Genomic characterization of metastatic pituitary neuroendocrine carcinoma (PitNET) in two cases

Shashank Rajkumar, MD[1]; Brianna C Theriault, MD, PhD[1]; RP Manes, MD[2]; James E Hansen, MD[3]; Ranjit S Bindra, MD, PhD[1,3,4]; Ryan A Rimmer, MD[2]; Silvio E Inzucchi, MD[5]; EZ Erson-Omay, PhD[1,6]; SB Omay, MD[1,2]

[1]Yale University School of Medicine, Dept of Neurosurgery
[2]Yale University School of Medicine, Dept of Otolaryngology
[3]Yale University School of Medicine, Dept of Therapeutic Radiology
[4]Yale University School of Medicine, Dept of Pathology
[5]Yale University School of Medicine, Dept of Endocrinology
[6]Yale University School of Medicine, Dept of Biomedical Informatics & Data Science

Introduction

- Primary pituitary neuroendocrine (PitNET) carcinomas are exceptionally rare, with only a few case reports in the literature.[1-6]
- We present two patients with high-grade pituitary lesions who developed metastases isolated to the central nervous system.
- In these cases, recurrence despite treatment was common, underscoring their difficulty to treat.

Methods and Materials

- Whole exome sequencing (WES) was performed on all available lesions and matched blood samples.
- Target capture was performed with IDT xGen Exome Research Panel Version 2 + GOAL region spike-ins.
- Sequencing was performed with Ilumina NovaSeq 600.
- Downstream analysis to identify somatic single nucleotide variations (SNVs), short insertion-deletions (INDELs), and copy number variations (CNVs) was carried out following the Genome Analysis Toolkit (GATK) Best Practices Guidelines.
- A literature search was conducted to identify similar cases for comparison.

Patient 1

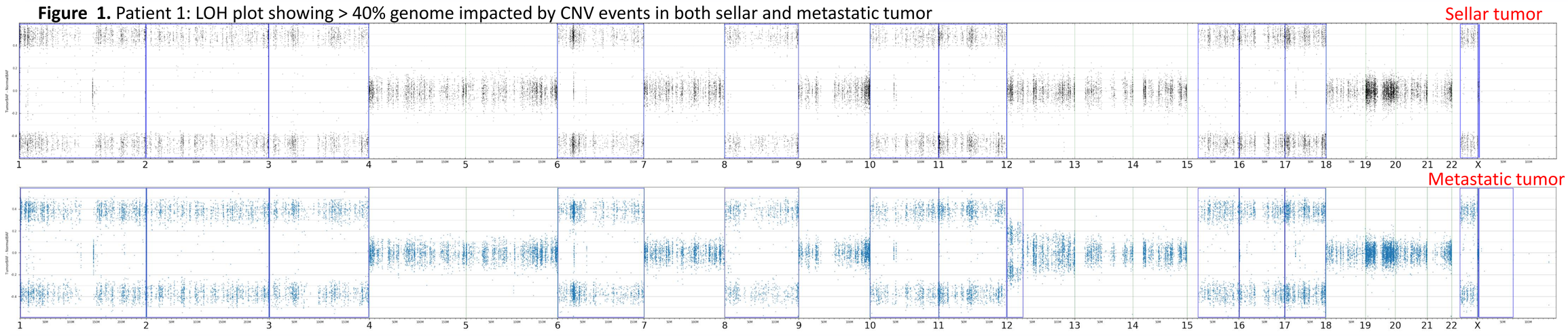
Clinical presentation:

- 47-year-old male with pituitary tumor resected twice before developing recurrent pituitary lesion.
- Treated with re-resection via EEA and adjuvant radiotherapy (50.4 Gy).
- Histological assessment revealed pituitary adenoma with Ki-67 index 4-5%.
- New extrasellar brain lesions identified on follow-up MRI after 2.5 years.
- Surgical pathology of one of the new lesions revealed neuroendocrine carcinoma.

Genomic profile (somatic WES):

- Both the sellar and metastatic tumors demonstrated **>40% of the genome altered by CNVs.**
- Both the primary and recurrent tumor had ***DAXX: frameshift mutation (K437Tfs).***
  - A nuclear protein involved in transcriptional repression, apoptosis, chromatin organization, telomere maintenance, and genomic instability.

Figure 1. Patient 1: LOH plot showing > 40% genome impacted by CNV events in both sellar and metastatic tumor



Patient 2

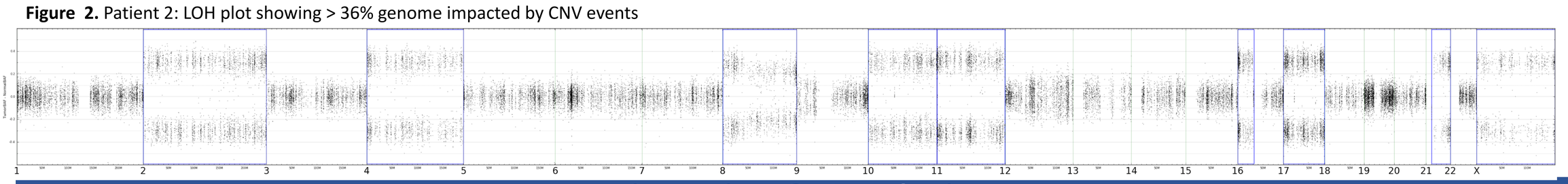
Clinical presentation:

- 26-year-old female with prolactinoma on cabergoline presented with pituitary lesion causing hydrocephalus.
- Required resection via EEA. Histology showed neuroendocrine tumor with Ki-67 10-15%. Patient was lost to follow-up.
- Lesion recurred in 6 months which required re-resection and adjuvant radiotherapy (50.4 Gy).
- She developed multiple CNS metastases including brain and intradural extramedullary spinal lesions.

Genomic profile (somatic WES):

- **36% of the genome altered by CNVs.**
- Had a deleterious ***TP53: missense mutation (R209Q).***
  - Consistent with the well-established role of TP53 loss in promoting chromosomal instability.

Figure 2. Patient 2: LOH plot showing > 36% genome impacted by CNV events



Discussion & Conclusions

- Metastatic PitNET is rare, and deleterious somatic alterations in key genomic stability regulators may underlie the aggressive biology of these otherwise typically benign tumors.
- Future work should emphasize early diagnosis and aggressive management (including the role of CSI) in the management of patients with disease limited to the CNS.

Contact

Shashank Rajkumar
Dept of Neurosurgery, Yale University School of Medicine
Shashank.Rajkumar@yale.edu
203-823-7169

References

1. Reed, C. T., Duma, N., Halfdanarson, T., & Buckner, J. (2019). Primary neuroendocrine carcinoma of the brain. *BMJ Case Reports CP*, *12*(9), e230582.
2. Hopster, D. J., Robinson, S. F., Chadwick, L., & Geddes, J. F. (1997). Widespread neuroendocrine malignancy within the central nervous system: a diagnostic conundrum. *Journal of clinical pathology*, *50*(5), 440-442.
3. Stepien, N., Haberler, C., Theurer, S., Schmook, M. T., Lütgendorf-Caucig, C., Müllauer, L., ... & Peyrl, A. (2022). Unique finding of a primary central nervous system neuroendocrine carcinoma in a 5-year-old child: a case report. *Frontiers in Neuroscience*, *16*, 810645.
4. Steinberg, S. N., Hewitt, K. C., & Block, C. K. (2025). A neuropsychological profile for high-grade primary central nervous system neuroendocrine tumor (CNS NET): A single-case study. *The Clinical Neuropsychologist*, *39*(1), 218-232.
5. Caro-Osorio, E., Perez-Ruano, L. A., Martinez, H. R., Rodriguez-Armendariz, A. G., Lopez-Sotomayor, D. M., & Perez-Ruano Sr, L. A. (2022). Primary neuroendocrine carcinoma of the cerebellopontine angle: A case report and literature review. *Cureus*, *14*(8).
6. Aziz Khan, A., Ahuja, S., & Zaheer, S. (2023). A rare case of primary neuroendocrine carcinoma of the central nervous system. *Neuropathology*, *43*(5), 421-424.