RESEARCH ARTICLE

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HPV Infection is Associated with FoxM1 Overexpression in Dysplastic Changes of Sinonasal Inverted Papilloma

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Abstract

Background: This study aims to describe the factors associated with dysplastic changes in sinonasal inverted papilloma (SIP) including somatic EGFR mutation, FoxM1 expression, HPV status, and their association with dysplastic changes. **Methods:** A cross-sectional, analytical study was conducted comprising 34 samples of histologically-confirmed diagnosis of SIP. The samples were further grouped into 2 groups: 20 samples without associated dysplastic changes, and 14 samples with associated dysplastic changes. The numbers of FoxM1 positively-expressed cells, EGFR mutation, and HPV status were compared among two groups using appropriate comparative statistics. **Results:** There was statistically-significant difference of FoxM1 expression between SIP and SIP with dysplasia (10% vs 100%; p<0.001). EGFR mutation was identified in 6 samples (30.0%) of the SIP and 5 samples (35.7%) of SIP with dysplasia. No difference of EGFR mutant proportion among two groups. HPV DNA was detected in 5 samples (25.0%) of SIP versus 9 samples (64.3%) of SIP with dysplasia. There was significant difference of HPV status among two groups (p=0.022). The high-risk subtypes were found in most HPV positive samples (57.1%), while low-risk subtypes and out panel subtypes were found 14.3% and 21.4%, respectively. **Conclusions:** FoxM1 was overexpressed in SIP with malignant transformation. FoxM1 along with HPV status is associated with dysplastic changes in the SIP. FoxM1 immunostaining is potential to be a biomarker of malignant transformation in SIP.

Keywords: Sinonasal inverted papilloma- dysplastic changes- FoxM1- EGFR mutation- HPV

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Introduction

Sinonasal inverted papilloma (SIP) is a benign inward growth of surface epithelia (the pseudo-stratified ciliated or Schneiderian epithelia) that line the nasal cavity and sinonasal tract. Although it is categorized as a benign neoplasm, SIP has been known for its "invasiveness", recurrency, and its tendency toward malignant transformation compared to the other histologic types (Kim et al., 2012). Malignant transformation of sinonasal inverted papilloma was reported to be as much as 5-15% of all cases, mostly in synchronous fashion (Bishop, 2017).

The mechanism of malignant transformation in SIP has not yet been fully understood. Recent studies found that epidermal growth factor (EGFR) mutations that has been previously reported in many cancers, notably in non-small cell lung cancer of the lung has been identified in SIP. The specific mutations aforementioned are within exons 18-21, which encode tyrosine kinase domain (Sharma et al., 2007). As many as 88% of sinonasal inverted papilloma and 77% sinonasal inverted papilloma-associated carcinoma were reported to be have EGFR mutation, with majority of mutations are exon 20 insertions (Udager et al., 2015).

The importance of human papillomavirus (HPV) infection in malignant transformation of SIP is still contradictory. The detection rates of HPV in literatures were ranging between 0 to 100% that may due to different method used in detecting HPV (Bishop, 2017). It has been known that HPV disrupts imbalance between cellular proliferation and apoptosis that leads to tumor development by integrating its genetic material into host DNA that leads into production of E6 and E7 oncoproteins (Re et al., 2017). HPV also plays a role to upregulate the expression of EGFR mediated by E6 activities. A significantly higher expression of EGFR was found in HPV positive compared to HPV negative tumors (Elliot et al., 2020). Additionally, other factors, including age (>25 years), are likely attributed to the increase in the positivity of HPV (Chalabiani et al., 2017). However, other study has found that HPV infection and EGFR mutation may involve separate pathways of SIP malignant

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transformation (Udager et al., 2017).

There were several new biomarkers recently reported to be involved in malignant transformation in sinonasal papilloma to be sinonasal squamous cell carcinoma. One of them is Forkhead box M1 (FoxM1), a transcription factor belonging to the Forkhead family.(Wang et al., 2019) FoxM1 is a transcription factor downstream of the EGFR/PI3K/AKT cascade, which main role in carcinogenesis is in cellular proliferation and cell cycle regulation (Saba et al., 2016). FoxM1 was reported to be upregulated in several malignancy including breast adenocarcinoma, cervical squamous cell carcinoma, pancreatic adenocarcinoma, nasopharyngeal carcinoma, and others (Laoukili et al., 2007).

In this study, we sought to describe factors associated with dysplastic changes in SIP including somatic EGFR mutation, the expression of FoxM1, and HPV status in SIP and their association with dysplastic changes.

Materials and Methods

Patients and samples

After approval by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia, a retrospective review was conducted for SIP patients' specimens over 6 years period (2014-2019). All cases were reviewed by 2 study pathologists to confirm the diagnosis of SIP and SIP with dysplastic changes using WHO Classification of Head and Neck Tumours criteria. (Hunt et al., 2017) Cases were further classified into groups: a) SIP, if the case were composed mainly of inverted growth in epithelia without any recognizable dysplasia; and b) SIP with dysplastic changes (SIP with dysplasia), if there was any component of dysplasia, without any clear invasion into lamina propria. We excluded cases with prior history of systemic therapy or other type of malignancy. The patients' demographics, recurrence, malignant transformation and radiological data were reviewed using the patients' medical record. The selected paraffin blocks were then processed to analyze FoxM1 expression, EGFR mutation, and HPV infection.

FoxM1 Immunohistochemistry

Sections of formalin-fixed, paraffin-embedded tissues were prepared for immunohistochemical analysis. Following deparaffinization and rehydration, the specimens were incubated with rabbit monoclonal anti-FoxM1 (EPR17379; Abcam, Cambridge, UK) at a dilution of 1:250, then incubated with the anti-rabbit peroxidase-conjugated secondary antibody (Novolink, Illinois, USA) for 30 minutes. Diaminobenzidine was used as a chromogen, and the sections were counterstained with hematoxylin and cover slipped. Two study pathologists performed a separated review of immunohistochemistry slides. The FoxM1 is localized in the nucleus. Therefore, the FoxM1 was assessed quantitively as the percentage of cells with positive staining in randomly ten high power fields. The cutoff was determined by ROC of the data. Percentage of lower than 11.67% would be categorized as negative, meanwhile percentage greater than equal to more than 11.67% would be categorized as positive. FoxM1 immunohistochemistry test was performed at Immunopathology Laboratory, Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, Indonesia.

HPV Detection

The DNA of the tissues inside the paraffin blocks were extracted using QIAamp DNA FFPE Tissue Kit (Qiagen). The extracted DNA was then processed into conventional PCR, targeting the MY09/11 primers first, and then GP5+/6+ primers. The resulting PCR products from both primers were then interpreted by electrophoresis using Gel doc (Biorad) by targeting 450 bp band for MY09/11 and 150 bp band for GP5+/6+. Samples with positive HPV then tested for subtyping. Human papillomavirus subtype testing was conducted by flow through hybridization technique using GenoFlow Human Papillomavirus Array Test-Kit, (GenoFlow; DiagCor Bioscience, Hong Kong). The HPV genotyping results were read from the cellulose membrane in the form of dot blots in a probe with a specific marker the the appropriate subtypes were recorded. HPV detection test was performed at Molecular Pathology Laboratory, Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, Indonesia.

EGFR Mutation Status

The DNA was harvested from the tumor-containing areas using GeneAll Exgene DNA Extraction Kit (GeneAll Biotechnology, Seoul, Korea, Cat. No. 108-101) according to the instructions of the manufacturer. The EGFR mutation was examined using qualitative real-time polymerase chain reaction (qRT-PCR). The DNA samples were assayed using the AmoyDx® EGFR 29 mutations detection kit (Amoy Diagnostics, Xiamen, China), according to the manufacturer instructions. The quantitative PCR was performed using Bioneer EicyclerTM 96 Real-Time Quantitative Thermal Block. The PCR condition was as recommended by the manufacturer. The EGFR mutation status was determined by qRT-PCR with high-resolution melting (HRM) analysis. EGFR mutation analysis was performed at Molecular Pathology Laboratory, Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Indonesia.

Statistical Analysis

Statistical analyses were performed using SPSS v25.0 software program. Chi-square or Fisher's test was used to compare between categorical groups, while unpaired T or Mann-Whitney test was used to compare nominal groups. A p-value of <0.05 was considered statistically significant.

Results

Patients' Characteristics

Thirty-four subjects of histologically confirmed diagnosis of SIP from which both slides and blocks were identified. Among them, 14 subjects showed areas of dysplastic epithelia without stromal invasion. The clinicopathologic features of both groups are shown in Table 1. Majority of subjects were male in both groups

(70% and 71.4%), with the mean of age was 53.3±11.9 in SIP and 48.3±10.1 in SIP with dysplasia. There was no significant difference in sex or age characteristics in both groups. Only 15% of SIP group was reported to be recurred.

On the other hand, 50% of SIP with dysplasia had at least one recurrence throughout time. No patient in the SIP group was recorded to progress to be carcinoma, while 85.7% patients of SIP with dysplasia did. Most malignant transformations were in synchronous fashion.

FoxM1 immunohistochemistry

In this study, FoxM1 expression was found to be localized in the nuclei. We observed that positive cells were preserved in basal and parabasal layers of hyperplastic epithelia in SIP group, meanwhile the positive cells were approaching the surface of epithelia in the SIP with dysplasia (Figure 1). The FoxM1 immunopositivity was found to be positive in 16 samples, with all SIP with dysplasia samples were positive with FoxM1 immunohistochemistry (Table 1). There was a significant difference of FoxM1 expression among the groups ($p<0.001$).

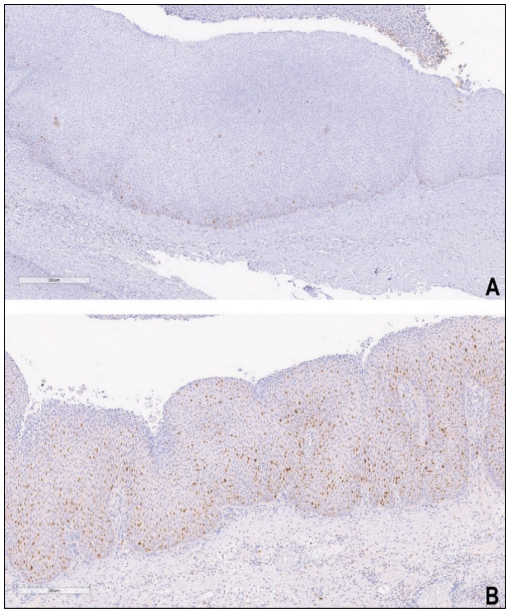

Figure 1. FoxM1 Expression in SIP Samples. A, Negative expression, less than 10% cells were expressing FoxM1; B, Positive expression, more than 10% cells were expressing FoxM1. A-B. FoxM1 immunohistochemistry, 8.4x. SIP, sinonasal inverted papilloma; FoxM1, Forkhead box M1

HPV status

Human papillomavirus DNA were found in 25% samples in SIP group and 64.3% samples in SIP with dysplasia group, with nested PCR using MY09/MY11 and GP5+/GP6+. Positive nested PCR then continued with flow through hybridization for genotyping. In SIP group there were 5 samples positive for HPV infection: 4 samples were positive for high risk-HPV (types 16, 18, 56, and 66/68) and 1 sample was positive for type 81 (low risk-HPV). In SIP with dysplasia there were 9 samples positive for HPV infection: 4 samples were positive for high-risk HPV (types 18, 56, and 66/68), 3 samples were positive with unknown subtype (out panel), 1 sample was positive for low risk-HPV type 43/44, and 1 sample was positive for both high risk-HPV type 56 and low risk-HPV type 11.

EGFR mutation

Overall EGFR mutation numbers in our samples were 30% in SIP group and 35.7% in SIP with dysplasia group. In SIP group, there were 6 samples EGFR mutant: 3 samples with common mutation (19 del, L858R), 2 samples with uncommon mutation (G719X, 20 ins), and 1 sample with mixture common and uncommon (19 del, 20 ins). In SIP with dysplasia there were 5 samples EGFR mutant: 4 samples with common mutation (19 del, L858R)

Table 1. Clinicopathologic Characteristics of Subjects

Parameter	SIP	SIP with dysplasia	p-values
Sex, n (%)			
Male	14 (70.0)	10 (71.4)	0.618[a]
Female	6 (30.0)	4 (28.6)	
Age, mean (SD)	53.3 (11.9)	48.3 (10.1)	0.209[b]
Recurrence, n (%)			
Yes	3 (15.0)	7 (50.0)	0.035[a]
No	17 (85.0)	7 (50.0)	
Malignant transformation			
Synchronous	0 (0.0)	5 (57.1)	<0.001[c]
Metachronous	0 (0.0)	4 (28.6)	
No progression	20 (100)	2 (14.3)	
FoxM1 expression			
Positive	02 (10.0)	14 (100)	<0.001[d]
Negative	18 (90.0)	0 (0.0)	
Total	20 (58.8)	14 (41.2)	

[a]Fisher's test; [b]Unpaired T-test; [c]Mann-Whitney test; [d]Chi-square test; SIP, sinonasal inverted papilloma; FoxM1, Forkhead box M1

Table 2. Factors Associated with Dysplastic Changes in SIP

Variables	Group		P value	OR (95%CI)
	SIP, n (%)	SIP with dysplasia, n (%)		
HPV infection	5 (25.0)	9 (64.3)	0.022[a]	5.4 (1.2–24.0)
EGFR mutation	6 (30.0)	5 (35.7)	0.505[b]	1.4 (0.30–6.47)
FoxM1 expression	2 (10.0)	14 (100)	<0,001[a]	214.6 (9.5– 4827.3)

[a]Chi-square test; [b]Fisher's test; SIP, sinonasal inverted papilloma; HPV, human papillomavirus; EGFR, epidermal growth factor; FoxM1, Forkhead box M1

Tabel 3. Association among HPV Infection, EGFR Mutation, and FoxM1 Expression

Variables	FoxM1 Expression		P value	OR (95%CI)
	Positive, n (%)	Negative, n (%)		
HPV infection				
Yes	9 (64.3)	5 (25)	0.022a	5.4 (1.22–23.96)
No	5 (35.7)	15 (75)		
EGFR mutation				
Mutant type	5 (35.7)	6 (30.0)	0.505b	1.3 (0.30–5.54)
Wild type	9 (64.3)	14 (70.0)		

[a]Chi-square test; [b]Fisher's test; HPV, human papillomavirus; EGFR, epidermal growth factor; FoxM1, Forkhead box M1

and 1 sample with uncommon mutation (20 ins).

Association between FoxM1 expression, HPV infection, and EGFR mutation

We sought the difference of HPV infection status, EGFR mutation and FoxM1 among SIP and SIP with dysplasia groups. (Table 2). There was significant difference in HPV infection status and FoxM1 expression in SIP and SIP with dysplasia (p=0.022 and p<0.001 respectively). However, we found there was no difference in EGFR mutation between both groups (p=0.505).

Further analysis between variables showed there were significant difference in FoxM1 between HPV positive tumor and HPV negative tumor (p=0.022), but not in mutant and wild-type EGFR tumor (p=0.505; Table 3). There were three cases (21.4%) that simultaneously detected for HPV infection and EGFR mutation, all of them are in SIP with dysplasia group.

Discussion

Sinonasal inverted papilloma is an uncommon benign neoplasm arising from sinonasal surface epithelia that has propensity to undergo malignant transformation. We observed 34 subjects that had previously diagnosed histologically as SIP. Most of subjects were male (70%) with male to female ratio of 2.4:1. There was similar distribution sex among groups (SIP vs SIP with dysplasia) and no significant difference between groups. The mean age of SIP was 53.3±11.9 and SIP with dysplasia group was 48.3±10.1 years. There was no difference in age distribution between groups. The sex and age distributions were consistent with previous studies that SIP were found mainly in male (2.5-3.5 times more frequent than female) with mean age of fifth decade of life.(Kim et al., 2012; Udager et al., 2017).

In literature, malignant transformation rate of SIP was reported to be between 5-27%. Malignant transformation occurs in a stepwise manner starting from epithelial dysplasia – in situ carcinoma – invasive carcinoma. There is no widely used-consensus in grading epithelial dysplasia in SIP currently.(Hunt et al., 2017) Dysplasia is associated with poor prognosis i.e., higher chance of tumor recurrence and more aggressive behavior.(Safadi et al., 2017; Lee et al., 2019) The presence of dysplasia will drive the surgeon to conduct a more aggressive surgery to prevent possibility of recurrence.(Ferrari et al., 2020) In this study we found that the presence of dysplasia was associated with higher chance of recurrence and malignant transformation.

The mechanisms of malignant transformation studies fell into these categories: the imbalance between cell proliferation and apoptosis, inflammation-mediated oncogenesis, and the role of adhesion molecules.(Yoon et al., 2013) HPV infection has been known to provoke tumorigenesis in various organs by disrupts p53 tumor suppressive activity by producing E6/E7 protein. We observed that HPV infection were more frequently detected in SIP with dysplasia rather than in SIP group (64.3% vs 25%, p=0.022). This result was complementary to previous study that HPV infection indeed played a role. The hypotheses regarding HPV involvement in malignant transformation of SIP has been referred as "hit and run phenomenon". To be developing into malignant, a SIP has to be re-introduced to high-risk HPV infection (whether primary or secondary) and HPV integration.(Lawson et al., 2008).

In this study, we analyzed 34 samples of SIP, and found EGFR mutations in tissue of 11 patients (32%): 6 patients (30%) in SIP group and 5 patients (35.7%) in SIP with dysplasia group without any significant difference between groups. All EGFR mutations detected laid in the TK domain of EGFR. Previous studies showed that EGFR mutation was detected in 38-88% of SIP papilloma and 50-77% in SIP papilloma with associated carcinoma.(Udager et al., 2015; Cabal et al., 2020)

Udager et al., (2015) found that EGFR mutation was specific to the SIP and SIP associated carcinoma. The team proposed that EGFR mutations were involved in the early carcinogenesis in SIP-associated carcinoma. Other prognostic significance of EGFR mutations were EGFR wild-type SIP associated with susceptibility to malignant transformation. In addition, Sahnane et al., (2019) suggested that EGFR wild type cared a higher risk of squamous cell carcinoma (SCC) transformation in SIP with hazard ratio 2.89.

Several studies have linked the EGFR mutation status and HPV infection. The follow up study from Udager et al., found that in SIP pathogenesis EGFR mutation and HPV infection are mutually exclusive (Udager et al., 2017). More recent studies, however, provided contradictory result (Cabal et al., 2020). In our study, we observed that in SIP group there were alternating result between EGFR mutation and HPV infection, but we did not find similar phenomenon in SIP with dysplasia. There were three subjects (21.4%) that showed both EGFR mutation and HPV infection, two subjects positive for high risk (oncogenic) HPV. We hypothesized that EGFR mutation had to be superimposed with other extrinsic factors e.g., HPV infection only then malignant transformation can occur.

Other biomarker that we used in this study is FoxM1 through an immunohistochemistry examination. FoxM1 is a transcription factor that is involved in cellular proliferation. The role of FoxM1 in carcinogenesis has been studied in several cancers including cervical squamous cell carcinoma, breast carcinoma, nasopharyngeal carcinoma and squamous cell carcinoma of the head and neck (Gomes et al., 2013). FoxM1 involve in carcinogenesis by inducing genomic instability, epigenetic modifications, and promoting angiogenesis. FoxM1 also plays role in progression and metastasis of tumors (Gemenetzidis et al., 2009; Yu et al., 2014). FoxM1 expression was found overexpressed in the SIP with dysplasia compared to the SIP group ($p<0.001$). This finding is helping us understand the molecular pathways of malignant transformation of SIP. Furthermore, FoxM1 is also potential to be a biomarker for early detection of malignant transformation in SIP.

We also observed that FoxM1 expression is higher in HPV positive tumor ($p=0.022$). FoxM1 was reported to be upregulated in HPV-associated cancer. There are several mechanisms that shows interaction of FoxM1 and HPV infection. Upregulation of FoxM1 are responsible for HPV-associated cancer poorer prognosis through the E6/MZF1/NKX2-1 axis, (Chen et al., 2014) Viral oncogenes E6 and E7 target promoters of FoxM1 gene hence increased expression of FoxM1 (Adrian, 2019).

In conclusion, we found that HPV infection and FoxM1 expression were associated with dysplastic changes in SIP. We also found that there was upregulation of FoxM1 in HPV positive-tumor, hence solidify the interaction of HPV infection and FoxM1 in carcinogenesis. We did not observe association of EGFR mutation to the dysplastic changes. We have shown that EGFR mutation and HPV infection represent alternating mechanism but only limited in the series of SIP but not in SIP with dysplasia. These findings may have important prognostic and therapeutic implication for management of SIP and associated carcinomas.

Author Contribution Statement

Lisnawati Rachmadi: Conceptualization, Funding acquisition, Methodology, Supervision, validation, writing - review and editing; Yayi Dwina Billianti Susanto: Investigation, Resources, Supervision, Validation; David Sitinjak: Formal analysis, Data curation, Project administration, Software, Visualization, Writing - original draft; Amelia Fosetta Manatar: Software, Writing - review and editing; Meilania Saraswati: Supervision, Validation; Marlinda Adham: Data curation, Supervision

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Ethical Declaration

The study protocol was approved by the Medical Ethics Committee of Faculty of Medicine, University of Indonesia-Cipto Mangunkusumo Hospital (Number: KET-137/UN2.F1/ETIK/PPM.00.02/2020).

Availability of Data and Material

All the data analyzed and produced in this study are accessible upon reasonable request from the corresponding author.

Conflict of Interest

No potential competing interest is disclosed in this study.

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