Original Article

Sinonasal Nonsalivary-Type Adenocarcinoma: A 9-Year Experience from a Tertiary Cancer Center in South India

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Abstract

Background: Sinonasal tract malignancies are uncommon, representing not more than 5% of all head and neck neoplasm. Primary non-salivary type adenocarcinomas of the sinonasal tract are rare and may originate from respiratory surface epithelium or the underlying seromucinous glands. They are classified into intestinal type adenocarcinoma (ITAC) and non-intestinal type adenocarcinoma (non-ITAC) based on immunophenotypic features. **Materials and Methods:** We retrieved five cases of ITACs and twelve cases of non-ITACs from our archives over a period from 2010-2018. **Results:** All cases of ITACs occurred in the nasal cavity. There was a male predilection with ratio of 4:1, mean age being 48 years. Two cases had association with occupational risk factors. All cases showed positivity for CK20. Non-ITACs occurred in older age group with mean age of 52 years. Male to female ratio was 2:1. Apart from nasal cavity, ethmoid, maxillary, frontal and sphenoid sinuses were involved. Though occupational risk factors have not been established for non-ITAC, five of our cases gave history of exposure to risk factors. Non-ITACs showed positivity for CK7 and were negative for CK20. **Conclusion:** Surgery is the first line of management followed by adjuvant radiotherapy. Three cases of non-ITACs developed recurrence while on follow up. Recurrence in one case was after five years of initial diagnosis. Follow-ups over long period of time are required. Multiinstitutional studies are needed for better understanding these rare cancers.

Keywords: *Adenocarcinoma, intestinal, nonintestinal, sinonasal*

Introduction

Primary nonsalivary-type sinonasal adenocarcinomas are rare malignancies. They are classified into intestinal-type adenocarcinomas (ITACs) and non-ITACs. ITAC is composed of growth patterns that resemble carcinomas or adenomas of intestinal origin, or it may mimic

normal histology of the intestinal mucosa.[1,2] Non-ITACs display histopathology features of neither ITACs nor salivary-type adenocarcinomas.

Occupational risk factors have been established for ITAC. Occupational exposure to wood dust, leather, formaldehyde, chromium, increased nickel content in rock dust and farming soil, etc., is mentioned in literature.[3,4] ITACs have a male predominance, possibly due to association with occupational risk factors, and are commonly seen in the nasal cavity and ethmoid. ITACs not only have morphological resemblance to colonic tubulovillous adenomas and adenocarcinomas, but also exhibit expression of intestinal-type markers. They exhibit expression of intestinal-type markers such as cytokeratin (CK) 20, CDX2, and villin, although they can also frequently express CK 7. CK20 is considered to be a more reliable marker than CDX2 for diagnosing ITACs.[5-7] Prognosis depends on stage and histological subtype/grade. Non-ITACs are rare. Tumors which do not have morphological resemblance to any known salivary gland carcinoma nor having intestinal-type morphology or immunophenotype fall into this group. Unlike ITACs, there is no occupational risk factor that has been established for this group of neoplasm.

Materials and Methods

A total of 19 cases designated as "non-ITAC," "tubulopapillary adenocarcinoma," "adenocarcinoma, not otherwise specified (NOS)," and "ITAC," who had treatment at this center during 2010–2018, were retrieved from the pathology archives and consult files

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of our institute. The medical records of all these patients were reviewed. The clinical, radiological, and treatment details of these cases were retrieved. The cases were reviewed for confirmation of initial diagnosis or possible reclassification. The follow-up clinical status was updated till December 2018. This study had approval from our Institutional Review Board (IRB no. 12/2018/01).

ITACs were defined as primary adenocarcinomas of the sinonasal tract with morphologic and/or immunophenotypic evidence of intestinal differentiation. Non-ITACs were defined as carcinomas showing predominantly glandular differentiation, did not fit into a salivary tumor category, and showed no evidence for intestinal or prominent neuroendocrine differentiation. On review, two cases of non-ITAC showed prominent neuroendocrine differentiation and were excluded from the study. After exclusion and reclassification, there were a total of 17 cases; 12 cases of non-ITAC and five cases of ITAC in this study.

ITACs were graded based on the Kleinsasser and Schroeder classification.[8] Well-differentiated tumors with papillary growth and monomorphic stratified nuclei and scattered goblet cells, resembling the epithelium of villous adenoma, were classified as papillary-tubular cylinder cell-I (PTCC-I); tumors with more infiltrative irregular tubuloglandular spaces and cytonuclear atypia were grouped as PTCC-II; and tumors with a solid growth pattern and marked cytological atypia were considered PTCC-III. Tumors with abundant mucin production reminiscent of a "colloid carcinoma" were considered alveolar goblet cell type. Tumors with predominant signet ring cell (SRC) growth were designated as SRC type. Tumors with mixed morphology were considered transitional (Trans).

Non-ITACs were graded into low grade and high grade. Low-grade tumors showed well-formed glands lined by a single layer of uniform cuboidal-to-columnar cells and no evident mitosis or necrosis. High-grade tumors were characterized by solid growth and ill-formed glands with atypia, mitosis, and necrosis.

Results

Out of the total 17 cases, 16 patients presented with complaints of nasal obstruction and epistaxis of varying duration. However, one patient presented with a neck nodal mass which on fine-needle aspiration cytology showed metastatic carcinoma and on further examination, the nasal mass was detected. Nasal endoscopy in all the patients showed growths in the nasal cavity, and biopsy were taken. Diagnosis was made on histopathology and immunohistochemistry. Computed tomography scan and/or magnetic resonance imaging were done to evaluate the extent of disease and to plan surgery. Surgery was the initial line of management in all these cases and based on extent of disease ranged from endoscopic resection of tumor, medial maxillectomy, total maxillectomy, or craniofacial resection. Based on final histopathology, cases with positive surgical margins were given radiotherapy.

The follow-up of these patients was updated till December 2018. While on follow-up, three patients developed recurrence. All the three cases were non-ITACs, and the initial presentation in all these cases was at an advanced stage. One patient had intracranial extension, another had nodal metastasis, and the third patient had involvement of the orbital plate at the time of initial diagnosis. Two of these patients developed recurrence 2 years after the initial diagnosis, whereas one patient developed recurrence 5 years after the initial diagnosis. One patient succumbed to the illness, whereas the other two patients were salvaged by surgery and radiation and were on follow-up. Out of the two patients who responded to therapy, one succumbed to the disease in late December 2018. The overall survival (OS) and disease-free survival (DFS) were 100% after 2-year follow-up; however, after 5 years, the OS was 83%, whereas DFS was only 62.5%.

The clinicopathologic features are summarized in Table 1. ITAC occurred in younger individuals (mean age: 48 years, range: 35–70 years), with a male predilection (4:1). Nasal cavity was the site of involvement in all the five cases (5/5, 100%). In this series of ITAC, there were three cases of PTCC-I [Figure 1a], one case of PTCC-II [Figure 1b], and one case of SRC [Figure 1c]. The cases showed positivity for CK20 [Figure 1d] and negativity for CK7.

Non-ITACs occurred in older individuals (mean age: 52 years, range: 31–84 years), with a male predilection (2:1). However, the male predilection was lower than that for ITAC. Nasal cavity was the most common site; few cases showed multiple sites of involvement, i.e., nasal cavity along with sinuses. Nasal cavity was involved in eight cases (8/12, 67%), followed by ethmoid, four cases (4/12; 34%); maxillary, two cases (2/12; 15.8%); frontal, one case (1/12; 9.3%), and ethmoid, one case (1/12; 9.3%). Ten cases were low-grade tumors [Figure 2a] and two cases were high-grade tumors [Figure 2b]. Non-ITACs

Table 1: Clinicopathological features

Sinonasal intestinal adenocarcinoma (5nos)	Sinonasal non-intestinal adenocarcinoma (12os)
Mean age 48 years (35-70)	52 years (31-84)
Male:female 4:1	2:1
Sites of involvement	
Nasal cavity 5	8[x]
Ethmoid	4[x]
Maxillary	2
Frontal	1
Sphenoid	1
Unknown	
Occupational risk factor 2	5

x-cases showing multiple sites of involvement

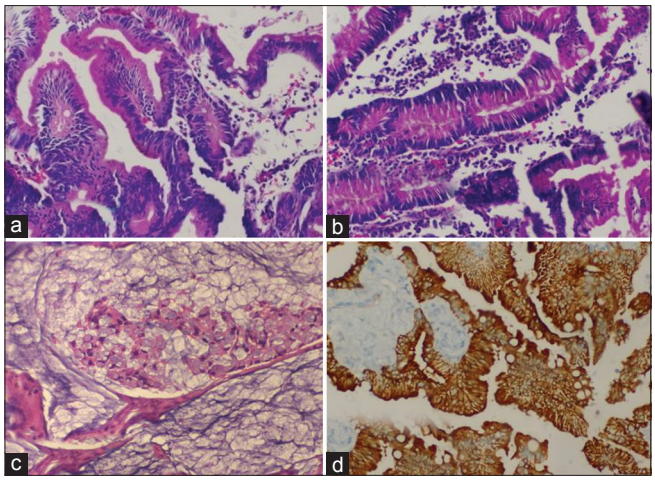

Figure 1: (a) Predominantly papillary growth pattern resembling the appearance of a colonic adenoma (H and E, ×20), (b) Tubular and cribriform growth with stromal reaction (H and E, ×20), (c) Signet ring cells suspended in mucin pool (H and E, ×20), (d) Cytokeratin 20 positivity (H and E, ×20)

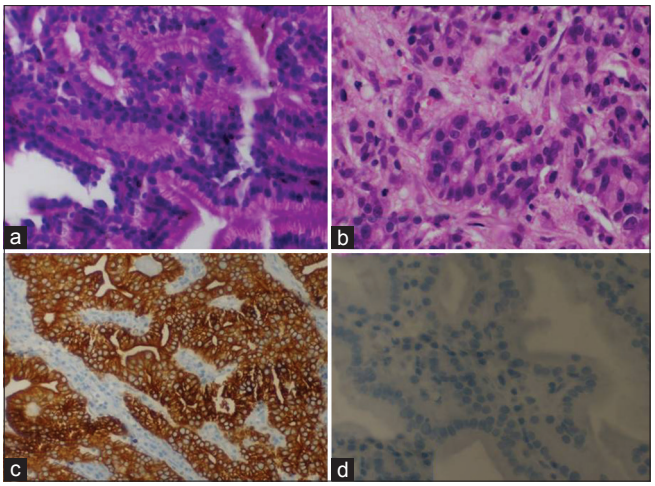

Figure 2: (a) Bland monomorphic glands lined by a single layer of cuboidal-to-columnar cells (H and E, ×40), (b) Ill-defined glands with nuclear atypia (H and E, ×40), (c) Cytokeratin 7 positivity (H and E, ×20), (d) Cytokeratin 20 negativity (H and E, ×20)

showed positivity for CK7 [Figure 2c] and negativity for CK20 [Figure 2d].

Out of the five cases of ITACs, two patients (2/5; 40%) had a history of association with occupational risk factor: one was a person involved in rock crushing and the other had a history of allergy to leather products. Although occupational risk factors have not been established for non-ITACs, five of our patients (5/12; 42%) had occupational risk factors of ITACs. One patient was a carpenter by profession and the other four patients were farmers.

Discussion

ITACs and non-ITACs of the sinonasal region are rare. ITACs are characterized by their immunophenotypic resemblance to carcinomas of the colon. The differential diagnosis of ITAC includes metastatic gastrointestinal carcinoma and sinonasal low-grade nonintestinal adenocarcinoma. Based on histology or immunophenotype, it is impossible to make a differential between primary intestinal-type sinonasal adenocarcinoma and metastasis to sinonasal region from a colorectal carcinoma. Both ITACs and colorectal carcinomas express CK20, CDX-2, MUC2, and villin, while the presence of CK7 may be suggestive of ITAC. Colonoscopy and other investigation modalities should be done to rule out primary colorectal carcinoma in case of an intestinal-type tumor in the sinonasal tract.[9] CDX-2 though helpful in diagnosing ITAC is not absolutely specific, as it can be expressed also in non-ITACs, sinonasal seromucinous hamartoma, and rarely in salivary-type adenocarcinomas.[10] More specific for ITAC is the expression of CK20. Non-ITACs are positive for CK7 and are negative for CK20.

Studies have shown that a subset of ITACs, mostly in woodworkers, expressed high levels of epidermal growth factor receptor (EGFR) protein.[11] In contrast to colorectal carcinomas, activating mutations of K-RAS and BRAF in the signal route of EGFR are rare.[12,13] This suggests possibilities for anti-EGFR therapies in ITAC.[14] Other molecular studies indicate preserved expression of mismatch repair proteins, β-catenin, and E-cadherin and overexpression of MET protein.[15] Annexin A1 and A2 are downregulated in ITAC.[16] High prevalence of TP53 mutations was seen in sinonasal carcinoma with work-related exposure to wood dust.[17]

Non-ITACs are classified into low grade and high grade based on the histology and presence of mitosis and necrosis. It is the infiltrative growth pattern that helps in making a diagnosis of malignancy in these tumors with deceptively bland cytomorphology. Immunohistochemically, they are constantly positive for CK7, but usually negative for CK20 and CDX-2. Metastasis from thyroid primary can arise as differential, and thyroid transcription factor-1 or thyroglobulin immunohistochemical markers can be used to perform the diagnosis.

High-grade ones display a diversity of morphologic patterns such as blastomatous, apocrine, oncocytic/mucinous, poorly differentiated/undifferentiated, and others.[18] Their nuclei tend to be pleomorphic, and there is mitotic activity.

In a study by Purgina *et al*. wherein they reviewed their cases over a period of 27 years, ITAC (17 NOS) occurred predominantly in the nasal cavity in elderly patients (mean age: 65 years), with a striking male predilection (15:2).[10] In our study also, over a period of 9 years, nasal cavity was the primary site (ITAC [5 NOS]). Male predominance (4:1) was also noted; however, our mean age was much lower, 48 years. The mean age of non-ITAC in their study was 51 years, which was comparable to our study wherein the mean age was 52 years. They observed a slight female predominance (10:13), whereas we had male predominance (2:1), though not as high as in ITAC. The sites of involvement were also comparable and included

predominantly the nasal cavity followed by maxillary, frontal, ethmoid, and sphenoid sinuses.

Conclusion

Treatment of ITACs and non-ITACs is surgery. Adjuvant radiotherapy is given when surgical margins are positive or when there is recurrence. Patients need to be kept on follow-up with nasal endoscopy and radiological evaluation for picking up recurrences and timely management. Late recurrences are known, and hence a long period of follow-up is required. Multi-institutional studies will be of help in better understanding these rare cancers.

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Conflicts of interest

There are no conflicts of interest.

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