosis to guide further therapy and to relieve symptoms secondary to endocrine dysfunction, or mass effect on nearby cranial nerves. Genetic alterations underlying metastasis to the sellar region remain uncharacterized, but this report highlights a potential key role for mutations in PTCH1 and BCOR, previously implicated in both primary neuroendocrine and pituitary tumors. Further genetic studies of these rare cases are needed to elucidate the mechanisms underlying sellar metastasis of systemic cancers.

Ethics approval

Genomic analysis was performed after consenting the patient to an institutional review board-approved protocol for whole-exome sequencing of resected brain tumor specimens.

Availability of data and material

The reported variants were submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession numbers SCV001335531-SCV001335537.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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