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Histopathological study of lesions of nose and paranasal sinuses and association of Human Papilloma Virus (HPV) with sinonasal papillomas and squamous cell carcinoma

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ABSTRACT

A variety of non-neoplastic and neoplastic conditions involve the nasal cavity and paranasal sinuses which are commonly encountered in clinical practice. The nose and paranasal sinuses are exposed to a variety of infections, chemically irritating, antigenically stimulating, traumatic and undoubtedly many other influences and consequences of these multifaceted deleterious exposures result in the formation of tumour-like and truly neoplastic conditions. To study histopathological pattern of sinonasal lesions and association of Human Papilloma Virus (HPV) with sinonasal papillomas and squamous cell carcinomas. The present study was a hospital based observational study conducted over a period of three years from January, 2010 to January, 2013 in the Department of Pathology, Government Medical College, Srinagar which included 181 cases of non-neoplastic and neoplastic lesions of nasal cavity and paranasal sinuses followed by study of association of HPV with sinonasal papillomas and squamous cell carcinomas by polymerase chain reaction (PCR). Out of total 181 cases, 114 were non-neoplastic and 67 were neoplastic. Out of 67 neoplastic lesions, 46 were benign and 21 were malignant. Nasal polyp was most common among non neoplastic lesions. Inverted sinonasal papilloma was most common benign lesion and squamous cell carcinoma was most common malignant lesion seen. Out of a total of 181 sinonasal lesions 101 (55.8%) were present in males and 80 (44.2%) were present in females with male to female ratio being 1.26:1. The age range of patients with sinonasal lesions varied from 5-75 years with a mean age being 34.67 (SD±16.58) years. HPV positivity was seen in 4 (13.33%) out of 30 cases of inverted papillomas, 3 out of 6 (50%) exophytic papillomas tested positive for HPV. Out of 9 squamous cell carcinomas HPV positivity was seen in 2 (22.2%) cases. Categorizing the sinonasal lesions according to histopathological features into various types helps us to know the clinical presentation, clinical outcome and prognosis of the disease. Also low risk HPV types 6 and 11 show an association with sinonasal papillomas and oncogenic HPV types 16 and 18 with squamous cell carcinomas.

Keywords: Sinonasalmass, Neoplastic, Inflammatory polyp, Human Papilloma Virus (HPV).

INTRODUCTION

Nose and its smell, role in beauty and sensuality, its relationship to major health have been major obsession to mankind. A variety of non-neoplastic and neoplastic conditions involve the nasal cavity and paranasal sinuses which are commonly encountered in clinical practice[1]. It is quite impossible to distinguish clinically between simple nasal polyps, polypoidal lesions which are caused by specific granulomatous diseases and polypoidal neoplasms, hence it becomes important that all polyps and polypoidal lesions of nose should be submitted for histopathological examination[2,3,4].

The nose and paranasal sinuses are exposed to a variety of infections, chemically irritating, antigenically stimulating, traumatic and undoubtedly many other influences and consequences of these multifaceted deleterious

exposures result in the formation of tumour-like and truly neoplastic conditions[5]. The commonest non neoplastic and benign sinonasal masses include inflammatory sinonasal polyps and inverted papilloma respectively, while squamous cell carcinoma constitute the common malignant mass[5,6].Despite the long history and frequent occurrence of sinonasal masses a great many questions still exist with regard to their incidence, pathogenesis and treatment [7].HPV is an epitheliotropic virus that has been implicated in premalignant and malignant lesions of the anogenital tract. Similarly, both the low-risk subtypes (i.e., HPV 6, HPV 11) and the high-risk subtypes (i.e., HPV 16, HPV 18) have been identified in sinonasal papillomas. HPV has been linked with inverted papilloma and squamous cell carcimoma[8]. The evidence of HPV as a potential etiological agent in sinonasal cancer is derived from two major lines of research; 1) the reports on malignant transformation of benign (HPV associated) papillomas, and 2) direct detection of HPV DNA in sinonasal carcinomas by hybridization assays and PCR[9]. Studies have found HPV DNA in 50-100% of tested septal (exophytic papillomas)[10]and in 0.86% of lateral wall (inverted papillomas)[11]. Some studies suggest that most HPV positive cases of sinonasalpapillomas are of inverted type[9].Benign papillomas are preferentially associated with the low-risk HPV types 6 and 11 where as their malignant counterparts are exclusively positive for HPV 16 DNA[12]. The frequency of HPV DNA detection in nasal papillomas has been variable(6-89%) according to the detection method used, the particular DNA probes or primers, and the patientsexamined[8,11,12,13-22]. It is possible that the aetiology of sinonasalpapillomas and carcinomas may be heterogeneous; i.e., HPV related and non-related lesions exist. This would explain the discrepant results reported by laboratories using almost identical and sensitive HPV detection techniques, which precludes technical reasons as the prime suspect for this discrepancy. The present study analysed the histopathological pattern of various sinonasal masses in relation to age and sex of patients and also focused on possible putative role of HPV in the aetiology of sinonasalpapillomas and squamous cell carcinomas.

Aims and objective

The main aim and objectives of the study undertaken are:

1. To study the histopathological pattern of various sinonasal masses in relation to age and sex of patients.
2. To study the association of HPV with sinonasalpapillomas and squamous cell carcinomas.

MATERIALS AND METHODS

This was a hospital based observational study conducted over a period of three years from January, 2010 to January, 2013 in the Department of Pathology, Government Medical College Srinagar. A total of 181 cases were included. Complete case history of the patients was recorded. Proper inclusion and exclusion criterias were met. The histopathological reports of the samples received in the Department from January, 2010 to March 2012, were reviewed and wherever necessary, blocks were recut, stained with Haematoxylin and Eosin (H&E) stain. The samples received in our Department from March, 2012 to January, 2013 were subjected to routine histopathological processing. The diagnosis of sinonasal lesions was made on the basis of clinical presentation, gross morphology and light microscopic features of H&E and special stained sections. The lesions were classified as non-neoplastic lesions, benign neoplastic lesions and malignant tumors. The tumors were classified as per WHO classification (2005) and observations were compared with other studies.

After histopathological diagnosis was made, association of Human Papilloma Virus type 6, 11, 16 and 18 with sinonasalpapillomas and squamous cell carcinomas was analyzed by DNA amplification using Polymerase chain reaction (PCR).The genetic studies were performed on the formalin-fixed, paraffin-embedded material in the Department of Biochemistry, Government Medical College Srinagar.

HPV analysis

Extraction of genomic DNA:

For the purpose, kit based method was used. The kit used was Quick-g DNA Mini Prep supplied by ZYMO RESEARCH. The DNA eluted was stored at -20^{o}C for longer duration storage till further downstream processes.

QUALITATIVE AND QUANTITATIVE ANALYSIS OF GENOMIC DNA

The quality and quantity of the DNA was determined by measuring optical density at 260nm and 280 nm by double beam spectrophotometer (Evolution 60S from Thermo Scientific). DNA was alliqouted so as to protect damage from frequent freeze-thawing and stored at -20^{o}C for longer duration of time.

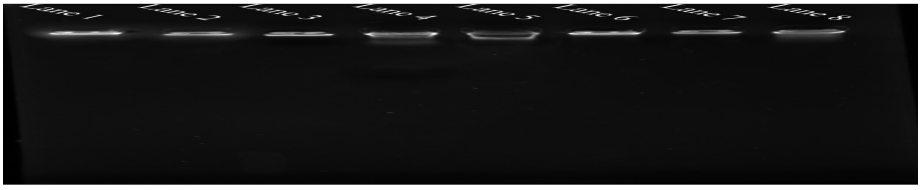

Fig. 1: Representative gel picture showing the integrity of the genomic DNA on 1.0 % agarose gel. Lane 1 to 8 contains the isolated genomic DNA

DNA AMPLIFICATION BY PCR: Amplification kit supplied by GeNei™ that contained all the reagents required for the amplification of the said strains of HPV was used and the protocol followed was as per the kit. Both positive and negative Control for HPV DNA were used. The amplification was performed using Thermal Cycler (Eppendorf). The amplified products were analyzed by gel electrophoresis after staining with ethidium bromide.

STATISTICAL ANALYSIS; Statistical analysis was done with the help of SPSS version 17.0 software. Continuous variables are presented as mean ± SD. Categorical variables are expressed as frequencies and percentages. Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. $p<0.05$ was considered statistically significant.

OBSERVATIONS AND RESULTS; Out of total 181 cases, 114 were non-neoplastic and 67 were neoplastic. Out of 67 neoplastic lesions, 46 were benign and 21 were malignant. The data shows that non-neoplastic lesions were common than neoplastic lesions in the nasal cavity and paranasal sinuses. Benign lesions were more in number than the malignant lesions in our study Out of a total of 181 sinonasal lesions 101 (55.8%) were present in males and 80 (44.2%) were present in females with male to female ratio being 1.26:1.

The age range of patients with sinonasal lesions varied from 5-75 years with a mean age being 34.67 (SD±16.58) years. The peak frequency of 27.1% was observed in the age group of 21-30 years and more than 60% cases were observed in adolescents and young adults.

Table 3: Age wise distribution of neoplastic and non-neoplastic lesions

S.No.	Age (Years)	Number	Frequency (%)
1.	<=10	10	5.5
2.	11-20	32	17.7
3.	21-30	49	27.1
4.	31-40	30	16.6
5.	41-50	31	17.1
6.	51-60	16	8.8
7.	>60	13	7.2
	Total	181	100
Mean ± SD		**34.67 ± 16.58**	
Min – Max		**5 - 75 years**	

Table 5: Histological diagnosis of non-neoplastic lesions

S.No.	Histologic Diagnosis	Number	Frequency (%)
1.	Inflammatory nasal polyp	85	74.6
2.	Allergic polyp	22	19.3
3.	Rhinosporidiosis	3	2.6
4.	Fibrous dysplasia	2	1.8
5.	Tuberculosis	1	0.9
6.	Glioma	1	0.9
	Total	114	100

Nasal polyps were the commonest type seen among non-neoplastic lesions with 107 cases (93.9%), followed by 3 cases of rhinosporidiosis, 2 cases of fibrous dysplasia, 1 case each of tuberculosis and nasal glioma**.**

Out of 46 benign neoplastic lesions, 26 (56.5%) were observed in males and 20 (43.5%) in females. Male to female ratio of 1.3:1 were observed and there was male predominance of benign lesions. The age of patients with benign lesions ranged from 9-69 years with a mean age of 34.02 (SD±15.95) years and benign lesions were most commonly seen in age group of 21-30 years.

Among the 68 neoplastic lesions, 46 were benign neoplasms. Inverted papilloma and hemangioma were the most common lesions among benign tumors.

Table 7: Histological diagnosis of benign lesions

S.No.	Histologic Diagnosis	Number	Frequency (%)
1.	Inverted papilloma	30	65.2
2.	Hemangioma	7	15.2
3.	Exophytic papilloma	6	13.0
4.	Cemento-ossifying fibroma	1	2.2
5.	Giant cell tumour	1	2.2
6.	Pleomorphic adenoma	1	2.2
	Total	46	100

We observed that malignant lesions were more frequent in males 13(61.9%) than females 8(31.8%) with a male to female ratio of 1.62:1.In the present study we observed that risk age groups for malignant lesions ranged from young adults in the 3rd decade to older adults in the 7th decade but age group 41-50 years were at the highest risk (Table 8).

Table 8:Age distribution of malignant lesions

S.No	Age (Years)	Number	Frequency (%)
1.	<=10	0	0.0
2.	11 – 20	0	0.0
3.	21 – 30	1	4.8
4.	31 – 40	5	23.8
5.	41 – 50	7	33.5
6.	51 – 60	2	9.5
7.	> 60	6	28.6
	Total	21	100
Mean ± SD		**51.05 ± 13.43**	
Min – Max		**30 – 75 years**	

We observed that paranasal sinuses (14 cases, 66.7%) were a more common site for malignant lesions compared to nasal cavity (7 cases, 33.3%).Table 9 gives histological diagnosis of malignant lesions of nasal cavity and paranasal sinuses. Squamous cell carcinoma was found to be most common histologic type.

Table 9:Histologic diagnosis of malignant lesions

S.No.	Histologic Diagnosis	Number	Frequency (%)
1.	Squamous cell carcinoma	9	42.9
2.	Adenocarcinoma	3	14.3
3.	Undifferentiated carcinoma	2	9.5
4.	Adenoid cystic carcinoma	2	9.5
5.	Malignant melanoma	2	9.5
6.	Olfactory neuroblastoma	2	9.5
7.	Chondrosarcoma	1	4.8
8.	Total	21	100

To determine the role of human papillomavirus virus (HPV) in the aetiology of sinonasalpapillomas and squamous cell carcinomas, 30 inverted papillomas, 6 exophyticpapillomas and 9 squamous cell carcinomas were examined for presence of HPV DNA by polymerase chain reaction (PCR). The size of the amplified product ranged between 215 to 278 bp and indicated infection with low risk and high risk HPV. Out of 30 cases of inverted papillomas HPV

positivity was seen in 4 (13.33%) cases, 3 out of 6 (50%) exophyticpapillomas tested positive for HPV. Out of 9 squamous cell carcinomas HPV positivity was seen in 2 (22.2%) cases.

Table 10:Relationship of different HPV strains with squamous cell carcinoma and histologic sub types of sinonasalpapillomas

HPV Type	Squamous Cell Carcinoma (N=2)	Inverted Papilloma (N=4)	Exophytic Papilloma (N=3)	*p* value
HPV 6	0	1 (25%)	2 (66.67%)	*p*<0.001 (chi-square test)
HPV 11	0	2 (50%)	0	
HPV 6/11	0	1 (25%)	1 (33.3%)	
HPV 16	1 (50%)	0	0	
HPV 18	0	0	0	
HPV 16/18	1 (50%)	0	0	

Overall, HPV-6 was detected in 5 cases (13.88%) of sinonasalpapillomas (3 exophyticpapillomas and 2 inverted papillomas) and HPV-11 was detected in 4 cases (11.11%) sinonasalpapillomas (3 inverted papillomas and 1 exophytic papilloma) whereas, none of 9 cases of squamous cell carcinomas showed positivity for HPV -6 or HPV-11. HPV-16 positivity was seen in 22.22% (2 cases) and HPV-18 in 11.11% (1 case) of squamous cell carcinomas. None of 36 sinonasalpapillomas showed positivity for HPV -16 or -18.

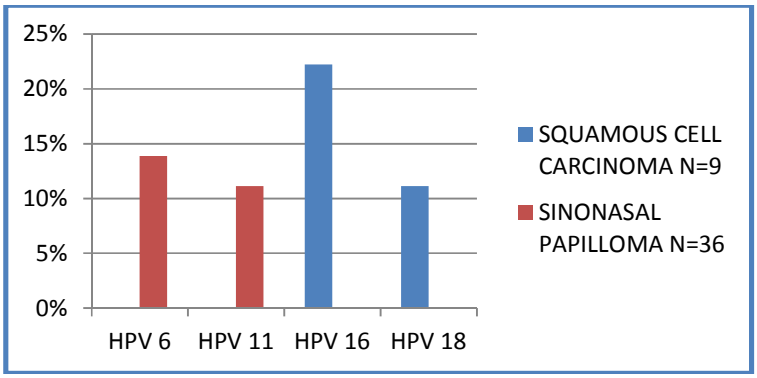

Fig. 2: Relationship of HPV strains with sinonasalpapillomas and squamous cell carcinomas

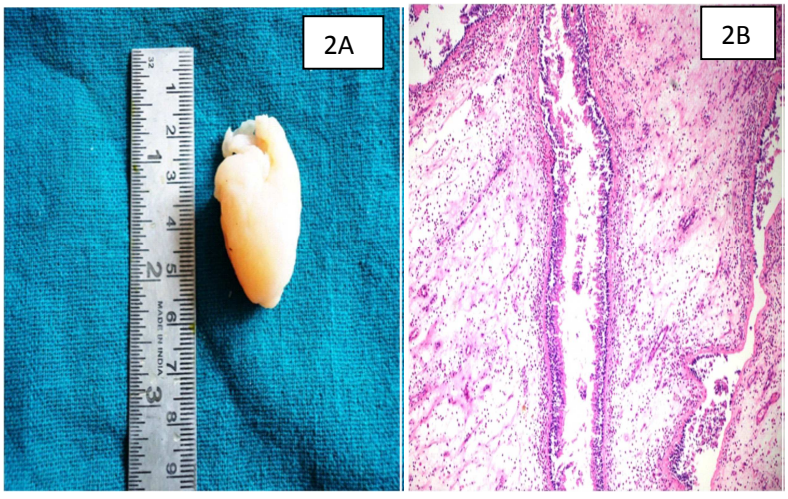

Fig 2A and Fig 2B showing gross and microscopy of nasal polyp

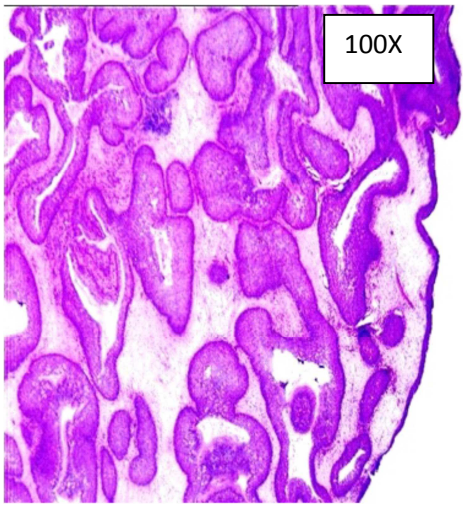

Fig 3 showing sinonasalpappiloma with inverted pattern of growth

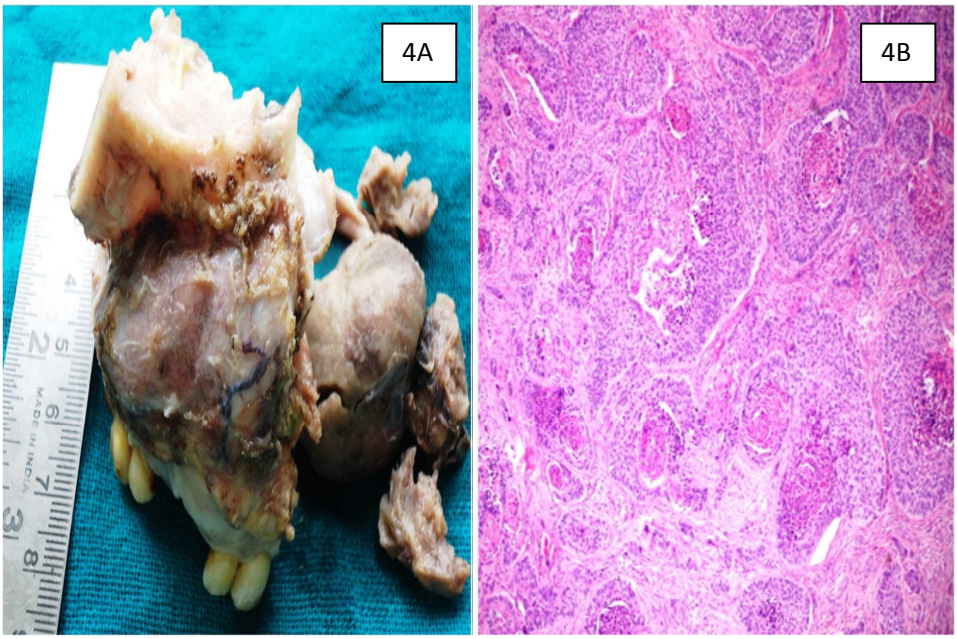

Fig 4Aand 4B showing gross and microscopy of squamous cell carcinoma of maxillary sinus

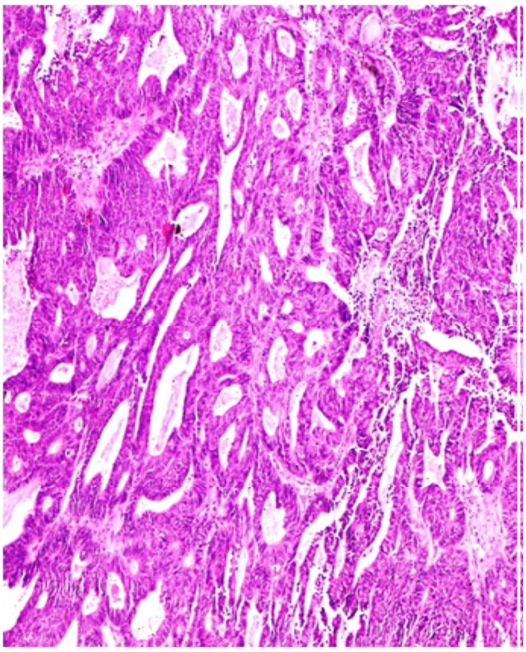

Fig 5 showing sinonasal adenocarcinoma

DISCUSSION

Histopathological examination of sinonasalpolypoidal masses show a spectrum of lesions ranging from non-neoplastic ones to neoplastic tumours including benign and malignant neoplasms. The present histopathological study included 181 non-neoplastic and neoplastic lesions of nasal cavity and paranasal sinuses .Of these lesions, 114 were non-neoplastic and 67 were neoplastic forming a ratio of non-neoplastic to neoplastic lesions as 1.8:1. Out of 67 neoplastic lesions, 46 were benign and 21 were malignant forming a ratio of benign neoplastic to malignant lesions as 2.2:1. Among non neoplastic lesions nasal polyp was most common lesion forming 107 cases. The incidence of nasal polyps in our study is 93.85% of all the non-neoplastic lesions of nasal cavity and paranasal sinuses; 85 (74.6%) being inflammatory nasal polyps and 22 (19.3%) being allergic polyps. As compared to the observation by Tondon et al 1971 (23) i.e. 64% and Anjali et al 1997 (3) i.e. 62.85%, the incidence of nasal polyps is slightly higher in our study. Zafar et al 2008[2] and Modh et al 2013[24]reported an incidence of 82.06% and 83.64% in their respective studies. These observations are comparable with our results. More than 50 % of our non-neoplastic cases were in the 2nd and 3rd decade of life which is comparable with study of Ghosh and Bhattacharya 1966[25] and there was male predominance similar to other studies conducted by Zafar et al 2008[2] and Ghosh and Bhattacharya 1966[25]. In our study of 67 neoplastic 46 were benign (68.65%) and 21 were malignant (31.3%). Tondon et al 1971 [23] observed 74.6% of benign lesions as compared to malignant lesions. Modh et al [24]observed that benign lesions (69.23%) predominated over malignant lesions (30.77%) in their study. Thus our study matches with the above mentioned studies.

Papillomas in the nose and paranasal sinuses are stated to be commonly occurring benign epithelial neoplasm[3]. We had 36 cases of papillomas forming 19.88% of all the lesions of nose and paranasal sinuses which is similar to results of other studies. In our study inverted papilloma (65.20%) formed the commonest lesion among benign neoplastic lesions. Panchal et al 2005[26] also observed inverted papilloma as the commonest benign neoplasm (80%) in their study which is consistent with our observation. In our study maximum number of cases was seen in the 3rd decade (10 cases) & 5th decade (9 cases) of life. Ghosh and Bhattacharya 1966[25] also observed the peak incidence in 3rd decade However, Robin et al 1979[27] had observed peak incidence in 2nd decade whereas, Panchal et al 2005[26]observed peak age incidence in 4th and 5th decade of life. So it appears that the age incidence of inverted paplloma is widely variable In the present study, there were 22 males and 14 females forming a sex ratio of 1.57:1. Buchanan &Slavin1972[28] and Bielamowicz et al 1993[29]also observed male preponderance in their respective studies.

Hemangioma formed the second most common benign neoplastic lesion in present study constituting 15.21% cases of all benign neoplastic lesions. Ghosh & Bhattacharya 1966[25], Tondon et al 1971[23] and Modh et al 2013[24] had found the incidence of hemangioma to be 7%, 5.88% and 4.32% respectively, which is close to our study.

The malignant polypoid tumours of nose and nasal sinuses constitute an important and a varied group.In our study squamous cell carcinoma was the most common malignancy encountered constituting 42.90% of all malignant neoplasms.The incidence of squmous cell carcinoma was 36.60% , 48.99% and 72.70% in studies respectively conducted by Panchal et al 2005[26] , Anjali et al 1997[3] and Ghosh & Bhattacharya 1966[25].In our study maximum cases were seen in 5^{th} and 7^{th}decade. Acheson et al 1970[30] and Sagar et al 2013[31]also observed peak incidence in 5^{th} to 7^{th} decade of life which matches with our observations.

HPV types 6, 11, 16 and 18 were initially identified in genital tract lesions. These same HPV types have been identified in upper respiratory tract lesions, most notably in respiratory papillomas (HPV 6 and 11)[32].

To determine the role of human papillomavirus virus (HPV) in the aetiology of sinonasalpapillomas and squamous cell carcinomas, 30 inverted papillomas, 6 exophyticpapillomas and 9 squamous cell carcinomas were examined for presence of HPV DNA by polymerase chain reaction (PCR).The genetic studies were performed on the formalin-fixed, paraffin-embedded material.

In the present study out of 30 inverted papillomas 4 (13.33%) were found positive for presence of HPV, whereas HPV positivity was observed in 3 (50%) exophyticpapillomas.Out of 9 squamous cell carcinomas HPV positivity was observed in 2 (22.2%) cases.

Out of 2 Squamous cell carcinomas positive for HPV, 1 (50%) was found to be positive for HPV 16 and 1 (50%) for both HPV 16 and 18. Out of 4 HPV positive inverted papillomas, 1 (25%) was positive for HPV 6, 2 (50%) for HPV11 and 1 (25%) for both HPV 6 and 11. Out of 3 HPV positive exophyticpapillomas, 2 (66.67%) were positive for HPV 6 and 1 (33.33%) for both HPV 6 and 11.

From our study we observed an overall HPV 6 positivity in 5 (13.88%) and HPV 11 positivity in 4 (11.11%) sinonasalpapillomas. None of 9 cases of squamous cell carcinomas showed positivity for HPV 6 or HPV 11.

HPV 16 positivity was seen in 2 (22.22%) and HPV 18 in 1 (11.11%) of squamous cell carcinomas. None of 36 sinonasalpapillomas showed positivity for HPV 16 or 18.

Weber et al 1988[16] observed HPV 6 and 11 in 16 (78%) of 21 inverted papillomas by ISH. The authors also concluded that one case revealed transition from papilloma to carcinoma in situ to invasive, moderately differentiated squamous cell carcinoma. Furuta Y et al 1990[33]had observed HPV 16 and HPV 18 in 4 cases (10%) of inverted papilloma and in one case (2.5%) of squamous cell carcinoma respectively. Also HPV 16 was detected in 2 of 7 cases in which IP was associated with SCC.

Brandweinet al 1989[34]detected HPV 6 and HPV 11 in 5 from 7 examined cases of inverted papillomas (71%).

Kashima et al 1992[8] observed HPV in 7 (24%) of 29 inverted papillomas, 4 (15%) of 24 squamous papilloma and 1 (4.16%) of 24 squamous cell carcinomas. Of these HPV 6 was identified in 5 specimens (3 exophytic and 2 inverted papillomas), HPV 11 in 6 specimens (1 exophytic and 5 inverted papillomas) and HPV 18 in 1 of 24 squamous cell carcinomas. HPV 16 was not identified in any of the specimens.

Furuta et al 1993[35] determined the prevalence of HPV types 16 and 18 in 60 cases of carcinoma arising from the nasal cavities (NC) and paranasal sinuses (PNS) by using the polymerase chain reaction (PCR). HPV 16 and 18 were detected in 7 of the 49 cases (14%) of squamous cell carcinoma. In the other histologic types of carcinoma (n = 11), neither HPV 16 nor HPV 18 was detected. These results are in accordance with our observations.

Tang et al 1994 [32]detected HPV 6/11 in six of seven exophyticpapillomas (86%) but there was no evidence of HPV in 26 cases of inverted papillomas.

Buchwald et al 1995[21] found HPV in 6% of 52 inverted papillomas and 69% of 16 exophyticpapillomas which are similar to our observations. HPV 6/11 was identified in all of these HPV positive cases. In SCC's, HPV was detected in 2 (1 HPV 6/11 and 1 HPV 18).

Kraft et al 2001[36] detected HPV in 60% of exophyticpapillomas and 3% of 29 inverted papillomas. In particular HPV -11 was found in 3 lesions (2 exophyticpapillomas, 1 inverted papilloma) (8%) and HPV 6b was detected in one lesion 1 exophytic papilloma (3%). No HPV was detected in any of four carcinomas.

CONCLUSION

Categorizing the sinonasal lesions according to histopathological features into various types helps us to know the clinical presentation, clinical outcome and prognosis of the disease. Also low risk HPV types 6 and 11 show an association with sinonasalpapillomas and oncogenic HPV types 16 and 18 with squamous cell carcinomas

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