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CASE REPORT

Secondary Nasopharyngeal Mixed Adenoneuroendocrine Carcinoma After Radical Radiotherapy for Nasopharyngeal Carcinoma: A Rare Case and Literature Review

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Abstract: The incidence of primary mixed adenoneuroendocrine carcinoma (MANEC) is rapidly increasing. MANEC mainly arises from the gastrointestinal tract, but occasionally it occurs as a pathological type of second primary malignancy (SPM). These SPMs can occur in the nasopharynx. Herein we describe the case of a first secondary nasopharyngeal MANEC that was detected 20 years after radical radiotherapy for nasopharyngeal carcinoma. The patient was a 50-year-old man who was admitted to our hospital after experiencing 1 month of left nasal congestion and ipsilateral tinnitus caused by a nasopharyngeal mass that was detected via physical examination and magnetic resonance imaging. A biopsy specimen from this nasopharyngeal lesion led to a histopathological diagnosis of recurrent nasopharyngeal carcinoma. He underwent high-dose palliative radiotherapy, followed by a course of gemcitabine–cisplatin-based adjuvant chemotherapy. These treatments failed to achieve local control of the tumor, and progressive left earache emerged. Another two forceps biopsies of the external auditory canal mass were conducted, and immunohistochemical testing for adenocarcinoma and neuroendocrine carcinoma markers including CK7, CK8, CK18, carcinoembryonic antigen, synaptophysin, chromogranin A, and CD56 was conducted. The diagnosis of MANEC was ultimately confirmed 5 months after the first visit, and one additional cycle of chemotherapy was subsequently performed. The patient died of hepatic metastases 8 months after the final diagnosis. Knowledge of this rare case will raise awareness of MANEC as a new pathological type of SPM originating in the nasopharynx, which will reduce delays and promote early diagnosis.

Keywords: adenocarcinoma, head and neck, neuroendocrine carcinoma, second primary malignancy

Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is a blended carcinoma with adenocarcinoma and neuroendocrine carcinoma (NEC) components, in which the percentage of each component is greater than 30%.[1] It is commonly located in the digestive system, including in the gastrointestinal tract, pancreas, and gallbladder.[2–5] Primary MANEC in the head and neck is rare, with only four reported cases to date,[6–9] located in the tongue, sinonasal tract, and soft palate (Table 1). No cases of primary MANEC in the nasopharynx have previously been reported.

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Table 1 Case Reports of Mixed Adenoneuroendocrine Carcinomas of the Head and Neck

Age	Sex	Presentation	Location	Invasion Area	CLNM	DMBT	RO	AO	Vital Status	OS (Months)	DMAT	Reference
52	Male	Midline tongue mass	Tongue	Adjacent skeletal muscle	No	No	Surgery	Radiation therapy	Alive	15	No	[6]
79	Male	Transitory ischemic attack	Ethmoid sinus	Anterior cranial fossa	No	No	Surgery	Radiation therapy	Dead	26	Bone	[7]
64	Male	Epistaxis and facial swelling	Nasal sinus	Orbit, anterior base of skull	No	No	Surgery	Radiation therapy	NA	> 24	Cervix and hilum	[8]
32	Male	Snoring and nasal obstruction	Soft palate	None	Level III	No	Surgery	Chemotherapy	Alive	NA	NA	[9]
50	Male	Nasal obstruction and tinnitus	Nasopharynx space	Parapharyngealspace, base of skull, ear	Level II	No	Radiation therapy	Chemotherapy	Dead	13	Liver	Current case

Abbreviations: AO, adjuvant oncotherapy; CLNM, cervical lymph node metastasis; DMAT, distant metastasis after treatment; DMBT, distant metastasis before treatment; NA, not available; OS, overall survival; RO, radical oncotherapy.

Nasopharyngeal carcinoma (NPC) is the most common malignant tumor of the nasopharynx. Population studies conducted in Taiwan and the USA indicate that patients with NPC have a high risk of second primary malignancy (SPM).[10,11] Squamous cell carcinoma is considered to be a general pathological type of SPM in patients with a previous history of NPC treated with radiotherapy,[12] but SPM with the pathological type of MANEC has not been previously reported. Herein we provide the first report of a case of SPM located in the nasopharynx with the pathological type of MANEC, after successful curative radiotherapy for NPC. In this case, the preliminary diagnosis was undifferentiated nonkeratinized carcinoma, and the definitive diagnosis was only confirmed after additional immunohistochemical staining for adenocarcinoma and NEC markers in additional two biopsy specimens.

Case Report

A 50-year-old Cantonese man was admitted to our hospital with a 1-month history of left-sided nasal congestion and ipsilateral tinnitus in July 2016. Physical examination revealed a mass occupying the left wall of the nasopharynx and left torus tubarius. Magnetic resonance imaging (MRI) depicted a 26 × 16 × 27 mm^3 contrast-enhanced nasopharyngeal mass extending into the left fossa of Rosenmüller, para-pharyngeal space and skull base (Figure 1C–E), with the involvement of a left cervical lymph node (level II, 12 × 6 × 14 mm^3) (Figure 1F). A biopsy of the nasopharyngeal mass was performed with direct nasopharyngoscopy (Figure 1A and B), and the microscopic pathology was interpreted as undifferentiated nonkeratinizing carcinoma (Figure 2A and B).

Neither chest x-ray nor abdominal sonography depicted any signs of lung or liver metastases. There were no gastrointestinal signs, and a stool occult blood test was negative. The patient declined positron emission tomography and further pathological immunohistochemical examination because his basic health insurance was not yet in place. A detailed patient history was obtained, including 4th edition American Joint Committee on Cancer (AJCC) stage III, and single conventional external radiotherapy (70 Gy/35 fractions) without chemotherapy for undifferentiated NPC in 1995. Based on these findings, a diagnosis of NPC recurring after radiotherapy with stage III (rT3N1M0) (AJCC 7th edition) was suggested.

The patient declined surgery and neoadjuvant and concurrent chemotherapy but did undergo nasopharyngeal re-radiotherapy at doses of 66 Gy to nasopharynx gross tumor volume, 60 Gy to gross tumor volume of lymph node and high-risk clinical target volume, and 54 Gy to the low-risk clinical target volume, delivered in 33 fractions with a radiotherapy treatment duration of 50 days. After re-radiotherapy for 2 months, the therapeutic effects on the progressive disease were assessed via MRI at another hospital. He returned to our hospital again and started a course of gemcitabine-cisplatin-based first-line chemotherapy. After chemotherapy, a left external auditory canal mass was detected via a physical examination prompted by a progressive left earache. Another MRI scan verified that parapharyngeal tumor had extended to the middle left ear and the external auditory canal (Figure 3E), although a partial reduction in nasopharyngeal tumor size (Figure 3C and D) and a complete response in the metastatic cervical lymph node (Figure 3F) were evident.

A forceps biopsy of the mass in the external ear was performed under electro-otoscopy (Figure 3A and B). Direct microscopic examination revealed that most of the tumor cells were arranged in a tubular pattern, although some were visibly squeezed (Figure 4A and B). An immunohistochemical test was then conducted because the patient's insurance had come into effect by that time. In that test, the Ki-67 index value at the hotspot was >90%, and CK7, CK8, and CK18 were strongly positive (Figure 4C–F). Accordingly, a pathological diagnosis of adenocarcinoma was made at that time. Considering that the squeezing of tumor cells might have affected the diagnosis, and that nasopharyngeal adenocarcinoma is rare, a biopsy of the lesion in the external ear was performed again to confirm the diagnosis. Morphology and immunophenotyping analysis of the second biopsy specimen from the external ear were similar to those of the first biopsy specimen from the external ear (Figure 5A–D), and the cells lacked CDX2 expression (Figure 5F). To further characterize the carcinoma the two biopsy specimens were stained for other tumor markers, and it was determined that most of the adenocarcinoma cells simultaneously expressed NEC markers including synaptophysin, chromogranin A, and CD56 (Figures 4G–I and 5E). Adenocarcinoma and NEC markers were simultaneously expressed in >50% of the tumor cells, and the adenocarcinoma cells were not of intestinal type. Thus, a pathological diagnosis of MANEC was clear.

To investigate the relationship between the external auditory canal tumor and the nasopharyngeal tumor, and confirm that the MANEC had originated in the nasopharynx, adenocarcinoma and NEC markers were added to the

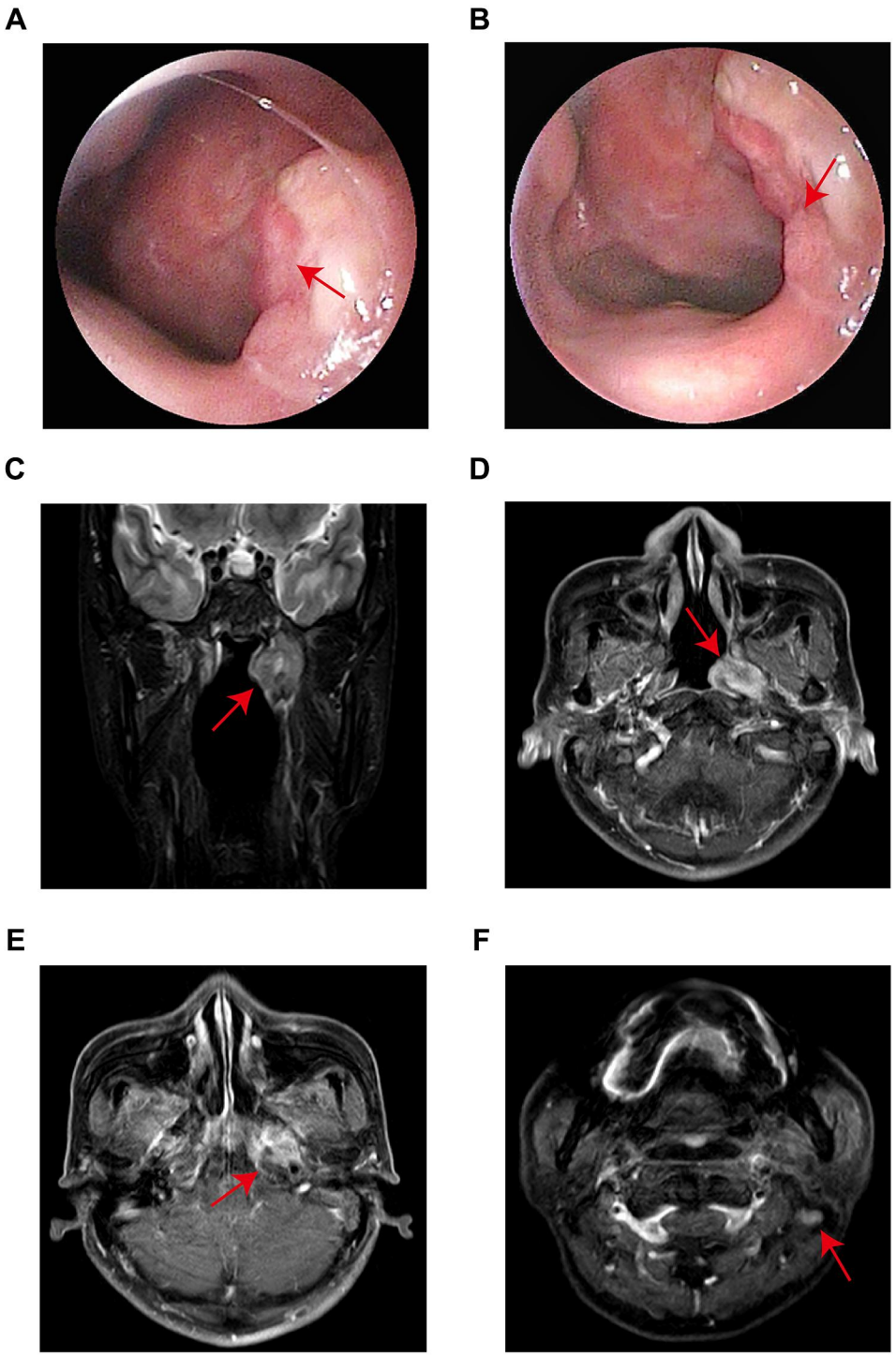

Figure 1 Pretherapy nasopharyngoscopy and MRI of the secondary nasopharyngeal MANEC. (**A**, **B**) The mass on the left superolateral portion of the nasopharynx and left torus tubarius (red arrow). (**C**–**E**) MRI depicting a 26 × 16 × 27 mm^3 enhancing mass in the nasopharynx, parapharyngeal space and skull base (red arrow). (**F**) MRI depicting a 12 × 6 × 14 mm^3 cervical lymph node (level II, red arrow).

immunohistochemical analysis of the previously obtained nasopharyngeal biopsy tissue. The tumor cells of the previous nasopharyngeal mass had parallel morphological and immunohistochemical profiles, i.e., >90% exhibited simultaneous expression of the adenocarcinoma markers CK7, CK8, and carcinoembryonic antigen, and the NEC markers CD56 and synaptophysin (Figure 2C–H), and in situ Epstein-Barr virus-encoded small RNA hybridization

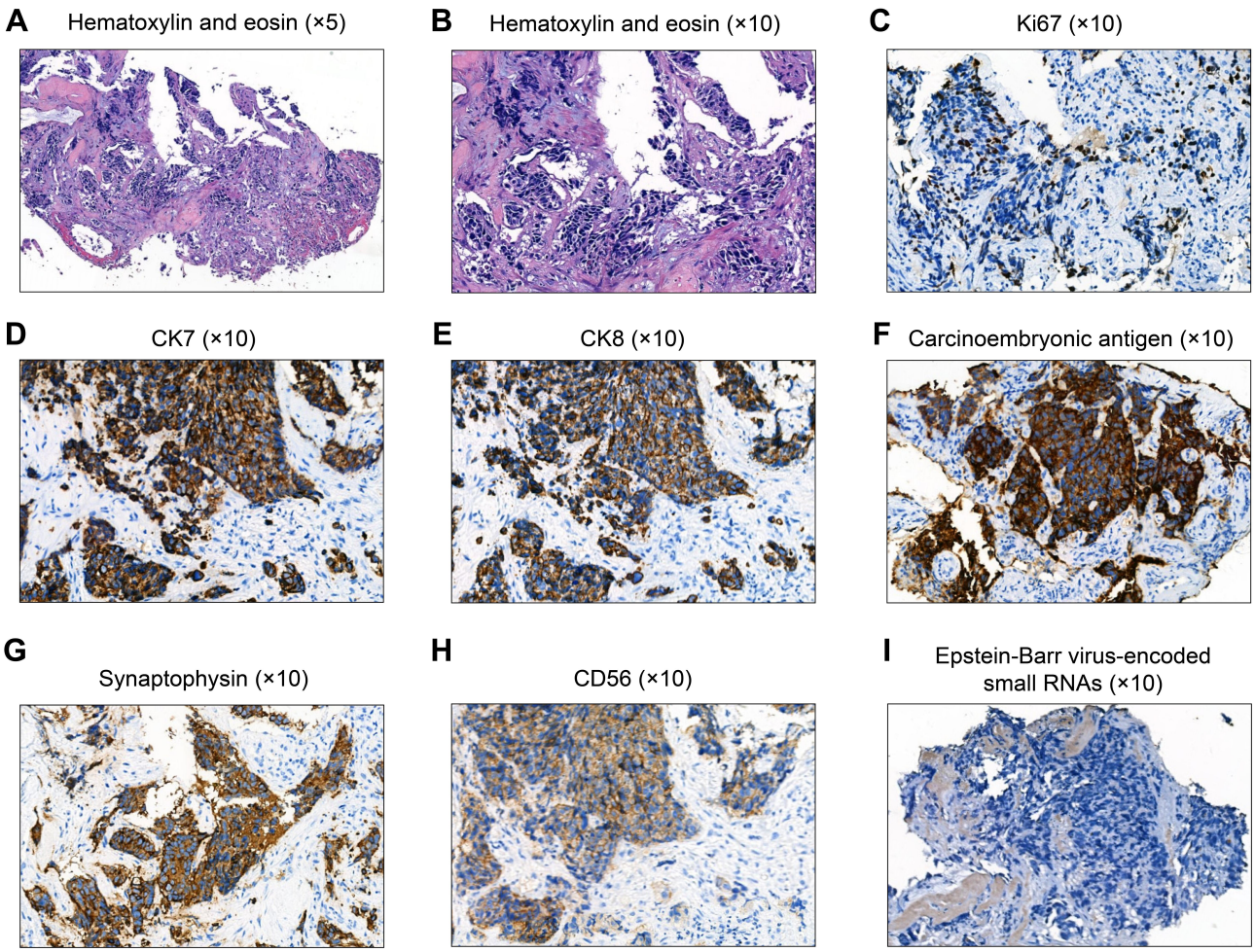

Figure 2 Histological analysis of nasopharyngeal biopsy tissue from the MANEC. (**A**, **B**) Hematoxylin and eosin-stained slides depicting undifferentiated tumor cells lacking a typical glandular structure. (**C**–**I**) Immunohistochemical analysis showing that the Ki-67 index value at the hotspot area was > 50% (**C**), and the expression of CK7 (**D**), CK8 (**E**), carcinoembryonic antigen (**F**), synaptophysin (**G**), and CD56 (**H**) occurred simultaneously in > 90% of the tumor cells. (**I**) The tumor cells were negative for Epstein-Barr virus-encoded small RNAs. Magnifications: a, ×5; b–i, ×10.

was negative (Figure 2I). Repeated fecal occult blood tests were also negative, and the patient declined gastrointestinal endoscopy. In December 2016 he was ultimately diagnosed with nasopharyngeal MANEC, which was consistent with the levels of the serum tumor markers neuron-specific enolase 22.81 ng/mL (reference range 0.00–16.30 ng/mL) and carcinoembryonic antigen 8.90 ng/mL (reference range 0.-00–5.00 ng/mL). Due to poor nutritional status and moderate anemia, he subsequently underwent one additional cycle of chemotherapy (paclitaxel liposomes 150 mg/m^2 and cisplatin 70 mg/m^2) when his left earache failed to be relieved. He received no oncotherapy thereafter, and was switched to conservative care. The patient died of multiple liver metastases as determined via contrast-enhanced computed tomography of the abdomen, having survived for 8 months after the definitive diagnosis.

Discussion

Most MANECs are located in the gastro-entero-pancreatic tract, where complete surgical specimens can be easily obtained, and there is usually a clear boundary between adenocarcinoma and NEC components. Given the lack of reports of MANECs in the nasopharynx, or of any SPM of this pathological type, the diagnosis of the case presented herein was a challenge for pathologists. Regardless of medical history, imaging features, and conventional pathology, the initial putative diagnosis was nasopharyngeal undifferentiated nonkeratinizing carcinoma rather than MANEC. The diagnosis of MANEC was made 5 months later, after immunohistochemical assessment of the markers CK7, CK8, CK18, CD56, chromogranin A, and synaptophysin. This indicates that supplemental staining of adenocarcinoma and NEC markers is required when

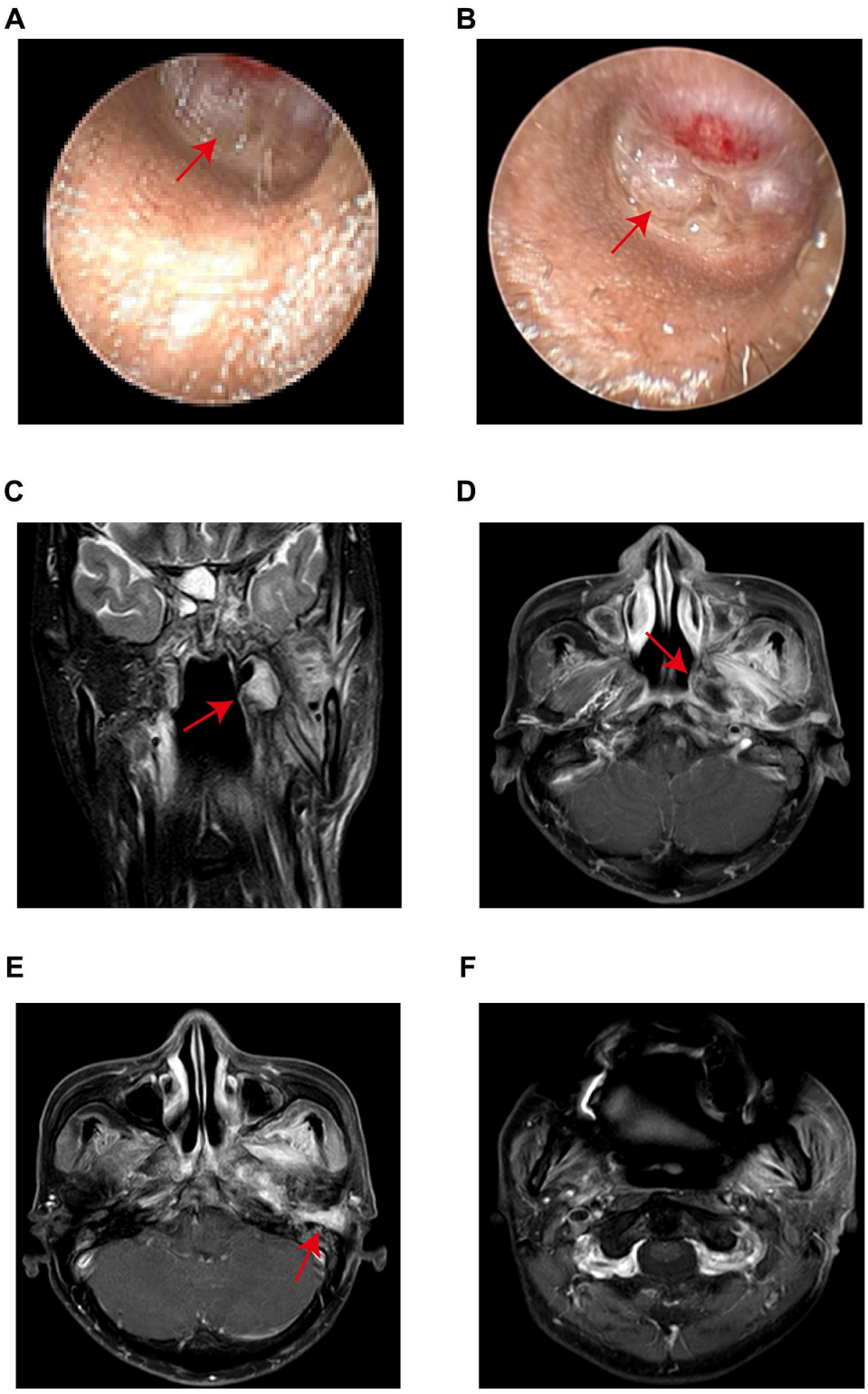

Figure 3 Post-treatment electro-otoscopy and MRI of secondary nasopharyngeal MANEC. (**A**, **B**) The mass in the left tympanic membrane and external auditory canal (red arrow). (**C**, **D**) MRI depicting a partial response to the nasopharyngeal and parapharyngeal tumor after chemoradiotherapy (red arrow). (**E**) Post-treatment MRI depicting parapharyngeal tumors extending to middle left ear and external auditory canal after chemoradiotherapy (red arrow). (**F**) Post-treatment MRI depicting a complete response to cervical lymph node after chemoradiotherapy.

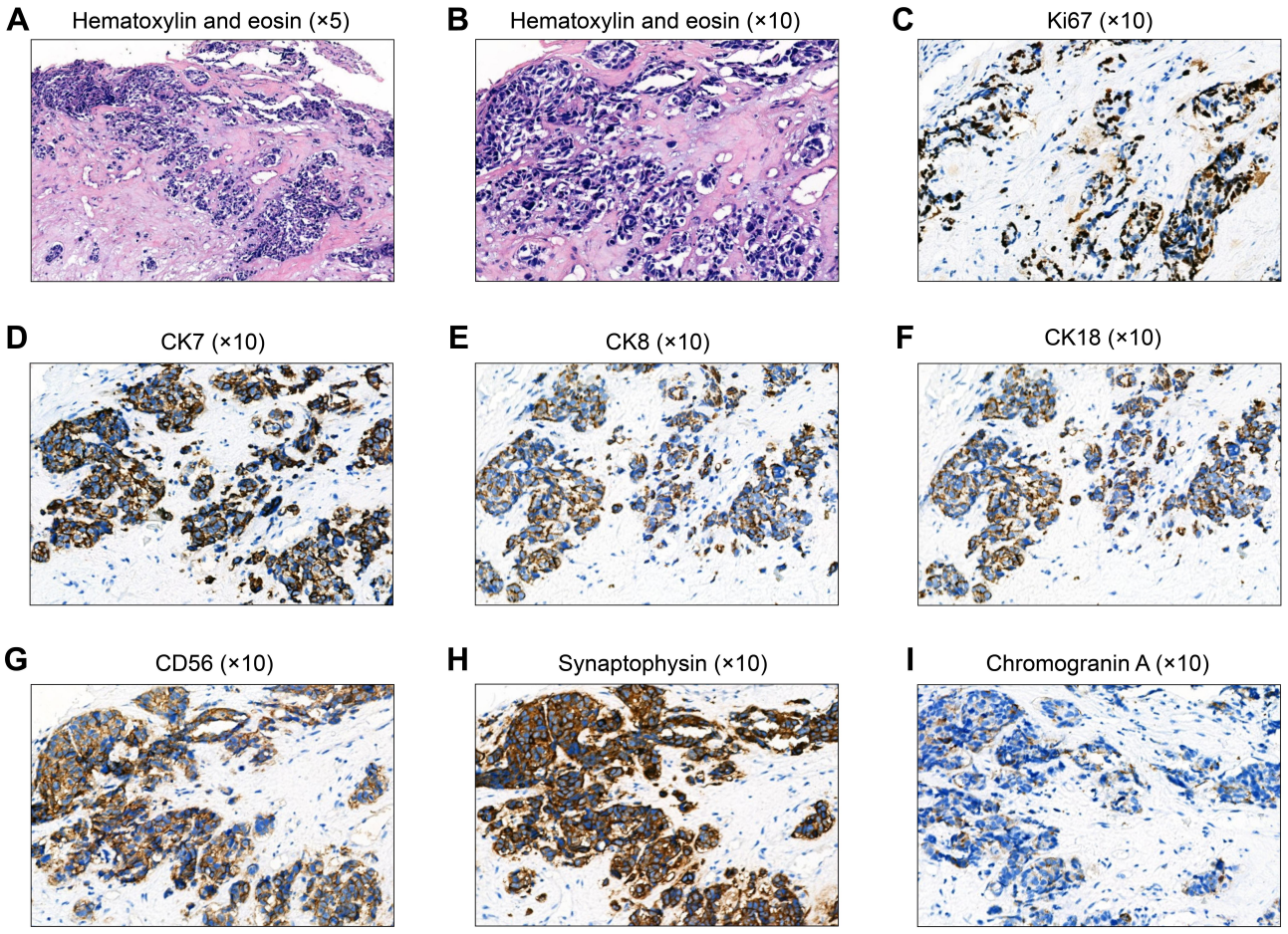

Figure 4 Histological analysis of the first external auditory canal biopsy. (**A**, **B**) Hematoxylin and eosin-stained slides showing some glandular structures in poorly differentiated tumor cells. (**C–I**) Immunohistochemical staining showing elevated proliferation rates (> 90% hotspot Ki-67) (**C**), and simultaneous expression of CK7 (**D**), CK8 (**E**), CK18 (**F**), CD56 (**G**), synaptophysin (**H**), and chromogranin A (**I**) in > 50% of the tumor cells. Magnifications: a, ×5; b–i, ×10.

nasopharyngeal epithelial malignancy cells exhibit poor differentiation.

The precise pathogenic mechanisms involved in MANEC are not yet understood.[13,14] In previous studies, molecular analysis suggested that the adenocarcinoma and NEC components of MANEC had a common clonal origin.[15,16] This was putatively confirmed in subsequent studies that indicated the early separation of two components during malignant transformation, with subsequent independent mutational evolution.[17,18] Similar indications were apparent in the current MANEC case in which there was no boundary between the adenocarcinoma, NEC cells were present, and CK18, carcinoembryonic antigen, synaptophysin, and chromogranin A were co-expressed in most of the tumor cells.

In the present patient, the diagnosis of MANEC was confirmed by three biopsies from different sites. These biopsies suggested that the pathological manifestations of MANEC are relatively heterogeneous, and that the accuracy of its diagnosis is related to biopsy depth and biopsy site. When the two components (adenocarcinoma and NEC) are longitudinally distributed in gastric tissue, the pathological manifestations may be inconsistent with those of tumor tissues from different biopsy depths.[19] Moreover, more than 60% of gastro-entero-pancreatic MANEC patients are initially diagnosed with a single adenocarcinoma or NEC based on the initial biopsy tissue sample.[20] Thus, horizontal and vertical multipoint biopsy should be performed to ensure the accuracy of diagnosis in inoperable carcinoma patients.

The therapeutic options for MANEC remain limited. In a systematic review summarizing 18 retrospective studies (n = 571), more than 90% of patients with gastro-entero-pancreatic MANEC were treated with surgery.[20] In another systematic review, surgical resection was the preferred treatment for MANEC in the gallbladder.[5] In a population-based

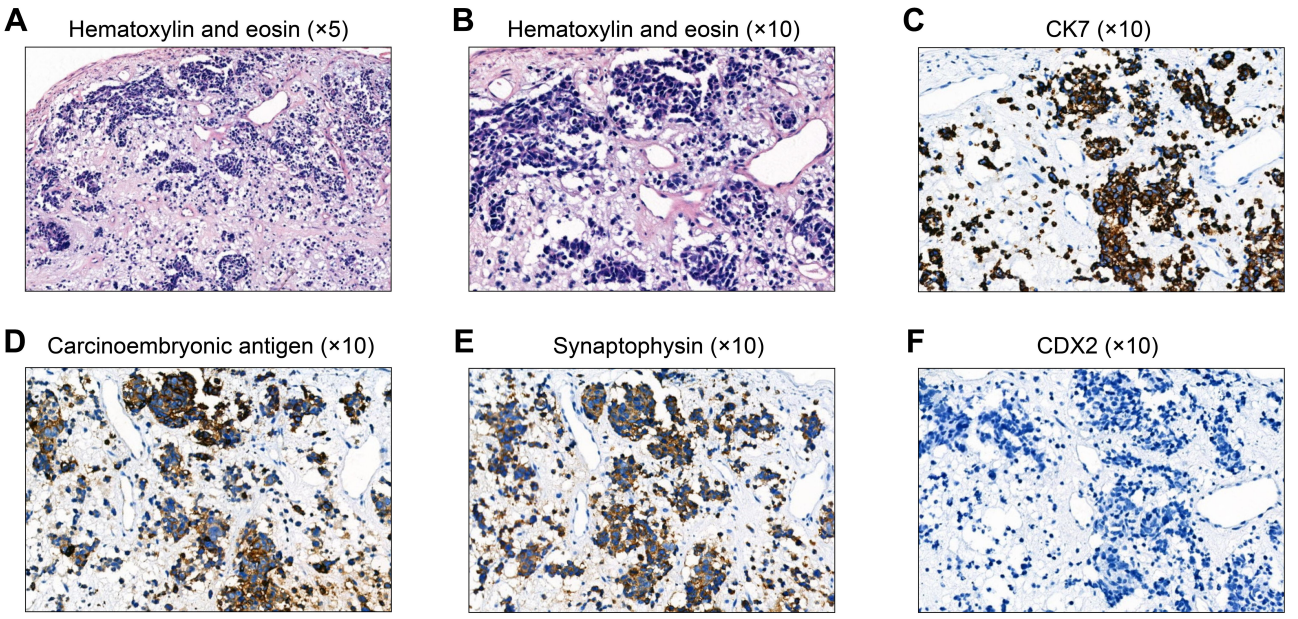

Figure 5 Histological analysis of the second external auditory canal biopsy. (**A**, **B**) Hematoxylin and eosin-stained slides showing partial tumor cells containing some glandular structure. (**C**–**F**) Immunohistochemical staining showing simultaneous expression of the adenocarcinoma and neuroendocrine carcinoma markers CK7 (**C**), carcinoembryonic antigen (**D**), and synaptophysin (**E**) in > 90% of the tumor cells, and no CDX2 expression in those cells (**F**). Magnifications: a, ×5; b–f, ×10.

study, surgery could significantly improve prognosis in colorectal MANEC, whereas radiation could not.[21] There are four previous case reports describing patients with head and neck MANEC who underwent surgical treatment (Table 1).[6–9] In the current patient the nasopharyngeal tumor surrounded the carotid sheath and invaded the skull base, where surgery is difficult due to complex anatomy. The patient declined this high-risk surgery and underwent radiotherapy, which ultimately failed to control the primary tumor. If he had undergone the operation at the beginning, his diagnosis may have been confirmed earlier and this may have resulted in a more beneficial clinical outcome. In most MANEC patients there is a characteristic tendency for metastasis to ensue, and MANEC in the head and neck is expected to be no exception. A recent study indicates that neoadjuvant chemotherapy can prolong the overall survival of MANEC patients and does not increase the risk of postoperative complications.[22] In the current patient, there was no obvious response to platinum-based adjuvant chemotherapy, and he ultimately died of liver metastases. The effective use of systemic therapy to reduce the risk of distant metastasis of MANEC remains a challenge. In recent studies, colonic MANEC has responded favorably to streptozocin monotherapy and anti-programmed death 1 receptor monoclonal antibody pembrolizumab therapy.[23,24] Therefore, we speculate that chemoradiotherapy with a combination of streptozocin and immune-checkpoint inhibitors may be a superior treatment option for inoperable MANEC.

In the present case of MANEC, some information that may have facilitated an earlier diagnosis was lacking. The patient's initial MRI images depicted the presence of cervical lymph node metastasis. This meant that there was a higher risk of distant migration, but he declined whole-body positron emission tomography/computed tomography scanning. When a definite diagnosis of MANEC was made, he declined gastroenteroscopic examination. Strictly speaking, there was a lack of hard evidence to exclude the tumor having originated in the gastrointestinal tract, but it is notable in this regard that the fecal occult blood test was negative.

Conclusion

Herein, we have presented the first report of a patient diagnosed with secondary nasopharyngeal MANEC after radical radiotherapy for NPC. Its rarity may have delayed the diagnosis, and performing surgery was problematic due to the complex anatomy involved and a previous history of definitive radiotherapy for carcinoma of the nasopharynx. A likely tendency to metastasize also had to be considered, and there was a limited response to platinum-based chemotherapy. Multipoint biopsy at different depths and sites is recommended in cases of poorly differentiated carcinomas, and further research to develop

more efficient therapies for nasopharyngeal MANEC is warranted.

Ethics Approval and Consent for Publication

This study was approved by the research ethics committee of Affiliated Cancer Hospital & Institute of Guangzhou Medical University and written informed consent for publication of the clinical details and images was obtained from the patient's wife.

Informed Consent Statement

Informed written consent was obtained from the patient's wife for publication of this report and any accompanying images.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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