Acta Scientific Otolaryngology (ASOL)

Volume 1 Issue 2 October 2019

Case Report

Endoscopic Resection of Human Papilloma Virus-Related Multiphenotypic Sinonasal Carcinoma

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Received: September 27, 2019; **Published:** September 30, 2019

Abstract

Background: Human papillomavirus-related multiphenotypic sinonasal carcinoma is a rare, emerging pathology of sinonasal carcinomas that can be difficult to diagnose. Although it displays strong association with transcriptionally active HPV, the prognosis of such tumors remains unclear.

Purpose: To describe a unique case of HPV-related multiphenotypic sinonasal carcinoma (HMSC) that was treated with successful endoscopic resection, and a second that initially demonstrated features of HMSC, but was ultimately diagnosed as a high-grade salivary-type adenocarcinoma.

Methods: Case report and literature review. The clinical presentation, radiographic features, histopathologic characteristics, surgical approach, and patient outcomes were assessed in the context of a literature review.

Results: A 72-year-old female presenting with progressive right-sided nasal obstruction, anosmia, facial pressure, and epistaxis underwent endoscopic resection of a sinonasal mass with negative margins followed by adjuvant radiation. The pathology demonstrated HPV-related multiphenotypic sinonasal carcinoma. The patient remains disease free 13 months after endoscopic resection.

A 66-year-old male presenting with unilateral epistaxis initially diagnosed as sinonasal undifferentiated carcinoma underwent endoscopic resection via a transcribriform approach with negative margins followed by adjuvant chemoradiation. The final pathology was interpreted as consistent with HMSC, but later modified to high-grade salivary-type adenocarcinoma following further immunohistochemical studies. The patient experienced distant metastases to the skin and liver 10 months after surgery.

Conclusions: HPV-related multiphenotypic sinonasal carcinoma is a rare clinicopathologic entity that can be challenging to diagnose. Endoscopic resection with adjuvant therapy may be effective in select cases, but additional studies with longer follow-up are needed to better understand the optimal treatment for this unique lesion.

Keywords: Endoscopic; Sinonasal; Carcinoma; Papilloma; Virus

Introduction

Human papillomavirus (HPV) has been associated with one fourth of head and neck carcinomas [1]. Most HPV-related head and neck malignancies are found in the oropharynx [2], but recent studies have shown that 20-25% of sinonasal carcinomas also harbor high-risk HPV [3-6]. While the role of HPV in the prognosis of oropharyngeal squamous cell carcinoma (SCC) is well established, its clinical importance in carcinomas of the sinonasal cavity is less

known. HPV positivity in the sinonasal tract is largely associated with a nonkeratinizing SCC phenotype, but recent reports have described a new type of carcinoma known as HPV-related multiphenotypic sinonasal carcinoma (HMSC) [7], This lesion had been previously termed HPV-positive carcinoma with adenoid cystic-like features [8]. Hallmark features of this tumor type include: (1) Origin in the sinonasal tract; (2) Predominantly solid histopathologic architecture, but with zones of cribriform and/or tubular growth; (3) Mixed phenotypes including basaloid cells showing myoepithelial differentiation, luminal cells showing true ductal differentiation, and surface lining cells showing squamous differentiation; (4) Evidence of transcriptionally active high risk HPV, most commonly HPV type 33; (5) No evidence of gene fusions that have been identified in true adenoid cystic carcinomas; (6) High-grade "salivary-like" features that are difficult to designate into a specific category. Bishop's histopathologic review of 49 cases showed that these tumors often present with advanced stage and high-grade histology [7]. However, optimal management and clinical outcomes for this rare entity have yet to be established. The purpose of this report is to describe a unique case of sinonasal HMSC successfully treated with endoscopic resection and adjuvant radiation.

Case Presentation

Case 1

A 72-year old female presented with progressive right-sided nasal obstruction, anosmia, facial pressure, and epistaxis for 2 years. Endoscopic examination showed a T2N0M0 friable, sinonasal mass that occluded the right nasal cavity and caused a septal deviation to the left with extension into the nasopharynx. A CT and MRI of the sinus showed a mass filling the right nasal cavity, with complete opacification of the maxillary, ethmoid, and sphenoid sinuses associated with bony erosion (Figure 1).

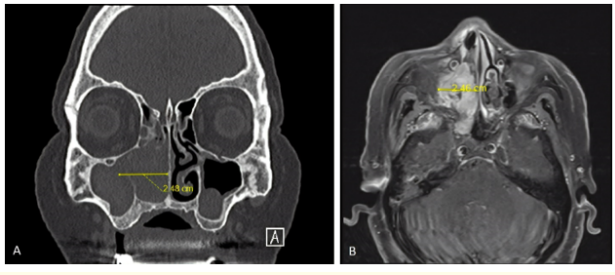

Figure 1: Imaging of MN

A. CT, coronal view

B. MRI, T1-weighted sequence, axial view

The patient subsequently underwent a right endoscopic resection of the sinonasal mass which included a medial maxillectomy, sphenoidotomy, complete ethmoidectomy, and frontal sinusotomy. The mass was highly vascularized wand was attached to both the middle and inferior turbinates. There was erosion of the medial wall of the maxillary sinus; however, the superior, lateral, and inferior maxillary sinus walls were intact. The maxillary sinus was filled with thick mucoid drainage, and the mucosa was noted to be thickened but without tumor involvement. Postoperatively the patient reported improvement in nasal airway obstruction and facial pressure.

Surgical pathology revealed an HMSC with myoepithelial and epithelial differentiation. The lesion had been resected in its entirety with negative margins. Characteristic histopathologic features are depicted in figure 2. The cells were diffusely positive for p16 and HPV ISH showed integration of high risk 31/33 HPV DNA. The sample tested negative for the high-risk HPV strains of 6, 11, 16, and 18. After surgery, the patient was treated with 6 weeks of adjuvant intensity modulated radiation therapy. Follow-up PET-CT scans at 1- and 6-months post-surgery demonstrated no evidence of recurrent disease. The patient remains disease-free 13 months after therapy.

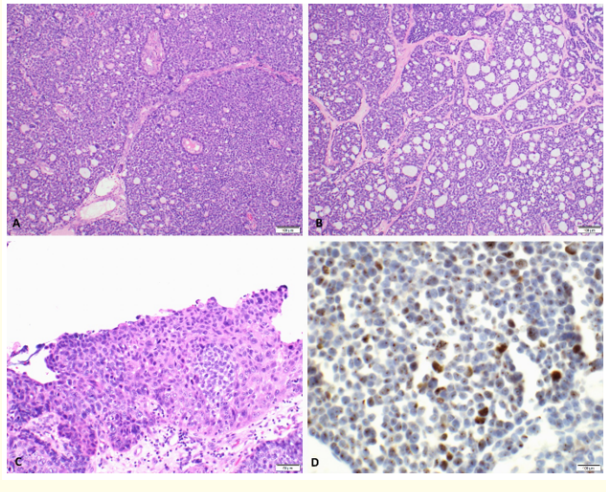

Figure 1: Histopathology of MN.

A. The tumor was predominantly solid with scattered, large pleomorphic cells

B. Areas with a cribriform pattern were observed, reminiscent of patterns seen in adenoid cystic carcinoma

C. Surface involvement of tumor displaying severe epithelial atypia

D. DNA in situ hybridization for high-risk HPV (types 31/33)

Case 2

A 66-year old male presented with left-sided epistaxis for 2 years as well as epiphora for several months. On nasal endoscopy, he was found to have a friable mass filling the left sinonasal cavity. CT and MRI revealed a 4.2 x 2.3 x 3.5 cm heterogenous, expansile mass centered in the left ethmoid sinus extending to the anterior skull base and medial wall of the orbit. A biopsy preliminarily suggested sinonasal undifferentiated carcinoma of the ethmoid sinus. Staging PET-CT showed a solitary hypermetabolic lesion in the left ethmoid sinus with no evidence of cervical lymphadenopathy or distant metastases (T4N0M0).

The patient subsequently underwent surgical resection via an endoscopic transcribriform approach. Intraoperatively, the patient was found to have a large, friable, ulcerative mass filling the left sinonasal cavity with erosion of the anterior skull base and lamina papyracea on the left. The tumor and its sites of attachment along the cribriform were successfully resected transnasally with negative margins. The skull base defect was then reconstructed using a multilayered repair with an underlay allograft and pedicled nasoseptal flap overlay. The patient did well with no complications and was discharged 48 hours after surgery.

Surgical pathology revealed the left nasal mass to be a p16-positive, biphenotypic neoplasm consistent with HMSC and was initially classified as such. However, the sample ultimately tested negative for HPV subtypes 6, 11, 16, 18, 31, and 33. Following additional staining, the sample appeared to demonstrate a salivary phenotype, but did not fit into a specific salivary gland carcinoma category including that of basal cell carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, etc. After extensive deliberation, the diagnosis was changed from HMSC to high-grade salivary-type adenocarcinoma NOS (not otherwise specified).

Postoperatively, the patient completed 7 weeks of radiation and weekly adjuvant radiation with cisplatin. Surveillance PET-CT showed no evidence of disease at 6 months. However, 8 months post-surgery, a scalp lesion was discovered. Biopsy and subsequent pathology revealed metastatic sinonasal carcinoma diffusively positive for p63, and positive for CK5/6. MRI showed no evidence of recurrent sinonasal or intracranial tumor, but a CT Chest-Abdomen-Pelvis identified liver lesions. The liver lesions were confirmed by pathology to be -p63 and CK 5/6 positive, metastatic, biphasic round cell undifferentiated basaloid neoplasm of salivary origin. The patient is currently 20 months out from surgical resection and continues to undergo adjuvant chemotherapy.

Discussion

Since its initial description in 2013 as "HPV-related carcinoma of the sinonasal tract with adenoid cystic-like features," there have only been a few case reports of HMSCs. Most of these studies have primarily focused on the histopathologic characterization of this unique lesion as opposed to clinical outcomes and surgical treatment. The largest published series of HMSCs to date was from Bishop., *et al*, who described the histopathologic features of 49 cases obtained from multiple centers. HMSC was described as a carcinoma that demonstrates (1) solid architecture with zones of cribriform/tubular growth; (2) mixed phenotype including basaloid cells showing myoepithelial differentiation, luminal cells with true ductal differentiation, and squamous differentiation of surface lining cells; (3) presence of transcriptionally active high risk HPV; (4) absence of gene fusions identified in true adenoid cystic carcinomas; (5) and presence of high-grade "salivary-like" features that are difficult to designate into a specific category. 7 Characteristic features of HMSC are illustrated in Figure 1 which depicts the pathologic specimen from case one. HMSC has also been typically found to be diffusely positive for p16 (as seen in both cases) and show incorporation of HPV type 33 or another high-risk type HPV.

From a clinical perspective, HMSCs have been reported to present with advanced stage and grade but no tumor-related deaths have been reported to date; suggesting that like its oropharyngeal counterpart, HMSCs may have a better prognosis than non-HPV related lesions [9].

In general, HPV-positive (HPV+) head and neck squamous cell carcinomas (HNSCCs) have been shown to be more responsive to treatment and exhibit better survival rates than HPV-negative HNSCCs. Similarly, HPV associated verrucous sinonasal squamous cell carcinomas have significantly favorable progress when compared to survival in conventional sinonasal SCC [10]. Surgery and radiation are still considered standard treatment for high-grade sinonasal carcinomas.

In Bishop's cohort, 4 of 18 patients who underwent treatment with primary surgery and adjuvant radiation therapy experienced

local recurrences and 2 had distant metastases. However, no data was provided regarding the type of surgery performed, whether negative margins were achieved, and the surgical approach that was used (endoscopic versus open). In our patient, the HMSC was successfully resected using a purely endoscopic technique followed by adjuvant radiation and has had no evidence of recurrent disease after 13 months. A review of the literature shows no publications to date that focus on the surgical approach to HMSC. Ultimately, additional studies are required to determine what the optimal therapy for HMSC should be and what the long-term outcomes of multimodality treatment will be in this patient population. Case 2 initially appeared to be a case of HMSC because it shared at least 3 of the 5 unique clinical and pathologic characteristics of HMSC. The cancer exhibited solid architecture with zones of cribriform appearance from focally small ductular lumena. The biopsy showed a mixed phenotype with an overall basaloid appearance and biphenotypic ductular-myoepithelial cell population. There was presence of high-grade "salivary-like" features that were difficult to designate into a specific category. However, although the biopsy diffusely tested positive for p16, there was no presence of transcriptionally active high-risk HPV. Diffuse p16 staining has shown utility in distinguishing HPV-related carcinomas with adenoid cystic features from classic adenoid cystic carcinomas [9]. The sample was not tested for *MYB, MYBL1*, and *NFIB*. In addition, the patient experienced 2 distant metastases within 6 months of chemotherapy, involving the scalp and liver. Although the case was ultimately determined to be a high-grade salivary-type adenocarcinoma not otherwise specified, the entire diagnostic process was challenging and required extensive consultation. Distinguishing between high-grade salivary-type adenocarcinomas and HMSC is nuanced and will likely continue to evolve as we learn more about this unique entity.

Conclusions

The diagnosis of HMSC remains a challenging endeavor. It is critical for clinicians to enhance their familiarity with this new and diagnostically evolving pathology to tailor appropriate management. In our patient, HMSC was effectively treated with endoscopic resection followed by adjuvant radiation. However, further study is necessary to delineate best practices for treatment of this rare entity and the long-term outcomes of such multimodality therapy.

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