Genetic characterization of sellar metastasis from primary bronchial carcinoid tumor of neuroendocrine pathology

Yale NewHaven Health

Christopher S. Hong, M.D.[1], Declan McGuone, MBBch[2], E. Zeynep Erson-Omay, Ph.D[1], Sacit Bulent Omay, M.D.[1],

[1]Department of Neurosurgery, Yale School of Medicine, New Haven, CT 06511
[2]Department of Pathology, Yale School of Medicine, New Haven, CT 06511

INTRODUCTION

Metastasis to the pituitary gland from neuroendocrine tumors is a rare occurrence that may originate from primary tumors the lung, gastrointestinal tract, thyroid, and pancreas, among others. Patients may present with signs of endocrine dysfunction secondary to pituitary involvement, as well as mass effect-related symptoms including headaches and visual deficits. Despite a small but accumulating body of literature describing the clinical and hispathological correlates for pituitary metastases from neuroendocrine tumors, the genetic basis underlying this presentation remains poorly characterized.

CASE DESCRIPTION

We report the case of a 68 year-old with a history of lung carcinoid tumor who developed a suprasellar lesion, causing mild visual deficits but otherwise without clinical or biochemical endocrine abnormalities (Figure 1). She underwent endoscopic endonasal resection of her tumor with final pathology confirming metastasis from her original neuroendocrine tumor (Figure 2).

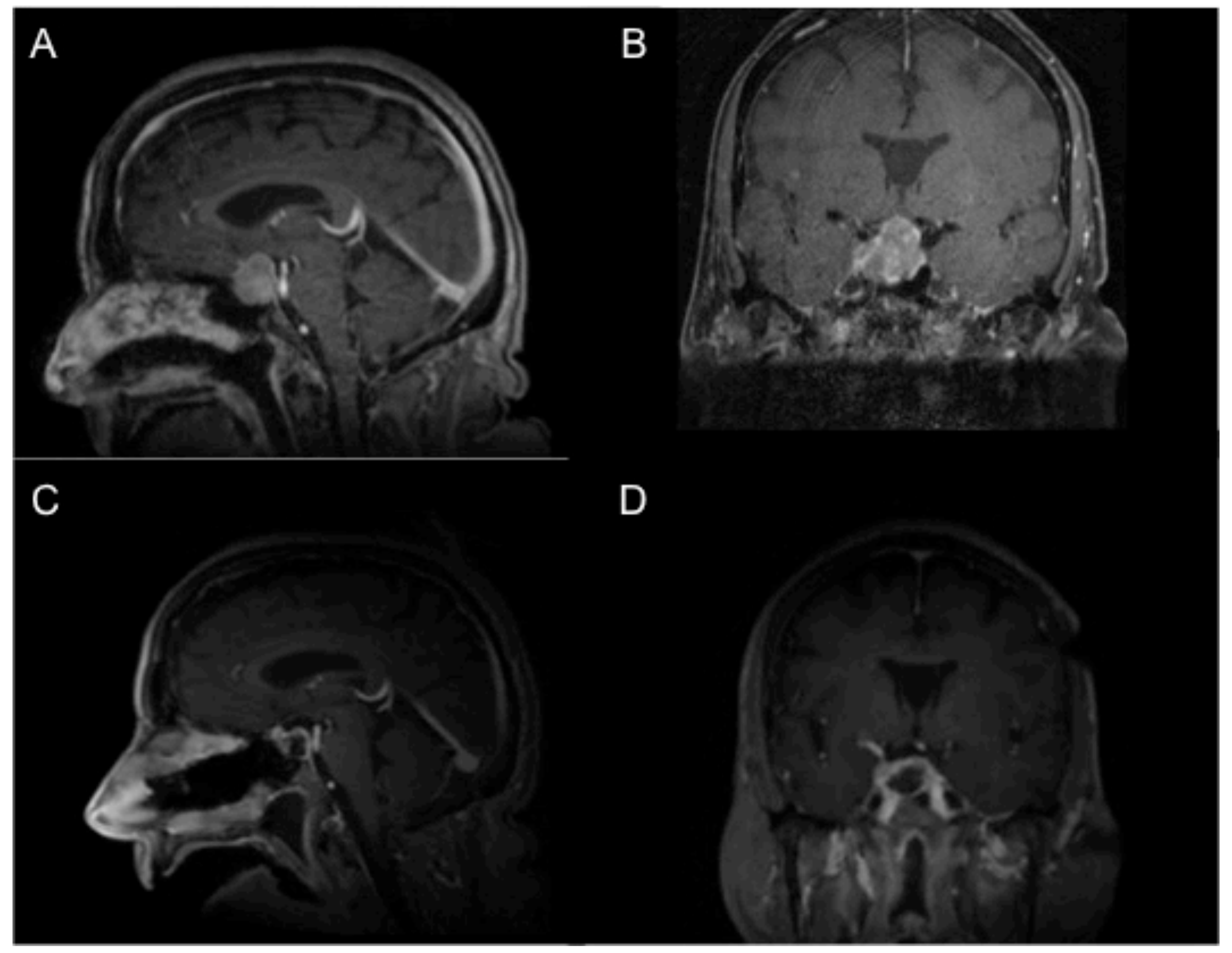

Figure 1. Magnetic resonance imaging pre- and post-operatively. Representative (A) sagittal and (B) coronal images of T1-weighted post-contrast MRI are shown at time of presentation. Intra-operative MRI was obtained, demonstrative gross total resection of the sellar tumor, as seen on representative (C) sagittal and (D) coronal images of T-weighted post-contrast MRI.

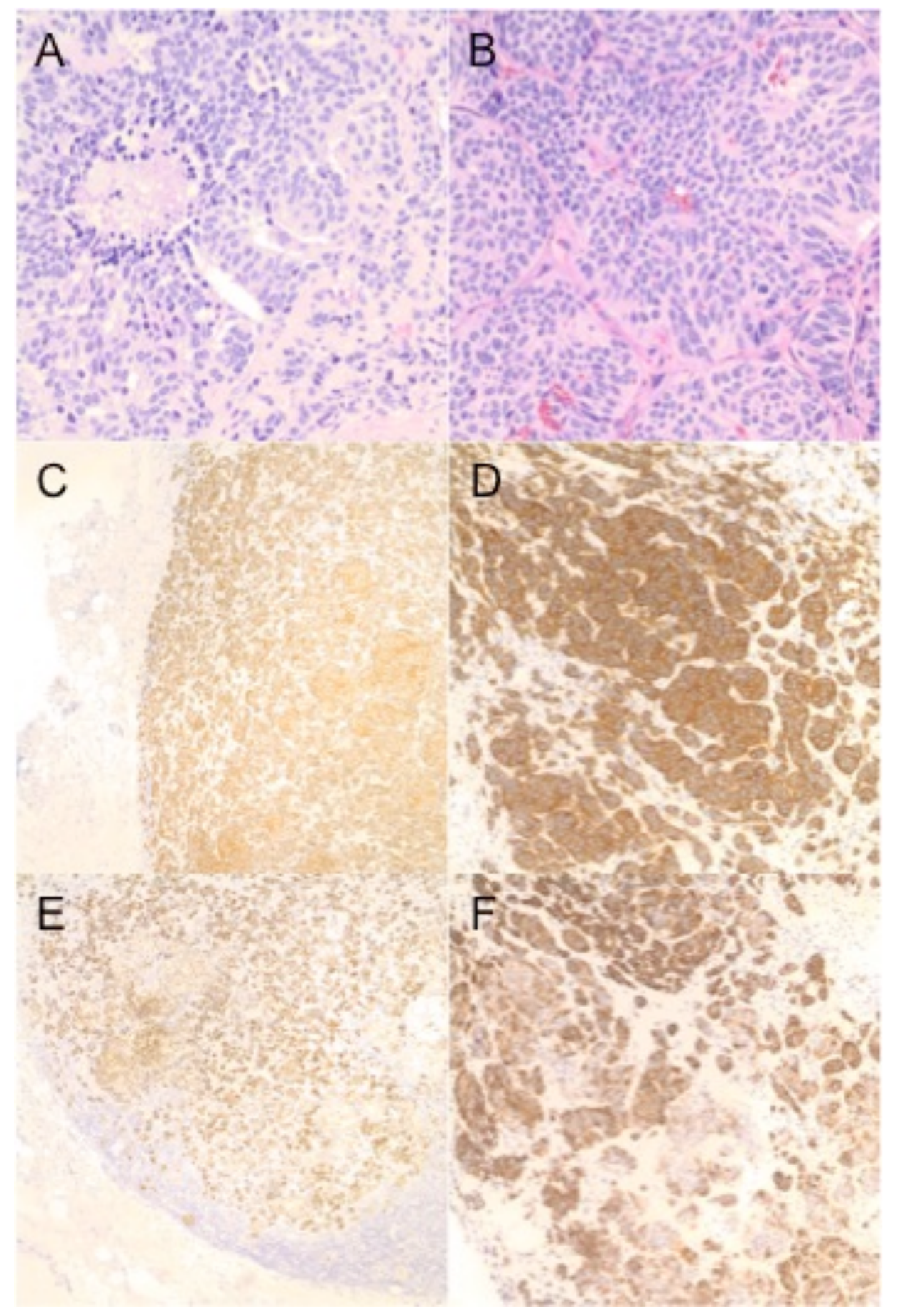

Figure 2. Histopathology of primary lung and sellar metastasis specimens. Routine H&E stains from the (A) lung and (B) sellar tumors demonstrate elevated mitotic activity and areas of focal necrosis (magnification, 400x). Neuroendocrine origin was confirmed via positive immunohistochemistry for synaptophysin in the (C) lung (magnification, 100x) and (D) sellar tumors (magnification, 200x), as well as for CK7 in the (E) lung (magnification, 100x) and (F) sellar tumors (magnification, 200x).

GENOMIC ANALYSIS

Whole-exome sequencing (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, PTPRK*). Notably, mutations in *BCOR* and *PTCH1* have been previously implicated in both systemic neuroendocrine tumors as well as primary tumors of the pituitary gland [1, 11, 13, 14, 25-27, 29, 35, 36]. 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.[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. Interestingly, acquisition of increased CNV events in non-small cell lung cancer metastases to the brain has been reported before with both amplifications and deletions [19].

DISCUSSION

The genetic changes underlying sellar metastases from systemic cancer remain poorly characterized. 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 [1] and previously reported in neuroendocrine carcinomas of the gastrointestinal system [14, 29]. *PTCH1* has also 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 [7]. Downstream consequences of *PTCH1* inactivation have been implicated in the pathogenesis of adamantinomatous craniopharyngiomas [13] and pituitary adenomas [35]. Clinically, vismodegib and sonidegib are SHH pathway inhibitors, approved for the use of treating advanced basal cell carcinoma[9] and is being tested in phase 2 clinical trials for medulloblastoma [34]. They have also been proposed as novel therapies for *PTCH1*-staining neuroendocrine cancers [14]. We also identified a deleterious loss-of-function mutation in *BCOR*, which encodes a co-repressor of the apoptotic protein, BCL6. *BCOR* acts as an epigenetic regulator through polycomb repressor complex-1 [3] and somatic *BCOR* mutations have been reported in neuroendocrine tumors such as small cell lung cancer [11, 26, 27], gastroenteropancreatic tumors [25], and pulmonary carcinoid. 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 [24, 37]. We also found a mutation in *PTPRK*, which encodes receptor-type tyrosine-protein phosphatase kappa, a protein tyrosine phosphatase with broad downstream signaling implications, whose downregulation or absence has been reported in numerous cancers, including melanoma [21], lymphoma [23], colorectal cancer [32], breast cancer [33], and glioma [2].

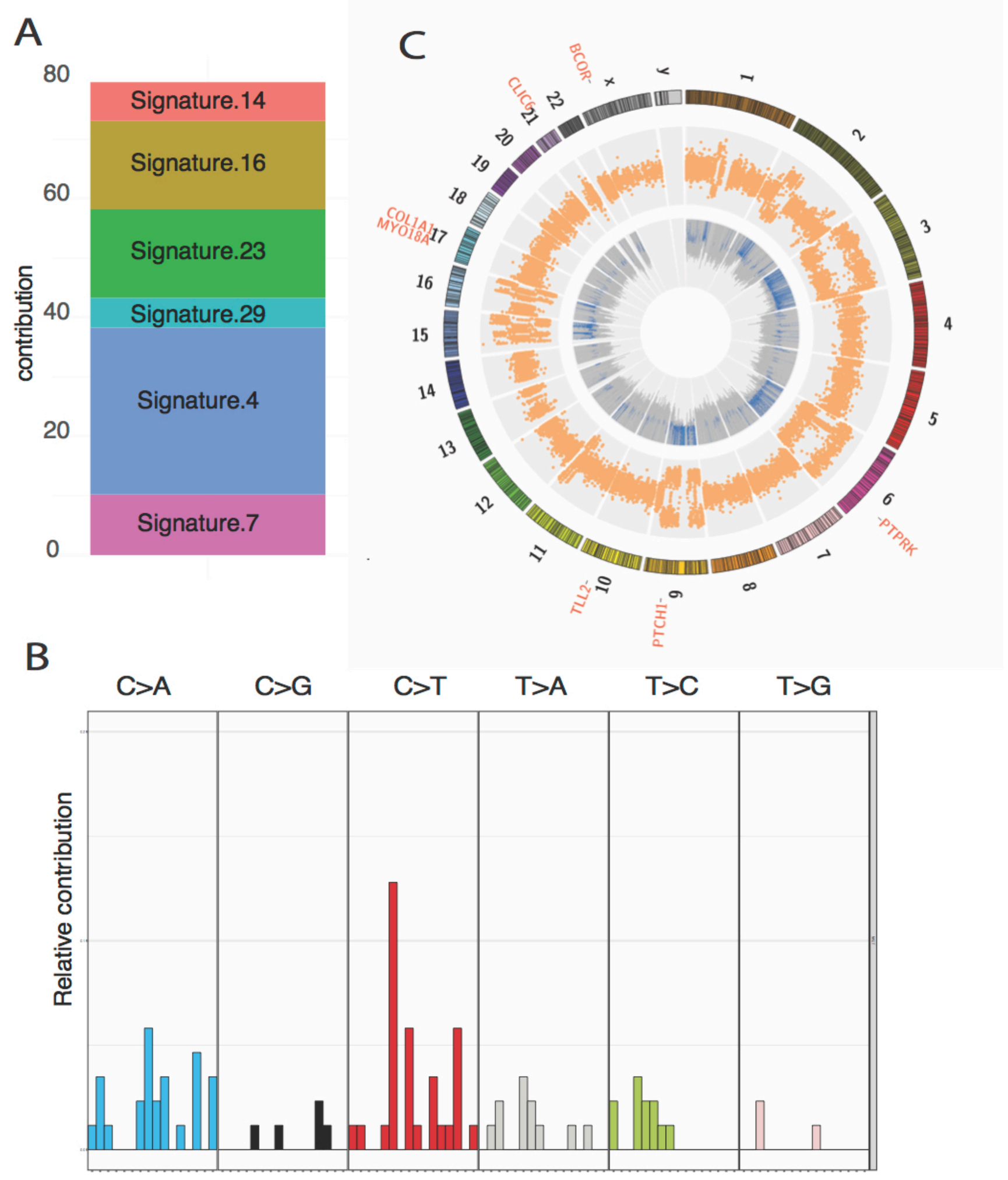

Figure 3. Genomics summary of the sellar specimen. (A) Mutation signature contribution to COSMIC signatures. (B) Distribution of 96 mutation signatures. (C) Circos plot depicting the CNV and LOH events in the inner and outer circles, respectively. The cancer associated somatic mutations are listed outside the karyotype.

CONCLUSION

In summary, 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.

REFERENCES

1. Adolphe C, Hetherington R, Ellis T, Wainwright B. Patched1 functions as a gatekeeper by promoting cell cycle progression. Cancer Res 2006;66(4):2081-2088.
2. Agarwal S, Al-Keilani MS, Alqudah MA, Sibenaller ZA, Ryken TC, Assem M. Tumor derived mutations of protein tyrosine phosphatase receptor type k affect its function and alter sensitivity to chemotherapeutics in glioma. PloS one 2013;8(5):e62852.
3. Astolfi A, Fiore M, Melchionda F, Indio V, Bertuccio SN, Pession A. BCOR involvement in cancer. Epigenomics 2019;11(7):835-855.
4. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. Cancer Discov 2015;5(11):1164-1177.
5. Brastianos PK, Shankar GM, Gill CM, Taylor-Weiner A, Nayyar N, Panka DJ, et al. Dramatic Response of BRAF V600E Mutant Papillary Craniopharyngioma to Targeted Therapy. J Natl Cancer Inst 2016;108(2).
6. Carreno G, Apps JR, Lodge EJ, Panousopoulos L, Haston S, Gonzalez-Meljem JM, et al. Hypothalamic sonic hedgehog is required for cell specification and proliferation of LHX3/LHX4 pituitary embryonic precursors. Development 2017;144(18):3289-3302.
7. Chiang MF, Brock M, Patt S. Pituitary metastases. Neurochirurgia (Stuttg) 1990;33(4):127-131.
8. Dummer R, Ascierto PA, Basset-Seguin N, Dreno B, Garbe C, Gutzmer R, et al. Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion. J Eur Acad Dermatol Venereol 2020.
9. Forbes SA, Beare D, Gunasekaran P, Leung K, Bindal N, Boutselakis H, et al. COSMIC: exploring the world's knowledge of somatic mutations in human cancer. Nucleic Acids Res 2015;43(Database issue):D805-811.
10. George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524(7563):47-53.
11. Goglia U, Ferone D, Sidoti M, Spaziante R, Dadati P, Ravetti JL, et al. Treatment of a pituitary metastasis from a neuroendocrine tumour: case report and literature review. Pituitary 2008;11(1):93-102.
12. Gomes DC, Jamra SA, Leal LF, Colli LM, Campanini ML, Oliveira RS, et al. Sonic Hedgehog pathway is upregulated in adamantinomatous craniopharyngiomas. Eur J Endocrinol 2015;172(5):603-608.
13. Gurung B, Hua X, Runske M, Bennett B, LiVolsi V, Roses R, et al. PTCH 1 staining of pancreatic neuroendocrine tumor (PNET) samples from patients with and without multiple endocrine neoplasia (MEN-1) syndrome reveals a potential therapeutic target. Cancer Biol Ther 2015;16(2):219-224.
14. He W, Chen F, Dalm B, Kirby PA, Greenlee JD. Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. Pituitary 2015;18(1):159-168.
15. Juratli TA, Jones PS, Wang N, Subramanian M, Aylwin SJB, Odia Y, et al. Targeted treatment of papillary craniopharyngiomas harboring BRAF V600E mutations. Cancer 2019;125(17):2910-2914.
16. Katoh M. Genomic testing, tumor microenvironment and targeted therapy of Hedgehog-related human cancers. Clin Sci (Lond) 2019;133(8):953-970.
17. Komninos J, Vlassopoulou V, Protopapa D, Korfias S, Kontogeorgos G, Sakas DE, et al. Tumors metastatic to the pituitary gland: case report and literature review. J Clin Endocrinol Metab 2004;89(2):574-580.
18. Li F, Sun L, Zhang S. Acquirement of DNA copy number variations in non-small cell lung cancer metastasis to the brain. Oncol Rep 2015;34(4):1701-1707.
19. Max MB, Deck MD, Rottenberg DA. Pituitary metastasis: incidence in cancer patients and clinical differentiation from pituitary adenoma. Neurology 1981;31(8):998-1002.
20. McArdle L, Rafferty M, Maelandsmo GM, Bergin O, Farr CJ, Dervan PA, et al. Protein tyrosine phosphatase genes downregulated in melanoma. J Invest Dermatol 2001;117(5):1255-1260.
21. Moshkin O, Rotondo F, Scheithauer BW, Soares M, Coire C, Smyth HS, et al. Bronchial carcinoid tumors metastatic to the sella turcica and review of the literature. Pituitary 2012;15(2):160-165.
22. Nakamura M, Kishi M, Sakaki T, Hashimoto H, Nakase H, Shimada K, et al. Novel tumor suppressor loci on 6q22-23 in primary central nervous system lymphomas. Cancer Res 2003;63(4):737-741.
23. Paret C, Theruvath J, Russo A, Kron B, El Malki K, Lehmann N, et al. Activation of the basal cell carcinoma pathway in a patient with CNS HGNET-BCOR diagnosis: consequences for personalized targeted therapy. Oncotarget 2016;7(50):83378-83391.
24. Park C, Ha SY, Kim ST, Kim HC, Heo JS, Park YS, et al. Identification of the BRAF V600E mutation in gastroenteropancreatic neuroendocrine tumors. Oncotarget 2016;7(4):4024-4035.
25. Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet 2012;44(10):1104-1110.
26. Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet 2012;44(10):1111-1116.
27. Schubiger O, Haller D. Metastases to the pituitary--hypothalamic axis. An MR study of 7 symptomatic patients. Neuroradiology 1992;34(2):131-134.
28. Shida T, Furuya M, Nikaido T, Hasegawa M, Koda K, Oda K, et al. Sonic Hedgehog-Gli1 signaling pathway might become an effective therapeutic target in gastrointestinal neuroendocrine carcinomas. Cancer Biol Ther 2006;5(11):1530-1538.
29. Shimon I, Hinton DR, Weiss MH, Melmed S. Prolactinomas express human heparin-binding secretory transforming gene (hst) protein product: marker of tumour invasiveness. Clin Endocrinol (Oxf) 1998;48(1):23-29.
30. Siqueira PF, Mathez AL, Pedretti DB, Abucham J. Pituitary metastasis of lung neuroendocrine carcinoma: case report and literature review. Arch Endocrinol Metab 2015;59(6):548-553.
31. Starr TK, Allaei R, Silverstein KA, Staggs RA, Sarver AL, Bergemann TL, et al. A transposon-based genetic screen in mice identifies genes altered in colorectal cancer. Science 2009;323(5922):1747-1750.
32. Sun PH, Ye L, Mason MD, Jiang WG. Protein tyrosine phosphatase kappa (PTPRK) is a negative regulator of adhesion and invasion of breast cancer cells, and associates with poor prognosis of breast cancer. J Cancer Res Clin Oncol 2013;139(7):1129-1139.
33. Thompson EM, Ashley D, Landi D. Current medulloblastoma subgroup specific clinical trials. Transl Pediatr 2020;9(2):157-162.
34. Vila G, Theodoropoulou M, Stalla J, Tonn JC, Losa M, Renner U, et al. Expression and function of sonic hedgehog pathway components in pituitary adenomas: evidence for a direct role in hormone secretion and cell proliferation. J Clin Endocrinol Metab 2005;90(12):6687-6694.
35. Wu Y, Yue L, Li J, Yuan M, Chai Y. Cushing's syndrome secondary to typical pulmonary carcinoid with mutation in BCOR gene: A case report. Medicine (Baltimore) 2017;96(34):e7870.
36. Yin M, Chung YJ, Lindsley RC, Walker RL, Zhu YJ, Ebert BL, et al. Engineered Bcor mutations lead to acute leukemia of progenitor B-1 lymphocyte origin in a sensitized background. Blood 2019;133(24):2610-2614.

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute