Nasopharyngeal non-intestinal-type adenocarcinoma: a case report and updated review of the literature

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ABSTRACT

Background Non-intestinal-type adenocarcinoma is a malignancy traditionally found in the sinonasal cavity. To our knowledge, this case is the first reported of this rare condition originating in the nasopharynx.

Case Presentation A 67-year-old woman with nasopharyngeal non-intestinal-type adenocarcinoma, with an accompanying parapharyngeal mass received primary radiation treatment for both lesions. Her tumour subsequently persisted, with a concomitant conversion in pathology from a low- to a high-grade malignancy.

Results Non-intestinal-type and intestinal-type adenocarcinomas of the nasopharynx are extremely rare tumours and do not appear in the World Health Organization classification system. We review the pathophysiologic features of these malignancies and propose modifications to the current classification system.

Conclusions Non-intestinal-type adenocarcinoma should be included in the differential diagnosis of nasopharyngeal masses. In our experience, this tumour in this location showed a partial response to primary radiation but later converted from a low- to a high-grade adenocarcinoma.

Key Words Non-intestinal adenocarcinoma, intestinal adenocarcinoma, sinonasal cavity, nasopharynx, disease classifications

BACKGROUND

Nasopharyngeal adenocarcinoma is a rare type of nasopharyngeal cancer. The World Health Organization (WHO) classifies malignant epithelial tumours arising in this region into nasopharyngeal carcinomas (NPCs), nasopharyngeal papillary adenocarcinomas, and salivary-gland-type carcinomas.

In the present report, we describe an extremely rare case of a nasopharyngeal adenocarcinoma not yet classified by the WHO: the first reported case of a non-intestinal-type adenocarcinoma (non-ITAC) originating from the nasopharynx. Tumours of this kind have previously been described in the sinonasal cavity, but never in the nasopharynx. We review the current literature on the pathophysiologic features of non-ITACs and propose modifications to the current classification system to include this rare condition.

CASE PRESENTATION

A 67-year-old woman was referred to The Ottawa Hospital Otolaryngology–Head and Neck Surgery clinic with a 2-month history of epistaxis. The patient’s past medical history was significant for a 15 pack–year history of smoking, but she denied known exposure to environmental or occupational carcinogens—such as wood dust or Epstein–Barr virus infection—typically associated with NPCs or sinonasal malignancies. No genetic risk factors such as Southeast Asian or Chinese descent were identified.

Nasal endoscopy revealed a pedunculated mass in the nasopharynx, emanating from the left fossa of Rosenmüller. A biopsy was performed, and histologic...
examination revealed numerous uniform glandular structures arranged in a back-to-back pattern with little intervening stroma, invading the submucosa (Figure 1). The glands were lined by a single layer of columnar cells with uniform round nuclei displaying mild-to-moderate nuclear atypia and ample foamy eosinophilic cytoplasm. No myoepithelial or basal cell component was identified. The tumour cells were immunoreactive for cytokeratin 7 (ck7) and negative for cytokeratin 20 (ck20), cdx2, p40, and calponin. Mucicarmine stain was positive (data not shown), confirming that the lesion was a low-grade non-rtac of the nasopharynx. The diagnosis was confirmed by 2 pathologists at our tertiary care institution. Subsequent investigations with computed tomography and magnetic resonance imaging (mri) revealed a left parapharyngeal mass (30×22 mm) in addition to the nasopharyngeal mass (19×14 mm) previously visualized by endoscopy. The mri confirmed that the parapharyngeal mass was not an extension of the tumour, but a metastatic lymph node or a deep parotid lobe tumour. Imaging further identified bilateral level ii lymph nodes (10×8 mm), confirming clinical stage iii disease (T1N2M0). A tumour board discussion resulted in a consensus treatment that included radiotherapy (rt) delivering 70 Gy in 35 fractions over 7 weeks.

The mri repeated at 7 weeks post-rt noted a slight reduction in size of the nasopharyngeal mass (now 8×12 mm) and a marginal reduction of the parapharyngeal mass (now 20×28 mm). However, follow-up imaging after 3 months revealed an interval increase in the size of the nasopharyngeal mass, with evident adherence to the eustachian tube and extension into the infratemporal fossa and base of the skull. The left parapharyngeal lesion remained stable in size.

At this point, a combined otolaryngology and neurosurgical resection was undertaken (Figure 2). Although the histopathologic features identified in the original biopsy and the post-rt excision were similar, the excised specimen showed significantly less mucinous differentiation and a greater degree of cytologic atypia (Figure 3). Furthermore, immunohistochemical analysis of the residual tumour compared with the primary tumour demonstrated a highly elevated Ki-67 index [36.8% vs. 6.1%, Figure 4(A,B)], suggesting progression from a low-grade to a high-grade non-rtac. Moreover, like the original tumour, the residual tumour expressed ck7 [Figure 4(C)] and was negative for ck20 [Figure 4(D)] and cdx2 (data not shown), which are usually expressed in intestinal epithelium4. The lack of a myoepithelial layer surrounding the glandular structures, as indicated by negative immunoreactivity for calponin, sma, p40, and cytokeratin 5 (data not shown) is compatible with a malignant glandular proliferation.
The patient tolerated the surgery well, with slight worsening of her dysphagia and persistent post-rtt xerostomia, anosmia, decreased appetite, and dysphagia to solids.

At approximately 1 year after endoscopic endonasal resection of her persistent disease, the patient presented in follow-up with a 1-month history of intermittent epistaxis, nasal obstruction, and mild dysphagia. Physical examination revealed bulging of the oropharynx causing uvular deviation. Flexible nasal laryngoscopy revealed a left nasopharyngeal mass and several skip lesions beginning in the left nasopharynx and extending to the aryepiglottic fold. An urgent MRI examination revealed a pedunculated mass in the left dorsal nasopharyngeal wall, measuring 1.2×1.5×1.5 cm, and confirmed evidence of recurrent disease in the left oropharyngeal and hypopharyngeal wall. No clinical or radiographic evidence of cervical disease was identified.

Given the diffuse and aggressive nature of her disease, the patient’s care was transferred to the medical oncology service for palliative therapy. She received a cycle of carboplatin plus gemcitabine, but clinical progression of her disease was observed. A second cycle of carboplatin plus paclitaxel was initiated; however, she experienced recurrent self-limiting epistaxis and further progression of her disease on computed tomography imaging. A trial of FOLFRIRI (irinotecan–fluorouracil–leucovorin) was subsequently initiated, and the patient responded to that treatment very well. She developed mucositis related to the fluorouracil, which responded to sucralfate therapy, but had no other gastrointestinal issues. By the second cycle of FOLFRIRI, she reported improvement in her nasal obstruction and dysphagia, and a decrease in the frequency of epistaxis. On examination, her uvular deviation had shifted to the midline. Given her response to treatment, she will continue to receive cycles of FOLFRIRI every 2 weeks as tolerated.

**DISCUSSION**

This case is the first reported of a non-itac nasopharyngeal cancer.

We used key words and mesh terms (non-intestinal, intestinal, adenocarcinoma, classification, sinonasal, nasopharyngeal, and nasopharynx) in varying combinations in a detailed electronic search of PubMed and MEDLINE for studies reporting on non-itac. The search identified thirteen potential studies. During title and abstract screening, we excluded non-English articles, and we further excluded studies based on relevance to our search. The qualitative synthesis therefore considered three studies, a very limited number for this malignancy. Importantly, no study included non-itacs in a classification system.

Non-itac of the sinonasal region is a rare tumour. The WHO classifies malignant glandular neoplasms arising in the nasal cavity and paranasal sinuses into two main groups: salivary-gland-type and non-salivary-gland-type adenocarcinomas. Non-salivary gland-type adenocarcinomas are further subdivided into intestinal-type adenocarcinomas (itacs) and non-itacs. Salivary-gland-type carcinomas are well-defined epithelial or myoepithelial cell neoplasms that histologically resemble their salivary counterparts. The itacs are defined by having an intestinal phenotype, sharing the histologic and immunohistochemical features of intestinal neoplasms. Non-itac morphologies fail to fit with either of the aforementioned adenocarcinomas, presenting with marked morphologic heterogeneity, including papillary and glandular patterns. Although most non-itacs have been shown to demonstrate a seromucinous phenotype, they are currently regarded as a diagnostic category of exclusion, with careful attention to rule out other possible primary tumours, including a metastatic malignancy.
For prognostication purposes, non-ITAC tumours are further subdivided into low-grade and high-grade types. Low-grade non-ITACs most commonly involve the nasal cavity, followed by the ethmoid and maxillary sinuses. Low-grade non-ITACs are more common in individuals more than 50 years of age and show no race or sex predilection; high-grade non-ITACs present more commonly in older men. In contrast to ITACs and other sinonasal carcinomas, no association between non-ITACs and occupational or environmental carcinogens has been reported.

Immunohistochemistry facilitates differentiation between ITACs and non-ITACs. Non-ITACs have been found to lack intestinal-specific markers and commonly demonstrate a respiratory-type profile (positive for CK7, and negative for CK20, CDX2, and villin). In contrast, ITACs are usually consistent with an intestinal-type profile (negative for CK7, and positive for CK20, CDX2, and villin). Given the proximity of the sinonasal and nasopharyngeal regions, it is essential to differentiate between sinonasal adenocarcinomas and the similar appearing nasopharyngeal papillary adenocarcinomas. Those tumours can be distinguished based on histologic differences in papillary adenomas of the nasopharynx, including infrequent mitotic figures, arborized papillae, and fibrovascular cores.

Treatment of sinonasal non-ITACs consists of either complete surgical excision with the option of postoperative RT, or RT alone for extensive local disease. Low-grade sinonasal ITACs generally have a favourable prognosis and, compared with non-ITACs, tend to be less aggressive, with 5-year survival rates exceeding 80%. Outcomes are poorer for high-grade tumours, with a 3-year survival rate of approximately 20% and a high local recurrence rate with potential for distant metastasis.

The treatment algorithm for our patient’s low-grade nasopharyngeal non-ITAC was further complicated by the concomitant parapharyngeal mass. Initial treatment used RT alone; however, despite prior studies describing an overall favourable prognosis for low-grade sinonasal non-ITACs, our patient’s nasopharyngeal tumour did not respond well to RT and persisted, with transformation into a high-grade non-ITAC. It is difficult to determine whether disease progression was related to the nature of the tumour or to the chosen course of treatment; however, the observed response accords with prior observations that rates of local control and disease-free survival are lower for nasopharyngeal adenocarcinomas treated with RT alone than for those treated with surgery plus RT. Unfortunately, surgery was not successful in the definitive management of our patient’s disease. Her...
case is the first reported use of folfiri in the treatment of nasopharyngeal non-rtac. Given the patient’s clinical response to folfiri, our report highlights a potential role for the use of that regimen in the palliative treatment of recurrent non-rtac.

The limitations of the histopathologic analysis in the present case are similar to those seen consistently in pathologic studies: inter-pathologist heterogeneity in pathologic analyses, and sampling inadequacies. Inter-pathologist heterogeneity, although present, was less likely in our study because the histopathologic analysis was performed by 2 independent pathologists before a confirmatory diagnosis was established. For this case, a complete excision of the persistent tumour was performed to ensure adequate sampling of the specimen.

Overall, the present case remains unique in that the origin of the patient’s tumour, her treatment, and the tumour response were all inconsistent with previously encountered non-rtacs of the sinonasal tract. To date, no established classification system describes the presentation of non-rtacs of the nasopharynx, only those that arise in the sinonasal region. The wto histologic classification system describes only select nasopharyngeal malignancies, excluding possible tumours such as adenocarcinomas and sarcomas. However, the 2001 Chinese NPC classification system proposed by Zong et al.14 introduced adenocarcinomas, traditional-type or salivary-gland-type, as a subset of NPCs. Notably, the "traditional-type" subset in that classification system includes rtacs, a rare finding in the nasopharynx, primarily described in case reports. Hence, given that no established classification system describes non-rtacs of the nasopharynx, we propose expanding the current wto histologic classification of nasopharyngeal malignancies to include non-rtacs and rtacs as outlined in Figure 5.

CONCLUSIONS

Our case demonstrates that non-rtacs can potentially originate in the nasopharynx, just as they can in the sinonasal cavity. The non-rtac subtype should therefore remain part of the differential diagnosis for NPC. In our experience, this tumour demonstrates behaviour that is unique from that of its sinonasal counterpart, including its response to treatment, rate of recurrence, and transformation to a high-grade lesion. Those observations highlight the need for the two entities to be classified separately. Overall, these tumours are so rare that nasopharyngeal non-rtacs should remain a diagnosis of exclusion, with careful attention to rule out metastatic disease. Immunohistochemistry is vital in distinguishing these lesions from other subtypes, especially given the diversity of their histologic presentations. We further suggest appropriate modifications to the current wto histologic classification system to include this unique tumour.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images.
CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES