High-Grade Neuroendocrine Carcinoma Within a Tracheal Polyp: A Case Report

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ABSTRACT

Introduction: Primary carcinomas of the trachea are rare, with a reported annual incidence of one in a million. We present a case of a previously undescribed polypoid high-grade neuroendocrine carcinoma of the trachea. Resection of the carcinoma revealed only superficial invasion of the mucosa and without evidence of local or distant metastatic disease. Histologically, the tumor had high-grade features with necrosis and a high mitotic index.

Methods: Characterization of this rare neuroendocrine carcinoma of the trachea was performed by immunohistochemistry and whole-genome sequencing.

Results: Immunohistochemistry result was positive for neuroendocrine markers, p16 and an elevated Ki-67. Whole-genome sequencing of the lesion was performed and revealed a very unusual and very distinct mutational signature without relationship to other relevant neuroendocrine carcinomas. Neither known driver nor targetable mutations were found by whole-genome sequencing. Analysis of the sequence of numerous viral elements of human papillomavirus-18 suggests that the pathogenesis of the lesion is related to viral integration. The patient developed distal recurrence, which progressed to widespread pulmonary dissemination, presumably through aerogenous spread of disease.

Conclusions: This is the first characterization of this type of tracheal tumor, including genomic findings, pathogenesis, and natural history.

Keywords: Neuroendocrine carcinoma/tumor; Tracheal tumor; Whole-exosome sequencing; Case report

Introduction

Primary carcinomas of the trachea are rare with a reported annual incidence of approximately one in one million. 1 Neuroendocrine carcinomas are the third most common histologic subtype (13.5%, including large cell carcinoma), behind squamous cell carcinoma (44.8%) and adenoid cystic carcinoma (16.3%). 2

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Figure 1. Imaging and histopathologic evaluation of the tracheal polyp. (A) Computed tomography of the tracheal polyp. (B) Intraoperative bronchoscopy view of the tracheal polyp. (C) Gross assessment of the resected tracheal polyp. HE of the tracheal polyp at (D) low power (×40) and (E) high power (×200). IHC staining of the tracheal polyp with the following markers: (F) synaptophysin (×40), (G) CD56 (×40), (H) chromogranin (×40), and (I) p16 (×200). HE, hematoxylin and eosin; IHC, immunohistochemistry.
Figure 2. WGS analysis of the tracheal polyp. WGS was performed on the FFPE tissues from the tracheal polyp and the adjacent normal trachea on an Illumina HiSeq X PE150 at the Genome Quebec. The raw DNA sequences were aligned and trimmed, and duplicates were flagged to the NCBI human genome, using Isaac aligner. Structural variant analysis calls were generated using Manta. Small variants in germline and somatic variations were achieved using Strelka. Copy number calls were generated using Canvas. (A) Annotation of the resulting calls was done with the Ensembl Variant Effect Predictor. Fastp was used to collect QC metrics of the raw reads. Circlize was used to generate the Circos plots of the tracheal polyp genome with a detail of the SNVs and SVs. (B) Pair-wise Venn diagrams looking at overlap in gene mutations of several related cancer type or location with the tracheal polyp were generated using our analysis results with the online tool InteractiVenn with comparative tumoral data set lists from cBioPortal. FFPE, formalin-fixed, paraffin-embedded; NCBI, National Center for Biotechnology Information; QC, quality control; SNV, single-nucleotide variant; SV, structural variant; WGS, whole-genome sequencing.
| Gene    | Freq | Gene    | Freq | Gene    | Freq | Gene    | Freq | Gene    | Freq | Gene    | Freq |
|---------|------|---------|------|---------|------|---------|------|---------|------|---------|------|
| MEN1    | 37%  | TP53    | 24%  | TP53    | 94%  | TP53    | 81.01%| TP53    | 47%  | TP53    | 60%  |
| DAXX    | 22%  | TTN     | 11%  | RB1     | 78%  | TTN     | 70.39%| TTN     | 40%  | TTN     | 53%  |
| ATRX    | 10%  | SPOP    | 18%  | TTN     | 70%  | RYR2    | 43.02%| MUC16   | 40%  | MUC16   | 33%  |
| PTEN    | 7%   | MUC16   | 22%  | TP53    | 60%  | TP53    | 46%  | TP53    | 36%  | TP53    | 26%  |
| TTN     | 5%   | ZNF729  | 47%  | RB1     | 46%  | RYR2    | 43.02%| MUC16   | 30%  | CSMD3   | 23%  |
| SETD2   | 5%   | SHANK1  | 42%  | ZFHK4   | 42%  | RYR2    | 36.31%| RYR2    | 30%  | CSMD3   | 21%  |
| DYN1C11 | 4%   | FOXA1   | 40%  | USH2A   | 40%  | ADAM6   | 29.61%| USH2A   | 30%  | FLG     | 27%  |
| MUC16   | 4%   | ZNF626  | 4%   | CSMD3   | 38%  | SYNE1   | 29.05%| FLG     | 27%  | CSMD1   | 20%  |
| FREM3   | 4%   | ZNF208  | 8%   | NAV3    | 32%  | RYR3    | 23.46%| SPTA1   | 25%  | PCLO    | 20%  |
| A2M     | 3%   | TMC8    | 8%   | PCDH15  | 29%  | SPTA1   | 22.35%| MUC17   | 21%  | DNH4    | 19%  |
| UGTT1   | 3%   | KMO     | 7%   | COL11A1 | 28%  | DNAH1  | 21.79%| XIRP2   | 20%  | FAT4    | 19%  |
| GBP2    | 3%   | CDP     | 7%   | CSMD1   | 25%  | FAM135B| 20.67%| PCLO    | 20%  | OBS CN  | 19%  |
| SLC12A8 | 3%   | DYN1CH1 | 7%   | EYS     | 25%  | PKHD1  | 20.67%| NAV3    | 20%  | RYR2    | 19%  |
| TRDN    | 3%   | RB1     | 7%   | SYNE1   | 25%  | KMT2D  | 20.67%| FAT3    | 19%  | HCN1    | 18%  |
| RYR2    | 3%   | OBS CN  | 7%   | MUC17   | 25%  | COL11A1| 20.11%| CSMD1   | 19%  | KMT2D   | 18%  |
| EFTU2   | 3%   | DHA4N   | 7%   | FAM135B| 24%  | FLG    | 20.11%| KMT2C   | 18%  | FAT3    | 17%  |
| KMT2C   | 3%   | METTL24 | 7%   | ANKRD30B| 24%  | SI     | 20.11%| ZNF536  | 18%  | SPTA1   | 17%  |
| RBX1    | 3%   | FSIP2   | 7%   | TMEH132D| 23%  | PKHD1L | 20.11%| PCDH15  | 18%  | ZFH4    | 15%  |
| DST     | 3%   | ZNF616  | 7%   | FSIP2   | 23%  | NAV3   | 19.55%| COL11A1| 17%  | USH2    | 15%  |

Highlighted in grey are the mutated genes that are common between the tracheal polyp and other cancers, the mutational status of which were obtained from The Cancer Genome Atlas (TCGA).
Case Presentation

A 64-year-old ex-smoker (30 pack-year) man presented with hemoptysis and dyspnea. Preoperative computed tomography (Fig. 1A) and intraoperative bronchoscopy (Fig. 1B) results revealed a left tracheal wall exophytic mass at the T2 level. Gross evaluation of the tracheal biopsy specimen revealed a pedunculated polyp measuring 1.5 cm in greatest dimension (Fig. 1C). Microscopic examination revealed poorly differentiated neuroendocrine carcinoma with large cell phenotype and superficial lamina propria invasion (Fig. 1D). Also present were rosette formation; focal necrosis; surface squamous metaplasia; and 15 to 20 mitoses per high-power field (Fig. 1E). There was no evidence of lymphovascular invasion; no lymph node metastases (0 of 9); and surgical margins were negative. Immunohistochemistry results revealed strong positivity for synaptophysin (Fig. 1F) and weak and patchy positivity for CD56 (Fig. 1G); chromogranin (Fig. 1H); TTF-1; CK7; and c-Kit. CK5/6 and p40 were negative. The Ki-67 index was 70%. In addition, immunohistochemistry for p16 was strongly positive (Fig. 1I).

Whole-genome sequencing (WGS) of the resected tracheal polyp revealed very little large-scale rearrangements and no copy number changes (Fig. 2A). Comparison of the mutational signature of this tracheal polyp with other neuroendocrine tumors (prostate and pancreatic) and to small-cell, squamous, and adenocarcinoma lung cancers and to esophagogastric cancers revealed that from a somatic mutation perspective, none of the major driver gene mutations that are found in those tumors are present in this tracheal polyp. Indeed, the mutated genes identified in this tracheal polyp are not present in the top 20 frequently mutated genes of any of the compared cancers (Table 1). The only similarities were found within large proteins, such as TTN, MUC16, and MUC17, that are often mutated owing to their large size (Table 1). Interestingly, 30% match of the tracheal polyp genes were common to the top 20 mutated genes in prostate neuroendocrine carcinoma (Table 1); however, the significance of this is unclear, given the histologic and pathologic differences. Furthermore, the tracheal polyp had approximately 5% homology with pancreatic neuroendocrine carcinoma (Fig. 2B). Interestingly, this patient has deleterious germline variants in seven of the 152 recently curated cancer susceptibility genes,3 namely DOCK8, ERCC5, FANCA, POLE, PRSS1, RHBDF2, and SERPINA1. Most interestingly, in the context of positive p16, whole-genome analysis revealed numerous copies of human papilloma virus-18 DNA, not present in the normal control.

The patient was initially treated with surgery, but he had persistent hemoptysis and was found to have recurrent/metastatic disease in the trachea and right bronchus on bronchoscopy 8 months after. Imaging results revealed multiple pulmonary nodules deemed to be metastases, and the patient was treated with carboplatin and etoposide.

Discussion

We present a previously undescribed polypoid high-grade neuroendocrine carcinoma of the trachea, which revealed limited invasion on initial resection but early recurrence and widespread metastases to distant superficial bronchi and lung parenchyma. Viral integration is likely the pathogenic origin for the carcinoma. Nevertheless, the pathophysiology of spread is not well understood but is hypothesized to be aerogenous given the anatomical location of metastases. It reveals a very unusual and very distinct mutational signature without relationship to other relevant neuroendocrine carcinomas. Neither known driver nor targetable mutations were found by WGS. An established TNM-based system is lacking for tracheal carcinomas,4 and given the natural course and spread in this case, depth of invasion does not apply.5

Conclusion

We herein describe an unusual case of a high-grade neuroendocrine carcinoma of the trachea, whose pathogenesis is likely related to a human papilloma virus-18 infection. WGS failed to identify known driver or targetable mutations. Unfortunately, the patient’s disease recurred with first locoregional disease but eventually disseminated to pulmonary metastases.

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