Original Article

Sinonasal mass lesions: A clinicopathological study with p63 and p16 immunohistochemical expressions

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Abstract

Introduction: The worldwide annual incidence of carcinomas of the sinonasal tract is 0.5 to 1.0 patients per 100,000 per year. P63 plays a role in epithelial development and is used as a marker for basal and myoepithelial cells. Expression of p16 occurs as a result of functional inactivation of the retinoblastoma protein (pRb) by the human papilloma virus (HPV) E7 protein.

Aims: This study aims to study the histological spectrum of benign and malignant sinonasal mass lesions and to study the immunohistochemical expression of p63 in different type of sinonasal mass lesions. It also aims to ascertain the incidence of high-risk HPV in primary sinonasal mass lesions with p16 immunohistochemistry and delineate the histological spectrum of HPV-related sinonasal lesions.

Materials and Methods: This cross-sectional study was conducted on 80 cases from June 2018 to June 2020 at a tertiary care hospital. Clinical history including demographic parameters were collected in the study proforma. The gross findings of the specimens noted and histopathological examination by H&E staining done. Immunohistochemistry staining for p63 and p16 expression was performed on all cases.

Results: Most common age group affected was 41–60 years with male:female ratio of 1.67:1. Nonneoplastic lesions (38.7%) comprised majority of the cases followed by benign neoplastic lesions (31.3%) and malignant neoplastic lesions (30%). Among the malignant neoplastic lesions, p63 showed positive expression in 75% ($p = 0.005$) and p16 showed positive expression in 41.7% ($p = 0.023$). Among benign and nonneoplastic lesions, p63 showed positivity in 21.4% ($p = 0.000$) and p16 showed positivity in 44.6% ($p = 0.040$).

Conclusion: We analyzed p63 and p16 expression in varied lineages like carcinomas, papillomas, and neuroectodermal differentiation arising from the sinonasal tract and also in relation to other clinicopathological parameters. This study revealed p63 expression was associated more with the squamous cell carcinomas and nasopharyngeal carcinomas. Sinonasal tract malignancies are also associated with HPV infections that are identifiable by p16 immunostaining and, thus, could provide new prospects in identifying any definite biological and clinical characteristics associated with HPV as well as advancement in the targeted therapies for this patient population.

Keywords: Immunohistochemistry, neoplastic lesion, sinonasal tract lesions

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INTRODUCTION

The nasal cavity, nasopharynx, and paranasal sinuses-including the maxillary, ethmoid, sphenoid, and frontal sinuses are collectively referred to as the sinonasal tract. Carcinomas of the sinonasal tract are distinct and comprises of tumours originating from the surface epithelium as well as the seromucinous glands with worldwide annual incidence of 0.5 to 1.0 patients per 100,000 per year.[1,2]

The p63 gene is a member of the p53 gene family based on their structural similarity and is located on chromosome 3q27–28. P63 has an important role in epithelial development and is normally expressed in the basal cells of many human epithelial tissues. P63 is used as a marker for basal and myoepithelial cells.[3] p16, also known as p16ink4a, cyclin-dependent kinase inhibitor 2A, is a tumour suppressor protein, located at 9p21, and in humans it is encoded by the CDKN2A gene. P16 plays a role in cell–cycle regulation by breaking the cell's progression from G1 phase to S phase. The human papilloma virus (HPV) E7 protein functionally inactivates the retinoblastoma protein (pRb) which results in the expression of p16. HPV viral oncogene products E6 and E7 play an important role in HPV-associated carcinogenesis abrogating p53 and retinoblastoma (Rb) tumour suppressor functions, respectively.[4]

The aim of our study was to show the histological spectrum of benign and malignant sinonasal mass lesions and to study the immunohistochemical expression of p63 in different type of sinonasal mass lesions, thus, helping to resolve diagnostic dilemma and to ascertain the incidence of high-risk HPV in primary sinonasal mass lesions with p16 immunohistochemistry and to delineate the histological spectrum of HPV-related sinonasal lesions.

MATERIALS AND METHODS

This was a cross-sectional observational study conducted on 80 cases for 2 years from June 2018 to June 2020 at a tertiary care hospital. The study was performed after obtaining the approval from Institutional ethical committee (Date of approval: 22/05/2018). Informed consent was also taken. Patients presenting with clinical features of nasal obstruction, epistaxis and rhinorrhoea, facial pain and paralysis, nasal discharge, facial swelling, nasal mass or ulcer, eye-related symptoms in advanced cases, and nasal masses apparent on computed tomography scan or magnetic resonance imaging and patients who are compliant and gave consent were included in the study. Patients who are uncooperative/not willing to do surgery, suffering from serious illness, and gave no consent were excluded from the study. Excised sinonasal tumour masses were sent to the department of pathology for further processing. Gross examination was done. Sections were taken from the representative areas and was processed, followed by haematoxylin and eosin (H & E) staining and histopathological reporting that was done in accordance with World Health Organization classification (2017).[5] Immunohistochemical staining (IHC) was done for expression of p63 [monoclonal mouse antibody, (clone: 4A4, Bio Genex), positive control: specimen of prostate; nuclear staining], and p16 [monoclonal mouse antibody, (clone G175-405, BioGenex), positive control: specimen of cervical cancer, squamous cell carcinoma; nuclear and cytoplasmic staining]. P63 and p16 expressions was studied and correlated with clinicopathological parameters. p63 and p16 immunostaining was analyzed quantitatively [Tables 1 and 2].[6,7].

For p63, the percentage positivity and intensity scores were summed up to get a total score ranging from 0 to 6. A total score of 3 or more was considered as a diagnostically significant positive reaction.

Statistical analysis

All data were thoroughly maintained on Microsoft excel worksheet. Graphical representation of the data using appropriate charts, tables, and diagrams were done. To evaluate the correlation between categorical variables including the clinicopathological parameters, the Chi-square test was applied. Statistical analyses were performed using SPSS software version 20.0 (IBM, Armonk, New York, USA). *P* Values <0.05 were considered statistically significant.

RESULTS

There was total 80 cases. Age ranged from 2 to 75 years, mean age (± standard deviation) of the patients was

Table 1: Quantification of p63 immunostaining[6]

Proportion score	Positive tumours cells, %	Intensity	Intensity score
0	< 1	Mild	1
1	1–10	Moderate	2
2	11–50	Intense	3
3	>50		

Table 2: Quantification of p16 immunostaining[7]

Result	Score	Criteria
Negative	0	Weak staining or strong staining in ≤70% of the tumours cells
Positive	1	Strong and diffuse nuclear and cytoplasmic staining in ≥70% of the tumours cells

40.99 ± 18.35 years with male:female ratio was 1.67:1. Median of age was 43.00 and mode was 50, respectively. Non-specific history was in majority of the cases, 50% followed by recurrent sinusitis (15%) and smoking (13.8%). Industrial exposure (8.7%), alcohol (7.5%), and oral contraceptive pills (5.0%) comprised rest of cases. Nasal obstruction (67.5%) was the most common symptom followed by nasal congestion (35%) and epistaxis (20%). Other symptoms comprised 17.5% that included enlarged lymph nodes seen in two cases of undifferentiated nasopharyngeal carcinoma, headache, fever, weight loss, eye symptoms, pain, foul smelling discharge, hyposmia, facial swelling, and external nasal deformity.

Majority of the cases are seen in nasal cavity (71.2%). Other sites affected are paranasal sinuses (16.2%), nasopharynx (10.1%), and cribriform plate (2.5%) [Table 3]. Non-neoplastic lesions (38.7%) comprised majority of the cases followed by benign neoplastic lesions (31.3%) and malignant neoplastic lesions (30%). Majority of the cases included inflammatory nasal polyp (25%) and sinonasal papilloma (16.5%) [Figure 1a]. Among the malignant neoplastic lesions, keratinizing squamous cell carcinoma (KSCC; 8.7%) [Figure 1b], non-keratinizing squamous cell carcinoma (NKSCC; 3.7%) [Figure 1c], and undifferentiated nasopharyngeal carcinoma (NPC; 5.0%) [Figure 1d] were in majority.

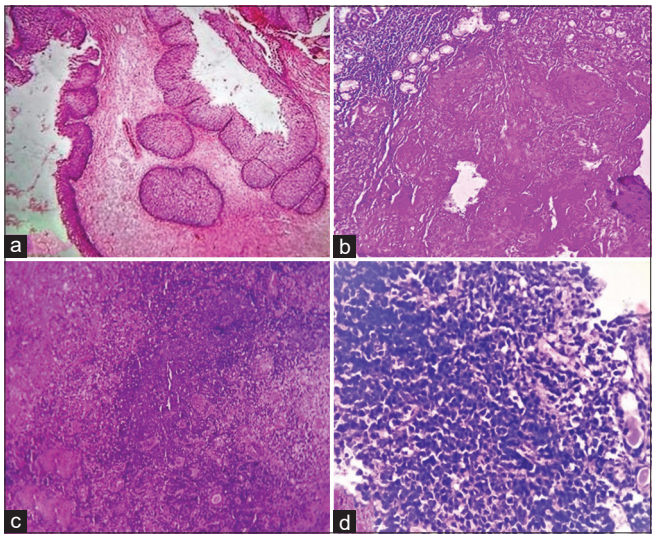

Figure 1: Sinonasal papilloma, inverted type (a) Section shows multiple inversions of surface epithelium into the underlying stroma with an intact basement membrane (×100, H&E) Keratinizing squamous cell carcinoma (b) Section shows squamous epithelium with abundant keratinization (×100, H&E); non-keratinizing squamous cell carcinoma (c) Section shows solid sheets composed of malignant cells with no keratinization (×400, H&E); Nasopharyngeal carcinoma, undifferentiated type (d) Section shows large tumours cells with a syncytial appearance, round to oval vesicular nuclei and large central nucleoli and scanty eosinophilic cytoplasm (×400, H&E)

Among the malignant neoplastic lesions, 18 cases (75%) showed p63 expression and negative expression in six cases (25%) with a significant *P* value of 0.005. The positive expression of p63 was seen in all the cases of KSCC[Figure 2a] and NKSCC [Figure 2b], undifferentiated NPC, and adenoid cystic carcinoma. Amongst the two cases of sinonasal undifferentiated carcinoma (SNUC) and two cases of olfactory neuroblastoma, one case from each variety showed positive expression. Chondrosarcoma, embryonal rhabdomyosarcoma and primitive neuroectodermal tumours (PNET) showed negative expression [Table 4].

Benign and non-neoplastic lesions showed p63 positive expression in 12 cases (21.4%) and negative expression in 44 cases (78.6%) with a significant ($p = 0.000$). Among sinonasal papilloma, all the cases of inverted type showed positivity for p63 but only three cases of the exophytic type showed positivity. Rest of all the cases showed negative expression for p63.

Malignant neoplastic lesions showed p16 positive expression in 10 cases (41.7%) and negative expression in 14 cases (58.3%) and a significant *P* value of 0.023. p16 positivity was seen in KSCC[Figure 3a and b] and NKSCC as well as in SNUC [Figure 3c]. Rest of all the cases did not express p16 [Table 5].

Among benign and non-neoplastic lesions, 25 cases (44.6%) showed positive expression and negative expression in 31 cases (55.4%) with a significant *P* value of 0.040. p16 was expressed in 18 cases out of the 27 inflammatory nasal polyp and antrochoanal polyp. In 13 cases of sinonasal papilloma, inverted [Figure 3d] and exophytic type, only 7 cases showed positive expression of p16. Rest of all the cases showed negative expression of p16 [Table 6]. No significant correlation was found between p16 expression and age ($p = 0.421$), sex ($p = 0.414$), and relevant history ($p = 0.059$).

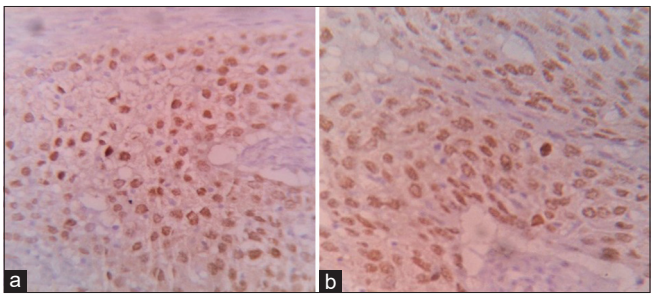

Figure 2: Keratinizing squamous cell carcinoma (a) IHC staining for p63 showing positivity (×400); non-keratinizing squamous cell carcinoma (b) IHC staining for p63 showing positivity (×400)

Table 3: Distribution of cases according to type of lesion (*n*=80)

Type of lesion	Histopathological diagnosis	No. of cases	Percentage (%)
Non-neoplastic	Inflammatory nasal polyp	20	25.0
	Rhinosporidiosis	3	3.7
	Rhinoscleroma	1	1.2
	Antrochoanal polyp	7	8.9
Benign neoplastic	Sinonasal papilloma (Inverted and Exophytic type)	13	16.5
	Sinonasal glomangiopericytoma	2	2.5
	Capillary haemangioma	3	3.7
	Respiratory epithelial adenomatoid hamartoma	2	2.5
	Pleomorphic adenoma of salivary gland	1	1.2
	Nasopharyngeal Angiofibroma	4	5.0
Malignant neoplastic	Keratinizing squamous cell carcinoma	7	8.7
	Non-keratinizing squamous cell carcinoma	3	3.7
	Chondrosarcoma	1	1.2
	Embryonal rhabdomyosarcoma	1	1.2
	Adenoid cystic carcinoma	2	2.5
	Primitive neuroectodermal tumours (PNET)	2	2.5
	Olfactory neuroblastoma	2	2.5
	Sinonasal undifferentiated carcinoma (SNUC)	2	2.5
	Undifferentiated nasopharyngeal carcinoma	4	5.0

Table 4: Correlation of p63 expression to malignant neoplastic lesions (*n*=24)

Histopathological diagnosis	p63 scoring							*P*
	0 *n*=3	1 *n*=2	2 *n*=1	3 *n*=4	4 *n*=2	5 *n*=6	6 *n*=6	
Adenoid cystic carcinoma	0	0	0	2 (8.3%)	0	0	0	0.005
Chondrosarcoma	1 (4.2%)	0	0	0	0	0	0	
Embryonal rhabdomyosarcoma	1 (4.2%)	0	0	0	0	0	0	
Keratinizing squamous cell carcinoma	0	0	0	0	0	2 (8.4%)	5 (20.8%)	
Non-Keratinizing squamous cell carcinoma	0	0	0	0	0	2 (8.3%)	1 (4.2%)	
Olfactory neuroblastoma	0	1 (4.2%)	0	1 (4.2%)	0	0	0	
PNET	0	1 (4.1%)	1 (4.2%)	0	0	0	0	
Sinonasal undifferentiated carcinoma	1 (4.1%)	0	0	1 (4.2%)	0	0	0	
Undifferentiated nasopharyngeal carcinoma	0	0	0	0	2 (8.3%)	2 (8.3%)	0	

Table 5: Correlation of p16 expression to malignant neoplastic lesions (*n*=24)

Histological diagnosis	p16		*P*
	0 *n*=14	1 *n*=10	
Adenoid cystic carcinoma	2 (8.3%)	0	0.023
Chondrosarcoma	1 (4.2%)	0	
Embryonal rhabdomyosarcoma	1 (4.2%)	0	
Keratinizing squamous cell carcinoma	1 (4.2%)	6 (25%)	
Non-keratinizing squamous cell carcinoma	1 (4.2%)	2 (8.3%)	
Olfactory neuroblastoma	2 (8.3%)	0	
PNET	2 (8.3%)	0	
Sinonasal undifferentiated carcinoma	0	2 (8.3%)	
Undifferentiated nasopharyngeal carcinoma	4 (16.7%)	0	

DISCUSSION

This study comprised of 80 cases. Mean age of presentation was 40.99 years with male:female ratio was 1.67:1. This was comparable to other studies.[8-11] The 2nd to 4th decades of life are the most vulnerable period for development of sinonasal masses and M:F ratio of 1.5:1 as shown by Lathi *et al*.[12] and Bakari *et al*.[13] had reported a peak incidence of 33 years with female preponderance of 1:1.2. Non-specific history comprised majority of the cases 50% followed by recurrent sinusitis (15%) and smoking (13.8%).

Nasal obstruction (67.5%) was the most common symptom followed by nasal congestion (35%) and epistaxis (20%). These findings were concordant with other studies.[9-13] Enlarged lymph nodes seen in two cases of undifferentiated NPC was similar to Patel and Katakwar[14] Majority of the cases were seen in nasal cavity (71.2%). Other sites affected are paranasal sinuses (16.2%), nasopharynx (10.1%) and cribriform plate (2.5%). This was similar to the study done by Zafar *et al*.[10] Non-neoplastic lesions (38.7%) comprised majority of the cases. This was similar to the other studies.[8-12] Benign neoplastic lesions (31.3%) were slightly more than malignant neoplastic lesions (30%) but Bist *et al*. reported more malignant lesions than benign.[11]

Among non-neoplastic lesions, inflammatory nasal polyps (25%) and antrochoanal polyps (8.9%) were in majority which was similar to many studies.[8-13] Rhinosporidiosis (3.7%) was reported more than rhinoscleroma (1.2%) and so as by Agarwal and Panigrahi.[9] But was dissimilar to other studies.[8] In our

Table 6: Correlation of p16 expression to benign neoplastic and non-neoplastic lesions (*n*=56)

Histological diagnosis	p16		*P*
	0 *n*=31	1 *n*=25	
Antrochoanal polyp	3 (5.4%)	4 (7.1%)	0.040
Capillary haemangioma	3 (5.4%)	0	
Inflammatory nasal polyp	6 (10%)	14 (25.5%)	
Nasopharyngeal angiofibroma	4 (7.1%)	0	
Pleomorphic adenoma of salivary gland	1 (1.8%)	0	
Respiratory epithelial adenomatoid hamartoma	2 (3.6%)	0	
Rhinoscleroma	1 (1.8%)	0	
Rhinosporidiosis	3 (5.4%)	0	
Sinonasal glomangiopericytoma	2 (3.6%)	0	
Sinonasal papilloma, exophytic type	2 (3.6%)	2 (3.6%)	
Sinonasal papilloma, inverted type	4 (7.1%)	5 (9.0%)	

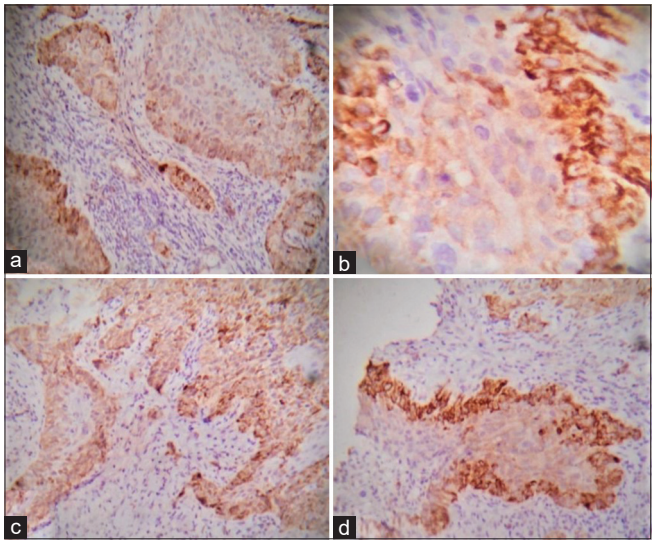

Figure 3: Keratinizing squamous cell carcinoma (a) IHC staining for p16 showing positivity (×100; b) IHC staining for p16 showing positivity (×400); Sinonasal undifferentiated carcinoma (c) IHC staining for p16 showing positivity (×100); Sinonasal papilloma, inverted type (d) IHC staining for p16 showing positivity (×100)

study, benign neoplastic lesions consisted mainly of sinonasal papilloma (inverted and exophytic type; 16.5%) and nasopharyngeal angiofibroma (5.0%) followed by capillary haemangioma (3.7%). This was concordant with Garg and Mathur.[8] But in the study done by Agarwal and Panigrahi[9] capillary haemangioma was diagnosed more than sinonasal papilloma. Lathi *et al*.[12] and Khan *et al*.[15] also reported capillary haemangioma more than sinonasal papilloma. Two cases of respiratory epithelial adenomatoid hamartoma (REAH) and one case of pleomorphic adenoma of salivary gland was also reported.

Among the malignant neoplastic lesions, Squamous cell carcinoma (SCC; 12.4%) was most common followed by undifferentiated NPC (5.0%). This was similar to other studies.[9,16] Two cases of Olfactory neuroblastoma and two cases of PNET were reported similar to Garg D and Mathur[8] Other lesions included were SNUC (2.5%), adenoid cystic carcinoma (2.5%), chondrosarcoma (1.2%) and embryonal rhabdomyosarcoma (1.2%).

Tonon *et al*.[17] established that genomic locus of p63 is constantly amplified in squamous cell carcinoma implying that upregulation of p63 promotes tumorigenesis. p63 is overexpressed in head and neck SCC in comparison to normal tissue control specimens as shown by Sniezek *et al*.[18] They specified that p63 plays an undifferentiating and antiapoptotic role in the mucosal epithelium of the head and neck region which leads to tumours formation. In this study p63 positivity was significantly higher in SCC group (100%) as which was comparable to Oncel *et al*.[19] NKSCC almost always exhibits diffuse strong positivity for p63 and so as in this study.[20]

SNUC carries a very poor prognosis even with a multimodality treatment approach. After nearly three decades of its first description by Frierson *et al*.[21] SNUC is still a conundrum for histopathologists and clinicians. The differential diagnosis of small blue round cell tumours is wide and includes undifferentiated NPC, poorly differentiated squamous cell carcinoma (PDSCC), small cell undifferentiated neuroendocrine carcinoma (SCNEC), high grade olfactory neuroblastoma, nasal-type natural killer (NK)/T-cell lymphoma and rhabdomyosarcoma, mucosal malignant melanoma, SNUC. These tumours share a similar light microscopic appearance that of a small, round cell tumour and they may present with diagnostic difficulties for a pathologist. Olfactory neuroblastoma (ONB) usually shows only focal positive immunoreactivity for this marker. Most but not all ONBs are also negative for p63.[22] In this study, only one case of ONB-stained positive and another one negative.

Guo *et al*.[23] suggested that p63 might be used as an adjunct diagnostic marker of NPC. The strong and diffuse p63 expression seen in four cases of undifferentiated subtypes of NPC supports the findings of previous studies that have described p63immunoreactivity in NPC.[22-24] NPC typically demonstrate diffuse strong positivity for p63so as in our study.[22,23] Our finding of focal p63 expression in cases of SNUC supports the observations of other studies.[24,25] The non-keratinizing or undifferentiated subtypes of NPC and SNUC both the tumours are usually strongly positive for cytokeratin and so p63 is useful in distinguishing them. Furthermore, this distinction is important clinically because NPC has a more favourable prognosis and is more responsive to radiation therapy than SNUC.[25] SNUC demonstrates sheets of non-descriptive malignant cells

with prominent nucleoli, abundant mitoses, and extensive necrosis.

Adenoid cystic carcinomas lack the capacity for squamous differentiation but are p63-positive and this positivity represents a neoplastic recapitulation of the p63-positivebasal/myoepithelial cell phenotype present in normal salivary gland.[26] Here, both the cases of adenoid cystic carcinoma stained positive for p63. Inverted papillomas (IP) are rare lesions with local aggressiveness, recurrence and malignant transformation. Sniezek *et al*.[18] and Massion *et al*.[27] reported that p63 immunostaining shows a progressive increase throughout the depth of the epithelium moving from metaplasia to severe dysplasia which relates to the pathology. In this study p63 expression showed a significantly elevated levels of p63 in the SCC of sinonasal tract compared with IP. In the statistical analysis using the *X2* test, p63 positivity was significantly higher in the SCC group (41.7%) when compared to the IP group (21.4%) similar to Oncel *et al*.,[19] Kim *et al*.[28] reported p63 positivity in all IP specimens, but the percentage of positive cells was significantly increased in IP with dysplasia. In REAH a basal cell layer could be appreciated that was maintained around the deep glands and was highlighted uniformly by p63, so as in our study the two cases showed basal layer staining positive for p63.[3]

In the world, SCCs of the head and neck represent the 6th most prevalent cancer.[29] However, sinonasal SCCs are rare accounting for less than 3% of all malignancies of the region.[2] Some studies have proposed a possible association of HPV in the development of several carcinomas of the sinonasal region, with a percentage of HPV-associated tumours (20–23.1%) similar to the percentage observed in our study.[30-32] As shown by this study, sinonasal SCCs should be included in the list of neoplasms related to HPV infection, with a rate of HPV-positive tumours of 20%. Among the 11 cases of SCC and SNUC, 10 cases (90.9%) expressed p16 positivity. This was similar to the studies shown by Alos *et al*.,[33] Bishop *et al*.[1]. The frequency of p16 expression in SNUC ranges from 20% to 100% and in our study both the cases were p16positive.[1,33,34] Inverted papilloma shows that out of 13 cases 7 (53.8%) cases were positive which was comparable to Lin *et al*.[35], Zydron *et al*.[36] Here, exophytic papillomas show 50%positivity and IP show 55.5% positivity. In this study, antrochoanal polyp showed 57.1% positivity and inflammatory nasal polyp showed 70%. HPV16 was the prevalent type with a detection rate of 75% in nasal polyps and 60% in antrochoanal polyps.[37] Expression of p16INK4a protein is an exponent of HPV infection, but there were reports to contradict this thesis. Yamashita *et al*.[38] detected p16INK4a overexpression in only ¼ of the HPV positive patients with squamous cell carcinoma and in 80% of cases of HPV positive with IP without a statistically significant correlation and concluded that p16INK4a cannot be considered a surrogate marker of HPV infection in the IP.

The statistical analysis of clinicopathological data confirmed that neither age nor sex nor smoking nor alcohol consumption correlates with the HPV status. This was similar to other studies.[39,40] In our study, HPV16 was identified in 90.9% of HPV-positive sinonasal tumours and the results confirms that HPV16 alone accounts for more than 90% of HPV positive carcinomas of the head and neck.[40,41] These results also suggests that the large majority of head and neck carcinomas associated with HPV infection can be prevented with the help of currently developed vaccines.

CONCLUSION

This study deals with the spectrum of p63 and p16 expression in sinonasal mass lesions. We analyzed p63 and p16 expression in varied lineages like carcinomas, papillomas and neuroectodermal differentiation arising from the sinonasal tract and also in relation to other clinicopathological parameters. This study revealed p63 expression was associated more with the squamous cell carcinomas and nasopharyngeal carcinomas. Sinonasal tract malignancies are also associated with HPV infections that are identifiable by p16 immunostaining. This could provide new prospects in identifying any definite biological and clinical characteristics associated with HPV as well as advancement in the targeted therapies for this patient population. p16 expression in IP and nasal polyps helps in identifying the patients with recurrence and malignant transformations.

Study Limitations and Future Scope

This was a single institution-based study and due to short study period, survival analysis and follow-up study could not be done. Hence a larger population-based study with long follow-up period is required to establish the impact of p16 status in long term survival and outcome in sinonasal tract malignancies. We have not evaluated HPV DNA by RT-PCR techniques because of financial constraints. So, application of reverse transcription polymerase chain reaction (RT-PCR) with type specific p16 assay is advocated to evaluate the prevalence and role of HPV DNA amplification in sinonasal tract malignancies in Indian population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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