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# Seed and soil? - Pharyngeal Merkel cell carcinoma after radiotherapy for laryngeal squamous cell carcinoma

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ABSTRACT

Merkel cell carcinoma (MCC) is a neuroendocrine cutaneous malignancy that may present as metastatic disease without a known primary site but, most commonly originates in the sun-exposed skin of the head, neck, and extremities. We present a 66-year-old male treated with chemo-radiation for T3N2cM0 laryngeal squamous cell carcinoma (SCCa) six years before he was diagnosed with MCC isolated to the radiated laryngopharynx. Mucosal MCC is rare and radiation-induced MCC has been hypothesized to occur in previously radiated tissue but, never before to the laryngopharynx. Implications regarding cancer biology and management is focused with discussion on relevant advances in pathologic assessment and immunotherapy.

## 1. Introduction

Merkel cell carcinoma (MCC) is a rare primary cutaneous neuroendocrine carcinoma that most commonly occurs in sun-exposed areas of the head and neck (41–50%), extremities (32–38%), and trunk (12–14%) [1]. Rarely, primary mucosal occurrence has been described in MCC [2]. The pathogenesis of MCC has also been linked to polyomavirus and frequently affects the elderly and immunocompromised [3–7]. MCC's classification as a neuroendocrine tumor is related to its characteristic histopathologic appearance and expression of neuroendocrine markers CD56, neurofilament protein (NFP), and Chromogranin A [8,9]. Reports of a subset of MCC have been described in the literature characterized as unknown primary MCC (UPMCC). The incidence of UPMCC is estimated to be 25% of all MCC cases [10] and diagnostic criteria require an involved lymph node basin and an unidentified primary site [11]. An even more uncommon etiology for MCC has been described in the literature—the occurrence of MCC in a location that was disease free after radiation treatment for a pathologically separate neoplasm [12–14]. The existence of such a correlation has led us to hypothesize a “seed and soil” relationship between our patient's previous radiation exposure and development of mucosal MCC.

## 2. Case presentation

A 66 year-old Caucasian male with prior history notable for chemoradiation of a laryngeal T3N2cM0 squamous cell carcinoma (SCCa) was referred to our clinic for a new pharyngeal lesion. The patient had hyperlipidemia, gastrointestinal reflux disease (GERD), and a 58-pack year smoking history.

He presented with chief complaints of progressive dysphagia and persistent cough. Flexible nasal endoscopy demonstrated a new lesion in the left piriform sinus. He subsequently underwent a CT of the neck with contrast and PET scan. The CT imaging showed a soft tissue mass 16 mm in diameter centered on the left piriform sinus and extending inferiorly along the margin of the left arytenoid cartilage corresponding to the site of the endoscopically visualized mass (Fig. 1). PET scan uptake was consistent with recurrent malignancy without regional or distant metastasis. He underwent resection of the lesion, which was found to be abutting the cricopharyngeus muscle (Fig. 2).

Histopathologic analysis showed the following phenotype: CK20+ (dot-like), CK8/18+ (dot-like), synaptophysin+, chromogranin+, p16+, p40-, CK5/6-, KIT-, S100-, CK7-, TTF-, NEP/CJ-. These findings were consistent with a high-grade neuroendocrine

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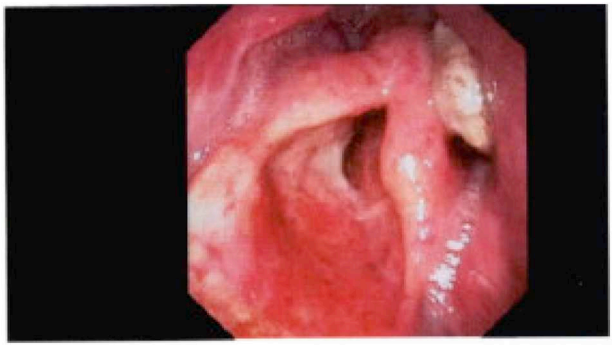

**Fig. 1.** Flexible fiberoptic laryngoscopy showing the lesion in the left piriform sinus. Mucosa shows evidence of prior radiation.

carcinoma, favoring Merkel Cell Carcinoma (Fig. 3). The deep margin was positive and lymphovascular invasion identified. A comprehensive dermatologic examination did not show a primary cutaneous lesion. At follow-up a few weeks after the initial resection, a second endoscopic examination identified two additional, separate lesions within the previously radiated field (Fig. 4). These were resected from the right epiglottis and right piriform sinus (Fig. 5). The tumor was CM2B4 + , Merkel cell polyomavirus, HPV-, PD-L1 tumor cell-, PD-L1 immune cell + .

## 3. Discussion

Merkel Cell Carcinoma (MCC) has been categorized into subsets based on its location and etiology. According to a large population study, 97.6% of primary MCC lesions arise in the skin. The study also categorized a small subset of MCC termed unknown primary MCC (UPMCC). UPMCC is characterized as a rare, aggressive malignancy with a total number of cases in the literature reported to be less than 200 [15]. UPMCC lacks a previously diagnosed or identifiable primary, cutaneous MCC lesion and instead presents with lymph node positive disease [16]. While our selected case resembles UPMCC because of the lack of a cutaneous primary, the patient did not exhibit lymph node positive disease. Therefore, our patient's disease can be more accurately categorized as mucosal MCC. Only twenty cases of MCC originating in mucosal sites exist in the literature [17].

Mucosal MCC is associated with a higher mortality rate compared to cutaneous MCC and differs from UPMCC and cutaneous MCC in etiology, and location. Cutaneous MCC appears on the sun-exposed region of the head and neck and has been associated with T cell immunosuppression. Whereas, mucosal MCC has been linked to tobacco smoking and alcohol consumption [2]. The most common location for mucosal MCC in the literature is the labial mucosa. However, cases involving the nasal mucosa, alveolar mucosa, and the tongue have also been reported [17]. No reports describe mucosal MCC occurring in a previously radiated laryngopharynx. Upon review of the literature, three case reports describe MCC occurring in tissues previously radiated for treatment of distinct cancers after a disease-free interval [12–14]. In light of this, our patient is the fourth case report of an MCC occurring in the site of a previously radiated neoplasm and the only mucosal MCC in the laryngopharynx.

As previously mentioned, three case reports in the literature profile cutaneous MCC occurring in previously radiated tissue for pathologically distinct cancers [12–14]. The patients in these studies had prior radiation therapy for basal cell carcinoma [13], dermatofibrosarcoma [14] and epidermoid carcinoma of the lung [12]. The time from radiation therapy to development of cutaneous MCC was between 5 and 47 years. In addition to the evidence of MCC development after radiotherapy, the established contribution of ionizing ultraviolet radiation exposure to the development of cutaneous MCC supports a radio-induced pathogenesis of MCC [13]. This raises the possibility that our patient's previously radiated pharyngolaryngeal mucosa provided an environment suitable for primary mucosal MCC seeding.

The histological analysis in this case demonstrated tumor cells diffusely and strongly positive for p16, a tumor marker strongly associated with human papilloma virus (HPV). This result is not unique to our case because p16 positivity has been previously described in high-grade neuroendocrine carcinomas, including cases of MCC. Additionally, the literature has reported a distinct HPV-associated high-grade neuroendocrine carcinoma in the oropharynx, which would be p16-positive

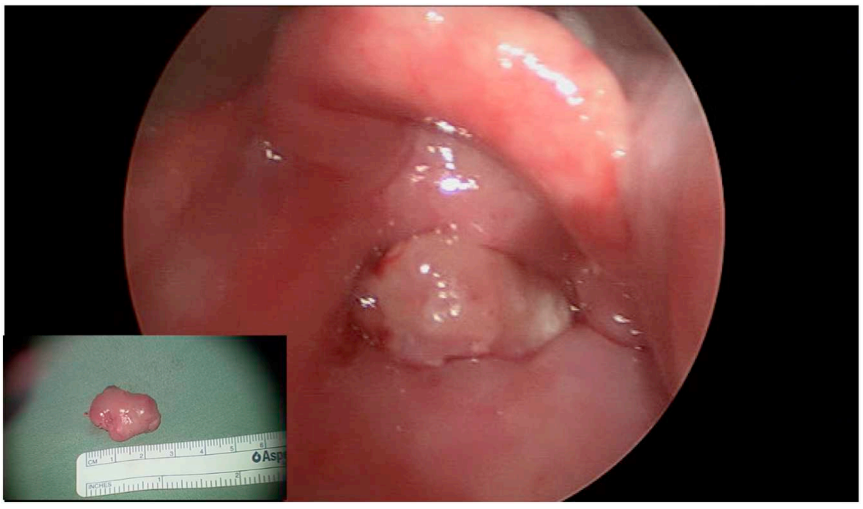

**Fig. 2.** Direct Laryngoscopy of hypopharynx showing the lesion in the left piriform sinus. Insert. Resection of left piriform sinus mass, found to be abutting the cricopharyngeus muscle. Histology indicated a high grade neuroendocrine tumor, consistent with Merkel Cell Carcinoma.

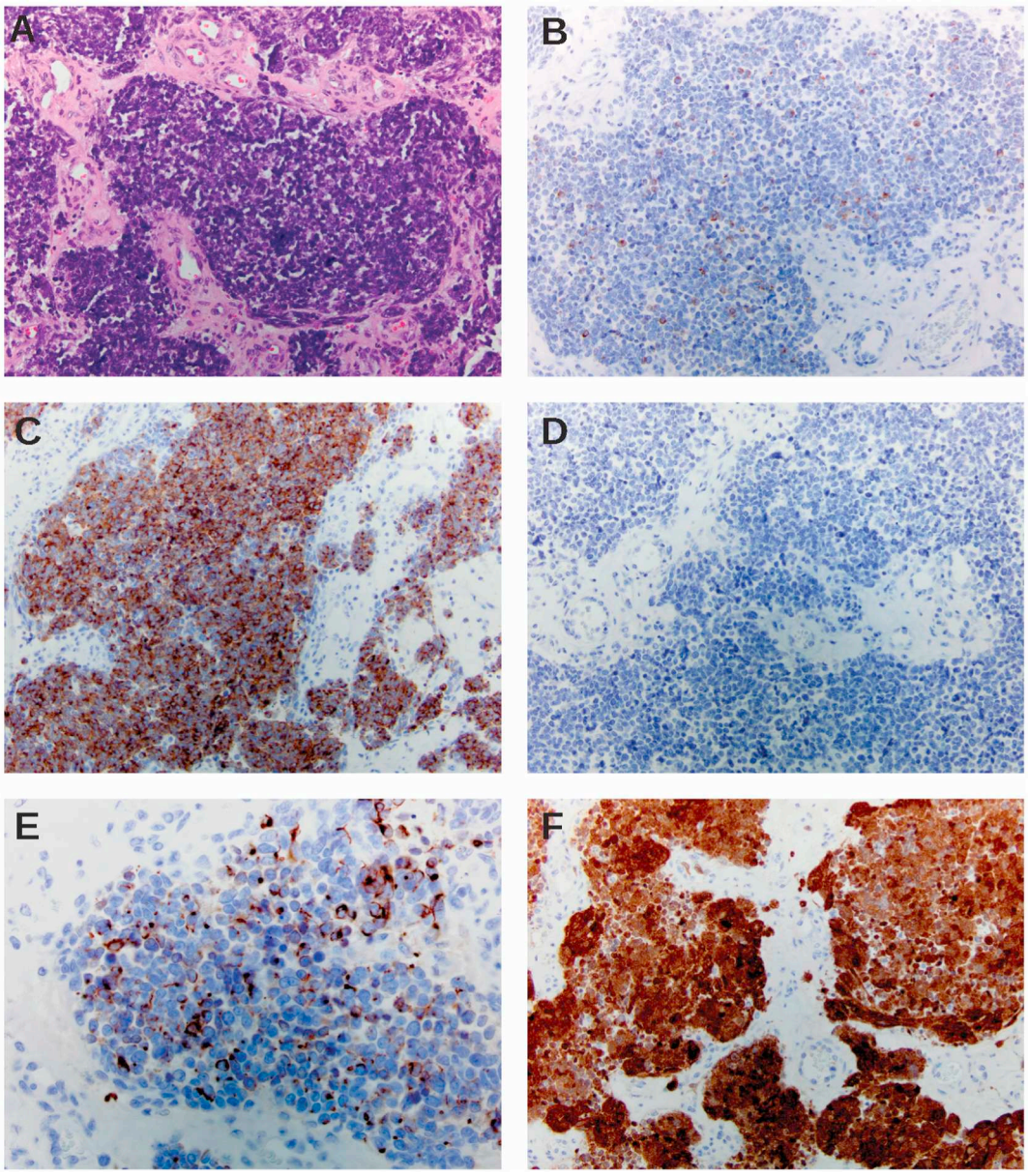


**Fig. 3.** Panels A–F. A – pharyngeal tumor composed of malignant small blue cells with hyperchromatic nuclei and scant cytoplasm, 200× original magnification, routine H&E. B – cytoplasmic moderate granular immunopositivity for chromogranin, 200× original magnification. C – strong, diffuse cytoplasmic positivity for synaptophysin, 200× original magnification. D – tumor negative for TTF1. E – Perinuclear dot-like and cytoplasmic positivity for CK20 in tumor cells, 400× original magnification. F – tumor with strong, diffuse nuclear and cytoplasmic positivity for p16, 200× original magnification. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

as well. However, further testing demonstrated negative DNA/RNA in-situ hybridization studies for high-risk HPV and positive immunohistochemistry with antibody directed at the Merkel Cell Polyomavirus (MCPyV) large T antigen (CM2B4+). Based on these results, our pathologists confirmed the diagnosis as high-grade neuroendocrine tumor favoring Merkel Cell Carcinoma and established that the p16 overexpression was unrelated to HPV [18,19]. These histological characteristics of our patient's tumor presented us with a treatment dilemma.

The paucity of literature studying patients with MCC in fields of previously radiated tissue made it difficult to recommend a treatment modality and discuss the projected course of disease with our patient.

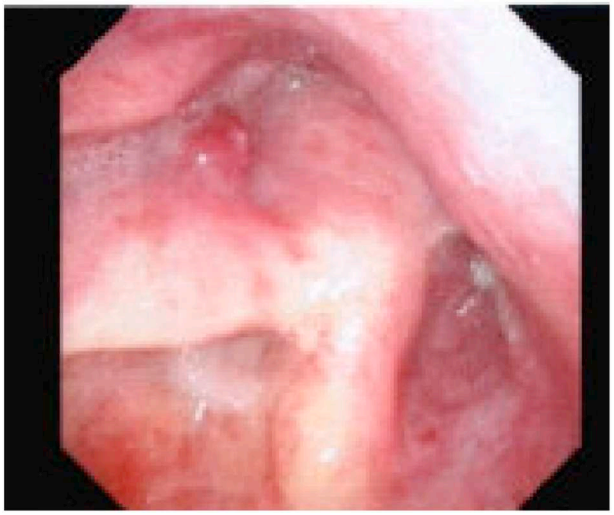

**Fig. 4.** Flexible fiberoptic laryngoscopy three weeks post-resection of left piriform sinus lesion showing a new lesion in the right piriform sinus.

predict the efficacy of anti-PD-1/PD-1 chemotherapy [20]. This information, coupled with the high morbidity associated with aggressive surgical resection, and discussion with the patient decided our management.

## 4. Conclusion

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma with the majority of cases presenting as a primary cutaneous lesion. A less common subset of MCC involves the mucosal surfaces of the head and neck. The pathogenesis of MCC has been linked to ultraviolet radiation, polyomavirus and immunosuppression while an even smaller body of evidence links MCC development to locations of previous radiotherapy. Our patient is the first case report of pharyngeal MCC occurring in an area of previous radiotherapy for laryngeal squamous cell carcinoma. Due to the lack of large population studies for radio-induced MCC, the PD-L1 + immune cell staining of the neoplastic tissue prompted us to investigate immune-directed chemotherapy. Further studies are needed to establish a significant relationship between radiotherapy and MCC as well as the single best approach to treatment.

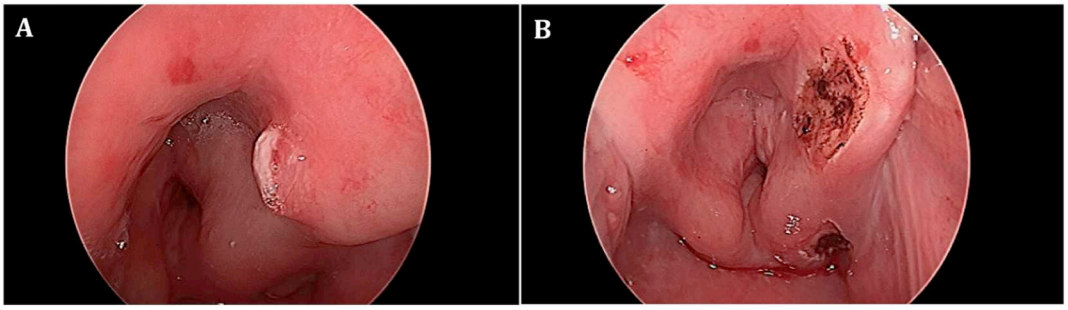


**Fig. 5.** A. Direct Laryngoscopy at the time of right piriform sinus lesion resection showing a new lesion on the epiglottis. B. Microscopic Laryngoscopy with $CO_2$ laser resection of the new right epiglottic and previously identified right posterolateral arytenoid lesions. All frozen sections consistent with Merkel Cell Carcinoma.

Therefore, in consultation with our medical oncologists, we relied on the phenotypic characteristics of the neoplastic cells to direct our treatment strategy. Programmed cell death protein-1 (PD-1) is an immune inhibitory receptor that interacts with programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). PD-L1 is widely expressed on immune cells and is up regulated on several different types of tumor cells, including head and neck squamous cell carcinoma. Immunotherapy against various cancer types employs immune checkpoint blockade and a recently identified target involves antibodies directed against PD-1/PD-L1. Clinical trials using pembrolizumab or durvalumab (MEDI4736) demonstrated that PD-L1 expression might

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