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CASE REPORT

Secondary Sinonasal Collision Tumor of Papillary Squamous Cell Carcinoma and Small Cell Neuroendocrine Carcinoma After Nasopharyngeal Carcinoma Radiotherapy: A Case Report and Literature Review of Sinonasal Collision Carcinomas

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Abstract: In the head and neck region, small cell neuroendocrine carcinoma (SmNEC) is extraordinary infrequent. Collision malignancy is also a rare entity in the nasal cavity, with merely sporadic 6 case reports on primary collision tumor associated with neuroendocrine carcinoma. The development of a secondary SmNEC within the previous radiation field had uncommonly been described, and there was no report on secondary sinonasal collision carcinoma with SmNEC component as a side reaction of nasopharyngeal carcinoma (NPC) radiotherapy. In light of the rarity of these neoplasms, we presented a case of a sinonasal collision carcinoma of papillary squamous cell carcinoma (PSCC) and SmNEC after NPC radiotherapy. To our knowledge, it may be the first case of a secondary coexistence of two malignancies synchronously in the nasal cavity after NPC treatment. Recognizing this peculiar kind of collision tumor associated SmNEC could promote our understanding of this entity and hence propose optimal treatment strategies.

Keywords: small cell neuroendocrine carcinoma, collision tumor, nasopharyngeal carcinoma, papillary squamous cell carcinoma

Introduction

Nasopharyngeal carcinoma (NPC), which arises from the nasopharyngeal mucosal lining, is an extraordinary common malignancy in Asia.[1] Although radiotherapy is regarded as the optimal and most curative treatment for NPC, its adverse effects regarding secondary malignancies must be taken into account.[2] It has been reported that the opportunity of occurrence of secondary malignancies is about 0.7% after 5–18 years of NPC radiotherapy.[3] The most common of all these secondary tumors is squamous cell carcinoma (SCC).[4] Papillary squamous cell carcinoma (PSCC) is a relatively rare histotype of SCC, which is generally considered to have a favourable prognosis.[5] Small cell neuroendocrine carcinoma (SmNEC) is a highly aggressive cancer with neuroendocrine differentiation, and it usually occurs in the lung.[6] It can also occur extrapulmonarily, but the extrapulmonary SmNEC is about 2–5% of all SmNEC.[7] In the head and neck, primary SmNEC is rare, and secondary SmNEC after radiotherapy is even more rarer.[8]

Collision carcinomas are defined as the coexistence of two or more distinct tumor components at the same anatomical site.[9] In the head and neck, collision malignancies are extremely rare and usually occur in the larynx or thyroid gland.[10] Sinonasal collision malignancies are also extraordinary peculiar, with no more than 6 previously reportorial primary cases.[11–16] Furthermore, there are no reports of simultaneous multiple malignant tumors secondary to radiotherapy in the same anatomic site in the nasal cavity in the English literature.

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Herein, we reported an unwonted case of a secondary collision tumor of combined PSCC and SmNEC after NPC radiotherapy to further understand these tumors. As far as we know, it may be the first case presentation of a secondary sinonasal collision carcinoma as an adverse effect of NPC radiotherapy. For the purpose of improving the awareness of such highly aggressive and peculiar tumor in clinical work, we also reviewed the literature to summarize the clinico-pathological features of these lesions.

Case Report

A 63-year-old female presented to neurology clinic of our hospital with right side headache and nasal obstruction for 3 months. In addition, her sleep was affected either. Her past illness history was dominated by NPC (T4N0M0), which had undergone successful radiotherapy 10 years earlier. Nasopharyngeal endoscopic examination revealed that the right nasal cavity was obstructed by an irregular mulberry-like lesion in the right inferior nasal meatus, which had a large amount of purulent material on the surface and was easily bleeding when touched (Figure 1A). The nasopharyngeal mucosa was hyperemic with no obvious neoplasm. A computed tomogram (CT) of the head and neck showed an irregular mass blocking the entire right nasal cavity, and there was no lesion was found in the nasopharynx (Figure 1B and C).

Subsequently, a fragmentized punch biopsy specimen, which was gray-white with medium in texture and 1.2 cm in size, was taken from the nasal cavity under local anesthesia. Histologically, the neoplasm consisted of two well-defined distinct components (Figure 2A). The principal component was PSCC, an unconventional non-keratinized squamous cell carcinoma with a complex papillary architecture, which accounted for about 70% of the tumor (Figure 2B). The minor component was located in the stroma and consisted of infiltrating small blue round or fusiform tumor cells with scant cytoplasm, pepper-salt-like nuclei and high nucleo-cytoplasmic ratio. This component accounted for the remaining 30% of the tumor (Figure 2C and D).

These two components demonstrated not only different morphological appearances, but also different immunohisto-chemical profiles. The PSCC component was diffuse positive for AE1/AE3 and P40, while it was negative for two neuroendocrine markers such as synaptophysin (Syn) and chromogranin A (CgA) (Figure 3A–D). Conversely, the small blue round or fusiform component was diffuse positive for Syn and CgA, while AE1/AE3 was partially weakly positive and P40 was negative (Figure 3A–D). The Ki-67 labeling index of the PSCC component was up to 50%, while the small blue round or fusiform component was up to 90% (Figure 3E). In situ hybridization for Epstein-Barr virus (EBV) was negative in both components (Figure 3F). Additional immunohistochemical stainings for S100, Desmin, and CD45 were negative in all neoplastic cells.

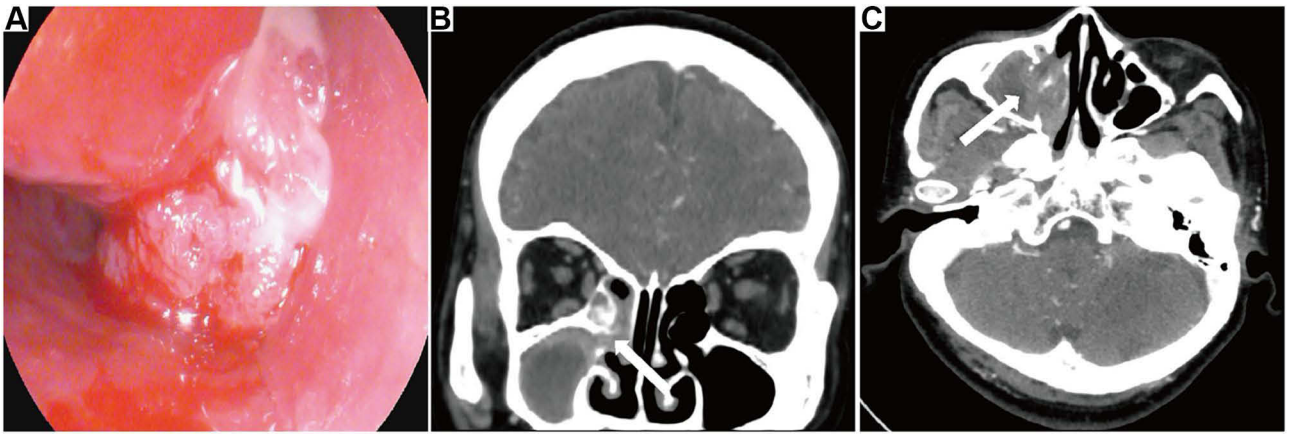

Figure 1 Nasopharyngeal endoscopic and radiological examinations. (**A**) Nasopharyngeal endoscope displayed an irregular mass obstructing the right nasal cavity. (**B** and **C**) Coronal and axial computed tomograms (CT) of the head and neck revealed an irregular mass in the right inferior nasal meatus blocking the whole right nasal cavity (white arrow).

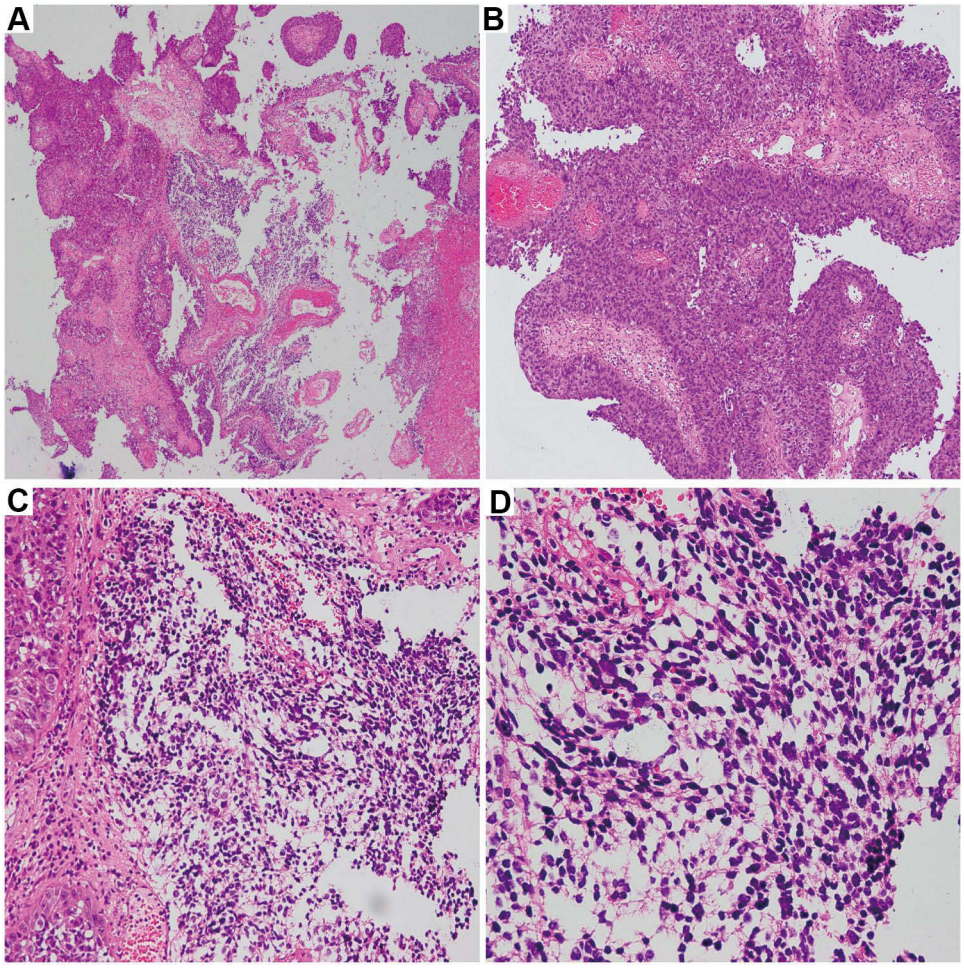

Figure 2 Histological features of the sinonasal neoplasm. (**A**) Low power view revealed that the tumor consisted of two sharply disparate separated components (hematoxylin and eosin [H&E], ×40). (**B**) The PSCC component had a complex papillary structure with a fibrovascular core and obvious atypia of the surface epithelium lacking keratinization (H&E, ×100). (**C**) The small blue roundish to spindle component was heterogeneous and located within the stroma (H&E, ×200). (**D**) High power view showed that the second type of tumor cells were poorly differentiated with scarce cytoplasm and hyperchromatic pepper-salt-like nuclei (H&E, ×400).

On the basis of these medically historical, morphologic, and immunohistochemical findings, the final pathological diagnosis of secondary collision tumor of PSCC and SmNEC was established. The patient abandoned treatment and was discharged. And after 3 months of follow-up, the patient was alive but had obvious cachexia.

Discussion

Sinonasal malignant neoplasms are relatively rare with the proportion of approximately 3% of all head and neck malignancies.[12] In the sinus, the commonest malignant tumor is SCC, which is followed by adenocarcinoma.[17] Histologically, nasal SCCs are classified by World Health Organization (WHO) as keratinizing SCC, non-keratinizing SCC and several kinds of uncommon SCC, such as basaloid SCC, verrucous SCC and PSCC, etc.[18] Among them, the incidence of PSCC is less than 1% of all SCCs.[19] In the head and neck, SmNEC is extraordinary unusual and it frequently occurs in the larynx.[20] To date, merely few case reports and small series are available for primary sinonasal SmNEC.[21] Although sinonasal SCC tends to have a relatively favorable prognosis, sinonasal SmNEC usually has a poor prognosis and is prone to recurrence and distant metastasis.[22]

NPC is a malignant tumor caused by a variety of factors, including genetic change, environmental influence and EBV infection.[1] Because of the radiation sensitivity and deep anatomical location of NPC, radiotherapy has been established as the mainstay of treatment since 1965.[23] Nevertheless, radiotherapy has been reported to increase the risk of secondary malignancies.[24] In the low-dose irradiation area, the most ordinary secondary malignancy is cancer or hematologic

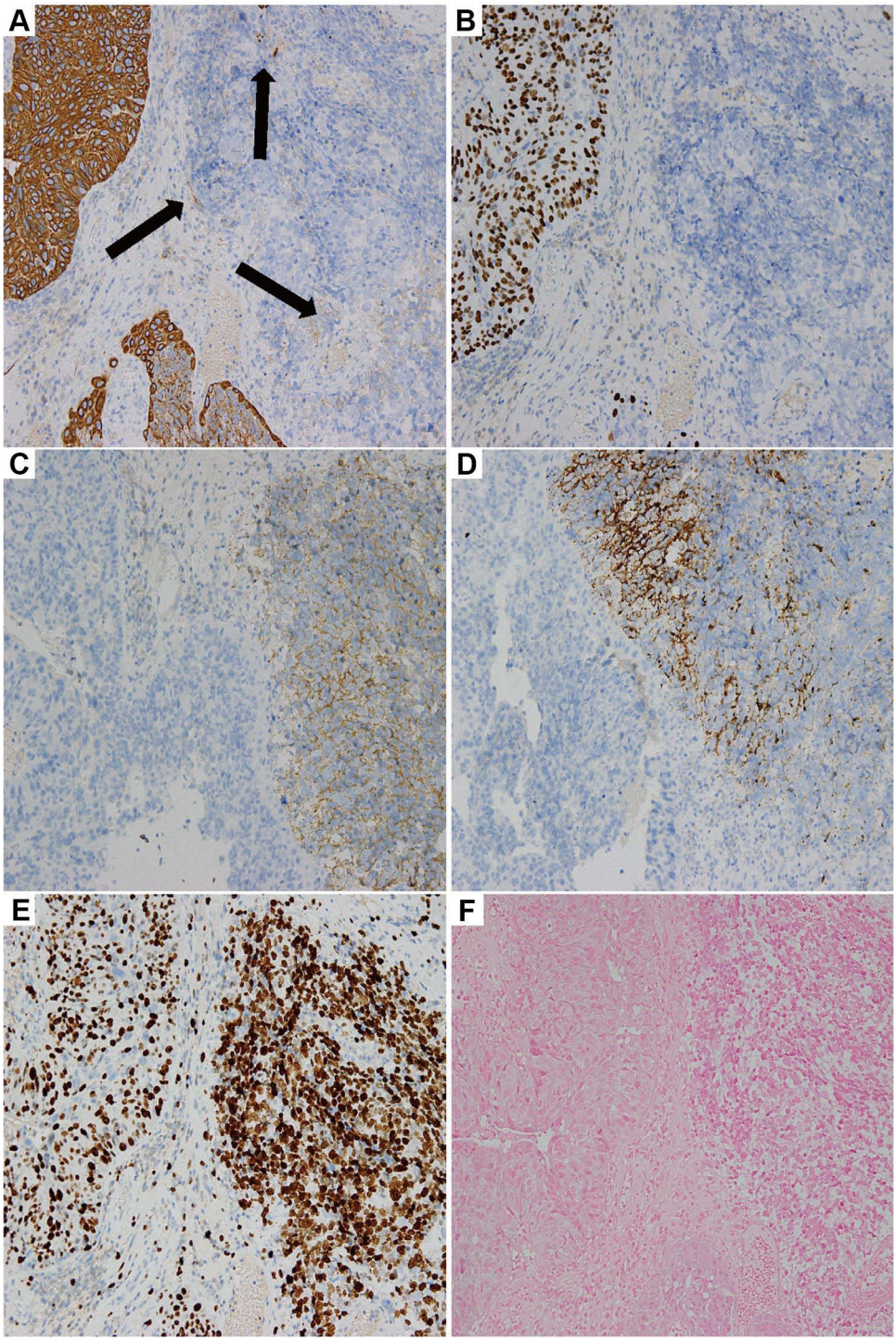

Figure 3 Immunohistochemical and in situ hybridization features of the sinonasal neoplasm. (**A**) AE1/AE3 was diffuse positive for the squamous component and partially weakly positive for the small blue round or fusiform component (black arrow). (**B**) P40 was diffuse positive for the squamous component and negative for the small blue round or fusiform component. (**C** and **D**) Syn and CgA were diffuse positive for the small blue round or fusiform component and negative for the PSCC component. (**E**) The Ki-67 indexes of these two entities were up to 50% and 90%, respectively. (**F**) EBV in situ hybridization were negative for these both portions [All figures magnification, ×200].

tumor; and in the high-dose irradiation area, the most common secondary malignancy is sarcoma.[24] The diagnosis of secondary tumors after radiotherapy should meet the following three criteria: (1) The tumor occurs more than 5 years after radiotherapy; (2) The tumor occurs in or near the radiation field; (3) The tumor is different from the histological type of the primary tumor.[8]

Table 1 A Summary of 7 Cases (Including the Current Case) of Collision Malignancy in the Nasal Cavity in the Literature

References	Gender/ Age (years)	Symptom	Tumors Location	Bioptic Histology	Surgical Histology	Treatment	Follow-Up
Huang et al 2010[11]	F/52	Left cheek swelling and persistent purulent mucoid nasal discharge	Maxillary sinus	SmNEC	SmNEC/ASC	Surgery + Chemotherapy	Died 8 months after surgery
Barham et al 2013[12]	M/83	Left nasal congestion and intermittent maxillary pressure	Paranasal sinus	SCC	SCC/SmNEC	Surgery	Multiple metastases occurred in the right rib and sternum 7 months after surgery
Kayakabe et al 2014[13]	F/80	A four-week history of right nasal discharge, nasal obstruction and left neck swelling	Paranasal sinus	Necrotic tissue with suppurative granulation	SCC/SmNEC	Surgery	Died 5 months after diagnosis
Franchi et al 2015[14]	M/75	Acute ischemic stroke	Maxillary Sinus	SCC	SCC/LNEC	Surgery+ Radiotherapy	Alive
Wu et al 2020[15]	F/47	Nosebleed	Paranasal sinus	SCC	SCC/SmNEC	Surgery+ Chemoradiotherapy	Alive
Sugianto et al 2022[16]	F/82	Pain in the upper right gingiva and cheek swelling	Maxillary sinus	SmNEC	SmNEC/SCC	Surgery+ Chemoradiotherapy	Died 8 months after surgery
Current case	F/63	Right side headache and nasal obstruction	Right inferior nasal meatus	SCC/SmNEC	None	None	Alive

Abbreviations: M, Male; F, Female; SmNEC, Small cell neuroendocrine carcinoma; LNEC, large cell neuroendocrine carcinoma; SCC, Squamous cell carcinoma; ASC, Adenosquamous carcinoma; NA, Not available.

Collision tumor of neuroendocrine carcinomas and other type carcinomas, also termed combined neuroendocrine carcinomas, frequently arise in the lung and are extremely rare in the head and neck region.[14] The definite mechanism of collision tumor is still unclear, but simultaneous proliferation of multiple cell lines or multiple directional differentiation of stem cells are considered to be the major hypotheses for collision tumor formation.[25] Including our case, barely 7 cases of nasal collision carcinomas have been reported in the English literature (Table 1). The major of these reported cases involved female. The female-to-male ratio was about 2.5:1, with significant difference in prevalence between genders. And this tumor is more likely to occur in the elderly, with the age between 47 years and 83 years (mean 71 years). The relatively common sites of these tumors are the maxillary sinus and paranasal sinus. Histologically, except for 1 case with large cell neuroendocrine carcinoma and squamous cell carcinoma components, the vast majority of these combined tumors were SmNEC and SCC components. Although all patients had been undergone preoperative biopsies, our case was the only one in which two tumor portions were effectively observed during preoperative biopsies. The precise diagnosis of collision neoplasms by preoperative biopsy is extremely challengeable, and it is critical to recognize the coexistence of two entities in the same anatomic site to avoid potential misdiagnosis and improper patient management. Adequate preoperative evaluation and obtaining tissue as much as possible may help to accurately identify such tumors. These 6 cases anteriorly reported had undergone surgical treatment, and 4 of them undergone postoperative adjuvant treatment. However, their prognosis was fantastically poor with 3 patients dead and 1 patient distant metastatic within one year. Although there is currently no consensus on treatment, correct diagnosis and thorough staging are absolutely essential to select the most appropriate treatment.[26] Current treatment options for these particular type of tumors have been developed primarily for the more aggressive components of neuroendocrine carcinoma.[11–16] For the SmNEC of the head and neck, Iqbal et al believed that it was best to avoid radical surgery and choose concurrent or sequential chemoradiotherapy instead, and they believed that the combined chemotherapy regimen of platinum and etoposide can provide best curative effect.[26] Furthermore, a veteran multidisciplinary group is required to develop an optimal treatment plan.[12]

To the best of our knowledge, there have been no anterior reports of the collision tumors in the nasal cavity after NPC radiotherapy. This presented case may be the first report on secondary collision malignancy in this location as an adverse effect of NPC radiotherapy. Histologically, the PSCC component was easily identified, but the SmNEC component may be overlooked or misdiagnosed. SmNEC tumor cells were unambiguously positive for AE1/AE3, Syn, and CgA, and negative for CD45, S100, and Desmin, which helped to exclude other types of small round cell malignancies such as lymphoma, malignant melanoma, and rhabdosarcoma.

In this study, we presented a case of secondary sinonasal PSCC associated with SmNEC after NPC radiotherapy. Histopathologic elaborate examination of the completely bioptic or surgical specimen is critical to the detection of collision tumor. Patients with collision carcinomas must adopt active multidisciplinary treatment with oncologists and pathologists, and this treatment may include administration of an individualized treatment plan based on the histologic findings of the particular tumor component. Our case is merely an extremely infrequent case report, more cases and studies thus are warranted for developing an effective treatment strategy and further clarification the possibility of the development of a secondary collision malignancy in treated NPC patients by radiotherapy.

Informed Consent Statement

Prior written permission was obtained from the patient for treatment as well as for the preparation of this manuscript and for publication. Our institution approved the publication of the case details.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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