Published in final edited form as:

Acta Neuropathol. 2017 April ; 133(4): 661–663. doi:10.1007/s00401-017-1689-7.

Genetic confirmation that ependymoma can arise as part of multiple endocrine neoplasia type 1 (MEN1) syndrome

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Multiple endocrine neoplasia type 1 (MEN1) syndrome is an autosomal dominant disorder resulting in neoplasia affecting the anterior pituitary, pancreatic islets, parathyroid, adrenocortical, and duodenal neuroendocrine cells with high penetrance. MEN1 syndrome is caused by inactivating germline mutation in one allele of the *MEN1* tumor suppressor gene on chromosome 11q13, and tumors arise from the neuroendocrine cells in these tissues due to somatic loss of the remaining wild-type allele. In addition to endocrine adenomas, a few individual case reports have described ependymomas in patients with MEN1 syndrome [1–4]. However, whether these ependymomas represent sporadic neoplasms or arose as part of MEN1 or an alternative multiple endocrine neoplasia syndrome has not been documented. Herein, we provide genetic confirmation that ependymoma can indeed arise and should be considered as one of the neoplasms that occur in patients with MEN1 syndrome. An 18 year old man initially presented with nephrolithiasis due to primary hyperparathyroidism and underwent resection of two parathyroid adenomas (not shown). His family history includes

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presumed MEN1 syndrome in his father and paternal grandmother who both had gastrinomas, and his father also had primary hyperparathyroidism and Cushing's syndrome due to ACTH-secreting pituitary adenoma. The patient suffered from recurrent nephrolithiasis but was otherwise well until 33 years of age when he presented with several months of nausea, epigastric pain, and diarrhea and was found to have elevated serum level of gastrin consistent with Zollinger-Ellison syndrome. He underwent endoscopy that revealed several sessile polyps in the duodenum, and biopsies demonstrated well differentiated neuroendocrine tumors within the duodenal submucosa (Supplemental Fig. 1). Two months later he underwent parathyroid scintigraphy demonstrating persistent focal uptake of Tc99m-sestamibi in the lower left thyroid bed. Surgical resection was performed that demonstrated parathyroid adenoma (Supplemental Fig. 2). Additionally, abdominal magnetic resonance imaging showed two exophytic enhancing pancreatic masses (Supplemental Fig. 3). One month after the parathyroid resection, surgical enucleation of the two pancreatic masses was performed that demonstrated well differentiated pancreatic neuroendocrine tumors.

One month later he presented with left-sided paresthesia, dysphagia, and ataxia of the left hand. Imaging revealed a 3 cm calcified, solid and cystic mass with heterogeneous enhancement arising from the cervicomedullary junction (Fig. 1a, Supplemental Fig. 4). A suboccipital craniotomy and resection was performed. Hematoxylin and eosin stained sections showed a solid ependymal neoplasm of moderate cellularity with well-developed perivascular pseudorosettes and rare mitotic figures (Fig. 1b, Supplemental Fig. 4). The tumor cells were strongly immunoreactive for glial fibrillary acidic protein (GFAP), had paranuclear dot-like immunopositivity for epithelial membrane antigen (EMA), and lacked significant immunostaining for synaptophysin (Fig. 1c, Supplemental Fig. 4). A diagnosis of ependymoma, WHO grade II, was made. Capture-based next generation sequencing was performed as previously described on genomic DNA extracted from the ependymoma and peripheral blood [5]. This sequencing revealed a 2 base pair deletion within exon 3 of the *MEN1* gene predicted to cause frameshift and early truncation of the encoded Menin protein (Fig. 1d). This *MEN1* mutation was present in one of two copies in the germline and was accompanied by somatic loss of the remaining wild-type allele due to chromosome 11 deletion in the tumor (Fig. 1e). Alterations affecting other genes important in the development of ependymomas including *NF2* and *RELA* were not identified. DNA methylation profiling using Illumina MethylationEPIC BeadChip (850k array) revealed that this tumor clusters most closely with spinal ependymomas as opposed to posterior fossa ependymomas, supratentorial ependymomas, subependymomas, or other CNS tumor types (Supplemental Fig. 5). Monosomy 11 loss as seen in this tumor is uncommon among spinal ependymomas, present in only 2 out of 40 cases in one recent study [6]. Together, the findings in this patient provide genetic confirmation that ependymoma can arise as part of MEN1 syndrome and should be recognized as a tumor type that occurs and potentially screened for in patients with this syndrome. No distinct radiographic or histologic features were identified in this case that distinguish MEN1-associated ependymomas from their sporadic counterparts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by NIH Director's Early Independence Award (DP5 OD021403) to D.A.S.

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Figure 1.

Radiographic, histologic, and genetic features of an ependymoma in a 33 year old man with MEN1 syndrome. **a** Sagittal T2-weighted fluid-attenuated inversion recovery MRI demonstrating an exophytic, solid and cystic mass arising from the cervicomedullary junction with associated hyperintensity in the superior cervical cord. **b** H&E stained section of the tumor demonstrating a solid ependymal neoplasm with perivascular pseudorosettes. **c** Immunostain for EMA demonstrating paranuclear dot-like positivity in tumor cells. **d** Next-generation sequencing reads for the *MEN1* gene demonstrating a 2 base pair deletion (c. 563_564delGG, p.P188fs based on transcript NM_130799) present in approximately half of the reads in DNA extracted from the peripheral blood and nearly all of the reads in DNA extracted from the ependymoma. **e** Genome-wide copy number plot for the tumor demonstrating loss of chromosome 11, which includes the remaining wild-type *MEN1* allele at 11q13. Clonal losses of chromosomes 10 and 11 are seen suggesting that they were early events in tumor development, and additional subclonal losses of chromosomes 3, 8, 14, 16, 17, and 22 are also seen that likely occurred later during tumor progression in only a subset of the ependymoma cells.