CASE REPORT

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

Victor Brochu, MDCM,[a] Gurdip Singh Tamber, MD,[a] Roni F. Rayes, PhD,[b,c] Benoit Fiset, BSc,[c] Derin Caglar, MD,[a] Sophie Camilleri-Broët, MD, PhD,[a] Roger Tabah, MD,[d] Logan A. Walsh, PhD,[c,e] Jonathan D. Spicer, MD, PhD,[b] Pierre Olivier Fiset, MDCM, PhD[a,*]

[a]*Department of Pathology, Faculty of Medicine, McGill University, Montreal, Quebec, Canada*
[b]*Division of Thoracic Surgery, McGill University Health Center, Montreal, Quebec, Canada*
[c]*Rosalind and Morris Goodman Cancer Research Centre, McGill University, Montreal, Quebec, Canada*
[d]*Department of General Surgery, McGill University Health Center, Montreal, Quebec, Canada*
[e]*Department of Human Genetics, McGill University, Montreal, Quebec, Canada*

Received 21 January 2021; revised 23 March 2021; accepted 26 March 2021
Available online - 9 April 2021

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]

*Corresponding author.

Dr. Spicer and Dr. Fiset contributed equally as co-senior authors.

Disclosure: Dr. Fiset has received honoraria from EMD Serono and consultation fees from Amgen, Bristol-Myers Squibb, AstraZeneca Canada, Merck Canada, Pfizer Canada, and Roche Canada. Dr. Spicer has received honoraria and expert consultancy fees from Amgen Canada, AstraZeneca Canada, Bristol Myers Squibb, Merck Canada, Trans-Hit Biomarkers and Roche Canada and grants from AstraZeneca Canada, Merck Canada and Roche Canada. The remaining authors declare no conflict of interest.

Address for correspondence: Pierre Olivier Fiset, MD, PhD, Department of Pathology, Faculty of Medicine, McGill University, 1001 Decarie, Glen site, E.04.4141, Montreal, QC H4A 3J1, Canada. E-mail: pierre.o.fiset@mcgill.ca

Cite this article as: Brochu V, Tamber GS, Rayes RF, et al. High-grade neuroendocrine carcinoma within a tracheal polyp: a case report. *JTO Clin Res Rep*. 2021;2:100169.

ISSN: 2666-3643
https://doi.org/10.1016/j.jtocrr.2021.100169

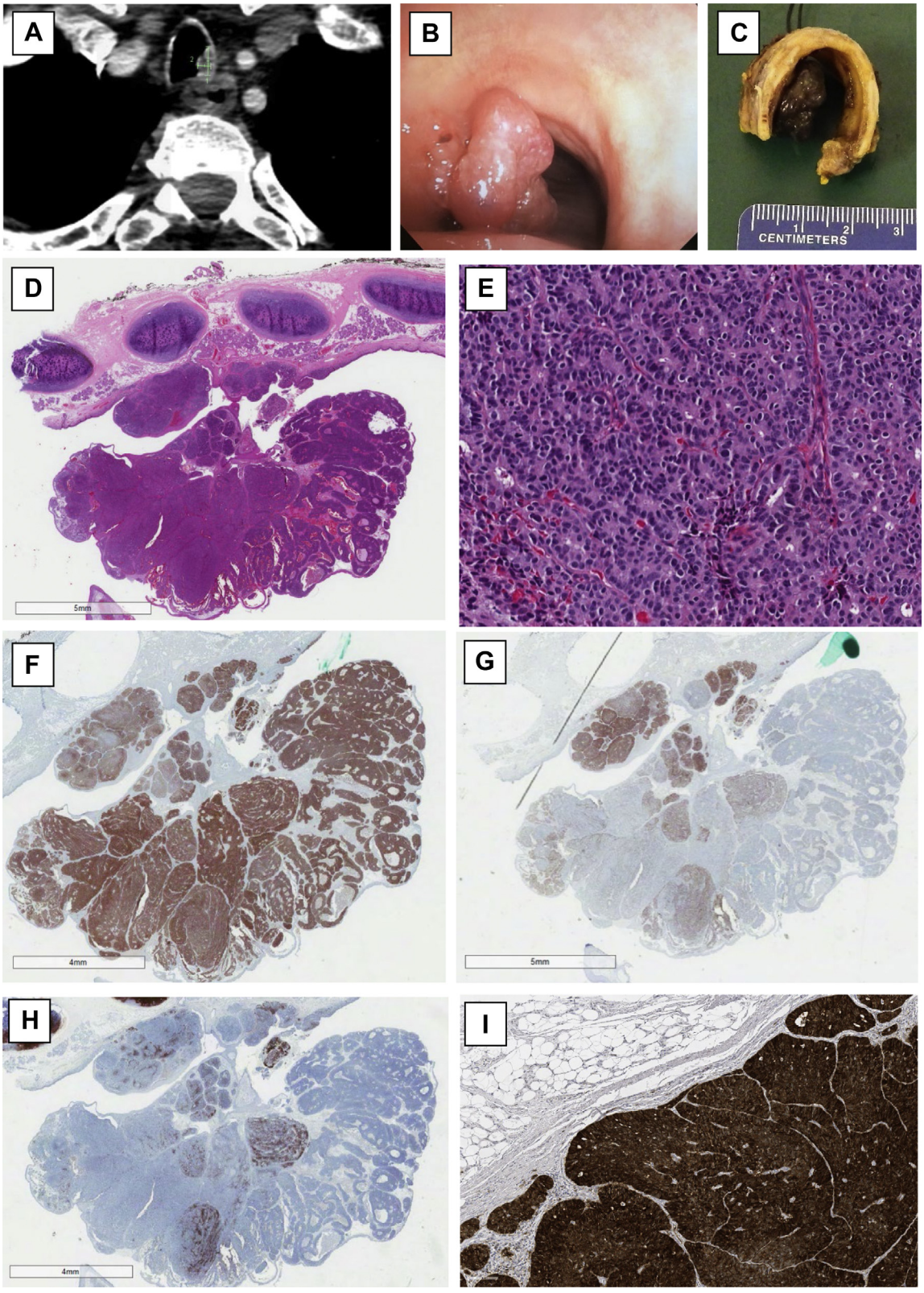

Figure 1. Imaging and histopathologic evaluation of the tracheal polyp. (*A*) Computed tomography of the tracheal polyp. (*B*) Intraoperative bronchoscopy view of the tracheal polyp. (*C*) Gross assessment of the resected tracheal polyp. HE of the tracheal polyp at (*D*) low power (×40) and (*E*) high 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.

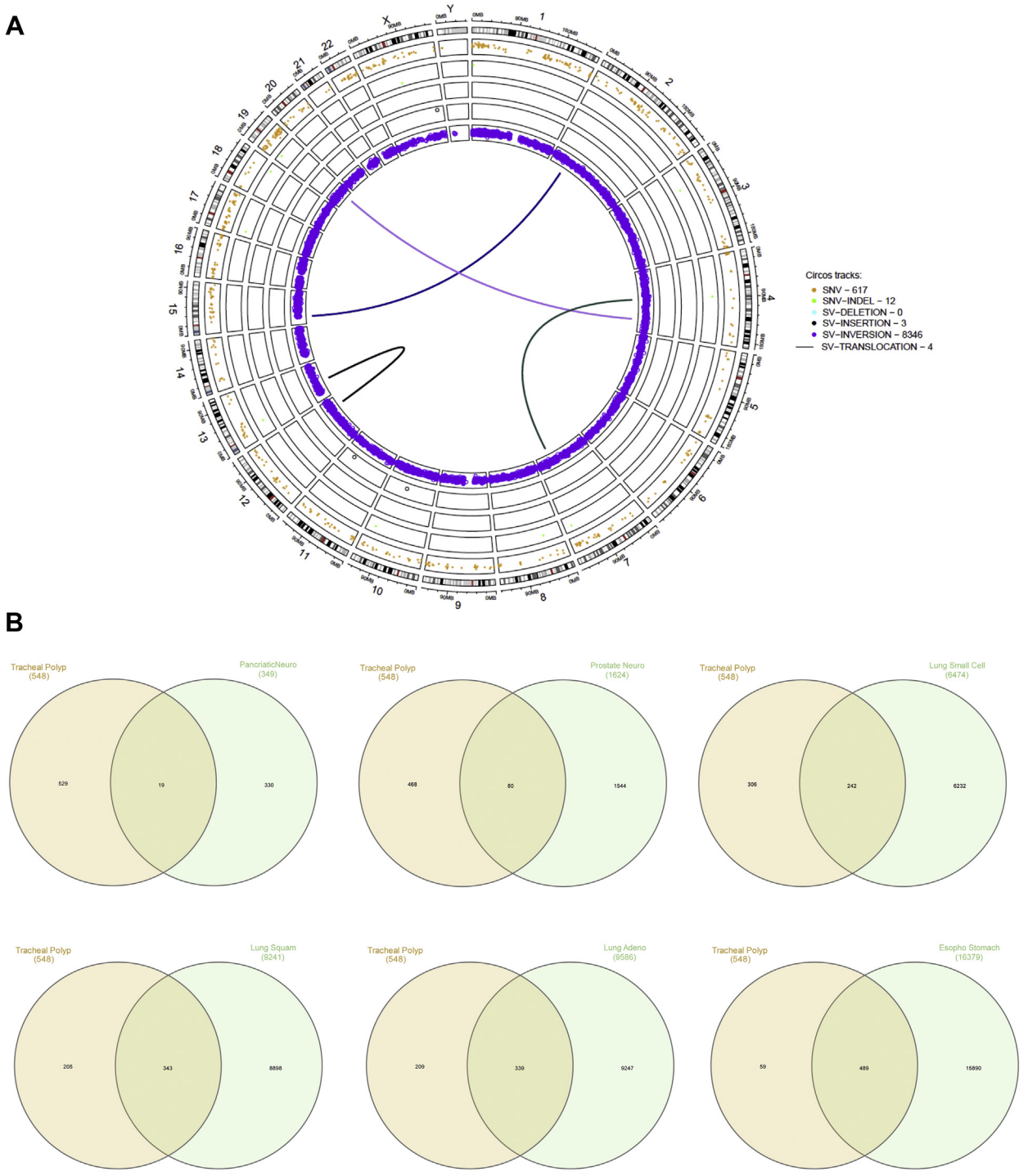

Figure 2. WGS analysis of the tracheal polyp. WGS was performed on the FFPE tissues from the tracheal polyp and the adjacent normal trachea on an Illumina HiSeq X PE150 at the Genome Quebec. The raw DNA sequences were aligned and trimmed, and duplicates were flagged to the NCBI human genome, using Isaac 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.

Table 1. Top 20 frequently mutated genes in neuroendocrine and upper GI cancers

Pancreatic - Neuroendocrine		Prostate - Neuroendocrine		Lung - Small-Cell		Lung - Squamous		Lung - Adenocarcinoma		Esophageal & Stomach	
Gene	Freq	Gene	Freq	Gene	Freq	Gene	Freq	Gene	Freq	Gene	Freq
MEN1	37%	TP53	24%	TP53	94%	TP53	81.01%	TTN	47%	TP53	60%
DAXX	22%	TTN	18%	RB1	78%	TTN	70.39%	TP53	46%	TTN	53%
ATRX	10%	SPOP	11%	TTN	70%	RYR2	43.02%	MUC16	40%	MUC16	33%
PTEN	7%	MUC16	10%	RYR2	49%	MUC16	43.02%	RYR2	36%	SYNE1	26%
TTN	5%	ZNF729	8%	LRP1B	46%	LRP1B	38.55%	KRAS	33%	LRP1B	24%
SETD2	5%	SHANK1	8%	MUC16	45%	USH2A	37.99%	LRP1B	30%	CSMD3	23%
DNAH5	4%	HMCN1	8%	ZFHX4	42%	ZFHX4	36.31%	USH2A	30%	FLG	21%
DYNC1I1	4%	FOXA1	8%	USH2A	40%	ADAM6	29.61%	ZFHX4	27%	ARID1A	20%
MUC16	4%	ZNF626	8%	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%	DNAH5	19%
UGGT1	3%	KMO	7%	COL11A1	28%	DNAH11	21.79%	XIRP2	20%	FAT4	19%
GBP2	3%	CPD	7%	CSMD1	25%	FAM135B	20.67%	PCLO	20%	OBSCN	19%
SLC12A8	3%	DYNC1H1	7%	EYS	25%	PKHD1	20.67%	NAV3	20%	RYR2	19%
TRDN	3%	RB1	7%	SYNE1	25%	KMT2D	20.67%	FAT3	19%	HMCN1	18%
RYR2	3%	OBSCN	7%	MUC17	25%	COL11A1	20.11%	CSMD1	19%	KMT2D	18%
EFTUD2	3%	DNAH3	7%	FAM135B	24%	FLG	20.11%	KMT2C	18%	FAT3	17%
KMT2C	3%	METTL24	7%	ANKRD30B	24%	SI	20.11%	ZNF536	18%	SPTA1	17%
URB1	3%	FSIP2	7%	TMEM132D	23%	PKHD1L1	20.11%	PCDH15	18%	ZFHX4	15%
DST	3%	ZNFX1	7%	FSIP2	23%	NAV3	19.55%	COL11A1	17%	USH2A	15%

Highlighted in grey are the mutated genes that are common between the tracheal polyp are 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. 1*A*) and intraoperative bronchoscopy (Fig. 1*B*) 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. 1*C*). Microscopic examination revealed poorly differentiated neuroendocrine carcinoma with large cell phenotype and superficial lamina propria invasion (Fig. 1*D*). Also present were rosette formation; focal necrosis; surface squamous metaplasia; and 15 to 20 mitoses per high-power field (Fig. 1*E*). 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. 1*F*) and weak and patchy positivity for CD56 (Fig. 1*G*); chromogranin (Fig. 1*H*); 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. 1*I*).

Whole-genome sequencing (WGS) of the resected tracheal polyp revealed very little large-scale rearrangements and no copy number changes (Fig. 2*A*). 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 esophago-gastric 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. 2*B*). 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.

Acknowledgments

The authors thank Mr. Alfred Cuellar, the immunohistochemistry director of the Research Institute of the McGill University Health Centre pathology laboratory, and Mrs. Louise Turcot, the manager of the Research Institute of the McGill University Health Centre pathology laboratory. The authors also acknowledge the Montreal General Hospital Foundation Award for Dr. Fiset. Dr. Walsh was supported by the Canada Foundation for Innovation (JELF-39178), Canadian Institutes of Health Research (PJT-162137), and a Rosalind & Morris Goodman Chair in Lung Cancer. Dr. Spicer is supported by the Fonds de la Recherche en Santé du Québec clinician scientist award. The authors are also grateful for support from the Quebec Cancer Consortium and the financial support from the Ministère de l'Économie et de l'Innovation du Québec through the Fonds d'accélération des collaborations en santé. Informed consent was obtained (MUHC authorization 2018-3960). The patient provided informed consent which allowed us to undergo and publish this case.

References

1. Honings J, van Dijck JA, Verhagen AF, van der Heijden HF, Marres HA. Incidence and treatment of tracheal cancer: a nationwide study in the Netherlands. *Ann Surg Oncol*. 2007;14:968–976.
2. Urdaneta AI, Yu JB, Wilson LD. Population based cancer registry analysis of primary tracheal carcinoma. *Am J Clin Oncol*. 2011;34:32–37.
3. Huang KL, Mashl RJ, Wu Y, et al. Pathogenic germline variants in 10,389 adult cancers. *Cell*. 2018;173:355–370.e14.
4. Heikal M. Small-cell cancer presenting as a tracheal polyp: a case report and review of the literature. *J Bronchology Interv Pulmonol*. 2012;19:132–136.
5. Bhattacharyya N. Contemporary staging and prognosis for primary tracheal malignancies: a population-based analysis. *Otolaryngol Head Neck Surg*. 2004;131:639–642.