World Journal of Otorhinolaryngology-Head and Neck Surgery (2021) 7, 23–27

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Research Paper

The serum squamous cell carcinoma antigen level in inverted sinonasal papilloma and nasal polyps patients

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Received 20 July 2019; received in revised form 29 January 2020; accepted 14 February 2020
Available online 23 March 2020

KEYWORDS
Serum squamous cell carcinoma antigen;
Inverted papilloma;
Nasal polyps;
Rhinitis

Abstract *Objective:* To clarify whether the serum squamous cell carcinoma antigen (SCCA) levels of patients with inverted papilloma (IP) are different from patients with nasal polyps (NP) and rhinitis.
Materials and methods: Serum SCCA levels were measured in 30 patients with IP and 30 patients with NP at one day before surgery and seven days after surgery and measured in 28 patients with rhinitis.
Results: Elevated serum SCCA levels (>1.5 ng/ml) were found in 80.0% of patients in the IP group, 6.7% of patients in the NP group and 14.3% of patients in the rhinitis group, which was a significant difference. The medians of serum SCCA levels in the IP, NP and rhinitis groups were 3.9, 0.8 and 1.1 ng/ml, respectively, which was a significant difference. The SCCA level in IP group was not significantly correlated according to Krouse Staging. There was a significant difference in serum SCCA levels between the pre- and postoperative stages in the IP group, at 3.9 and 0.8 ng/ml, respectively, while in the NP group the levels were 0.8 and 1.0 ng/ml, not significantly different. With regard to the IP diagnosis in the IP and NP group based on the SCCA level (>1.5 ng/ml), sensitivity and specificity was 80.0% and 93.3%, respectively.
Conclusions: The serum SCCA level in patients with IP was elevated and then it decreased after surgery. This was different from NP and rhinitis patients who mostly had normal levels, which did not change.

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.wjorl.2020.02.002

Introduction

Inverted papillomas (IP) are relatively uncommon benign sinonasal tumors with an incidence of 0.5—1.5 cases per 100,000 per year,[1] and are approximately 0.5%—4% of all sinonasal tumors.[2] The male to female ratio is between 3:1 and 5:1, and patient's age ranges from 6 to 89 years (average age 53 years).[3] The clinical problems of IP are a tendency towards local destruction, recurrence, and malignant transformation.[4] The most common presenting symptom is unilateral nasal obstruction and the examination usually detects unilateral masses with polypous appearance, more opaque and rugged than inflammatory polyps. However, inflammatory polyps can coexist with IP in 3.7%—10% of cases.[5,6] For this reason, sometimes on clinical examination, it is difficult to distinguish IP from inflammatory nasal polyps (NP), especially in the patient that the initial tissue biopsy cannot get the pathology to confirm a definite diagnosis of IP, and cause problems due to difference treatment between IP and NP patient.

The squamous cell carcinoma antigen (SCCA) was first isolated biochemically from squamous cell carcinoma (SCC) tissue of the uterine cervix.[7] Serum levels of this antigen in those patients with gynecologic, head & neck, lung, and esophageal SCC are elevated, and the SCCA has been used as a tumor marker in SCC patients.[8,9] However, serum levels of this antigen also have been reported to be elevated in patients with nonmalignant skin, lung disease and IP.[10—12] High serum SCC antigen levels in IP patients may be due to its direct release from the squamous epithelium into the circulation. The serum SCC antigen may have the potential to be a useful biologic marker in patients with IP. Recent studies have shown a close relationship between SCCA levels and IP patients.[12—17] However, there are to date no specific studies which have compared SCCA levels between IP and NP groups.

The aim of this study was to evaluate the clinical usefulness of serum SCCA to distinguish IP patients from the other most common benign tumors, especially NP. We also investigated whether serum SCCA levels correlate with disease status in both IP and NP patients, using rhinitis patients as a control group.

Materials and methods

This prospective study was performed after proper approval by the hospital ethics committee and written informed consent was obtained from all participants. The potential confounders in patients with pulmonary, renal and skin diseases showed elevated serum SCCA levels were excluded. The 30 patients in each group of IP, NP and 30 patients rhinitis included in the study were all treated at Songklanagarind hospital between 2015 and 2018.

IP patients must have nasal endoscopic examination, pathological result to confirm diagnosis with IP and accept to definite treatment with surgery.

NP patients must have nasal endoscopic examination and pathological result to confirm polypoid mass at unilateral or typically bilateral that failed medical treatment, and have to do surgery.

Rhinitis patient must have two or more symptoms of watery rhinorrhea, sneezing, nasal obstruction and nasal pruritus persist more than 1 h on most days, and 2 patients were excluded due to have skin disease (eczema).

Blood samples from enrolled patients in the IP and NP groups were examined to determine their serum SCCA levels at the day before surgery and one week after surgery, with only one sample from each patient in the rhinitis group who had not surgeries related.

Surgical specimens from the patients with IP and NP were examined to confirm the pathology before and after surgery.

The SCCA levels were measured by using the SCCA microparticle enzyme immunoassay (Abbott Laboratories) by laboratory physicians who calibration this test first and did not know details of the patient. An SCCA level below 1.5 ng/ml was considered normal according to the manufacturer's instructions.[18] that was used as the upper limit of normal, representing the 95th percentile in a control group.

The demographic data were recorded and the IP patients underwent a preoperative CT scan and were divided into four staging groups, based on the Krouse's Staging.[19]

Statistical analysis

The differences between patients with normal and elevated serum SCCA levels in the IP, NP and rhinitis groups were statistically evaluated by Chi-square test and within each group by Fisher's exact test. The serum SCCA levels in the IP, NP and rhinitis groups were statistically evaluated by Kruskal—Wallis test (Non normal distribution) and subgroup analysis by Wilcoxon rank sum test. The serum SCCA levels in the IP group according to Krouse Staging were statistically evaluated by Kruskal—Wallis test. The sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of the outlier serum SCCA levels (>1.5 ng/ml) were measured by receiver operating characteristic (ROC) curve analysis. The Wilcoxon signed rank test was used to determine differences between pre- and postoperative SCCA levels in the IP and NP groups. All analyses were performed by using R Software version 2.13.1. Statistical significance was established at the $P < 0.05$ level.

Results

The clinical characteristics of the 30 patients in each group of IP, NP and 28 patients of rhinitis are shown in Table 1. The IP group consisted of 18 male and 12 female participants, and their mean age was significantly higher than that in the NP and rhinitis groups; the mean ages was 55 (45–66), 42.9 (27–64), and 42.7 (22–63) years, respectively. Elevated serum SCCA level (>1.5 ng/ml) was found in 80.0% of the IP group, 6.7% of the NP group and 14.3% of the rhinitis group, which was a significant difference ($P < 0.001$). The median serum SCCA levels in the IP, NP and rhinitis groups was 3.9, 0.8 and 1.1 ng/ml, respectively, which was a significant difference ($P < 0.001$), showed in Table 1. The serum SCCA level in IP group was not significantly correlated according to Krouse Staging (Table 2). There was also a significant difference in serum SCCA levels between the pre- and postoperative stages in the IP group ($P < 0.001$). In the IP group, the pre- and postoperative serum SCCA level was 3.9 and 0.8 ng/ml, respectively, and in the NP group the levels was 0.8 and 1.0 ng/ml, respectively (Table 3). The IP diagnosis in the IP and NP group based on the SCCA level (>1.5 ng/ml), sensitivity and specificity was 80.0% and 93.3%, respectively (Fig. 1).

Discussion

Our results, most of the IP patients (80%) had elevated serum SCCA levels that were in line with previous study that reveal from 81.8 to 90.9% (Table 4).[12–16] Furthermore, we found that higher than NP and rhinitis significantly, but did not had a relation to Krouse's staging system as Yasumatsu et al[13] study. The later study by Yamashita et al[16] reported this controversy, that the SCCA levels more correlated with tumor volume that measure by MRI, because the Krouse staging system is based on tumor location and not tumor size. In the present study, measurement of the SCCA level was found to be useful for IP detection, with high sensitivity (80%) and specificity (93.33%) were similar to Yamashita et al[16] (83.3%, 94.7%) also. We found that the SCCA levels decreased to normal limits (90%) by seven days following the surgery. In line with the other authors,[13–16] that SCCA level was significantly lowered after primary tumor resection. This suggests that the presence of primary tumor is closely correlated with SCCA level. In three cases, the serum SCCA levels were not decreased to normal limits within the 7 days, but we followed these patients closely, and there was no residual or recurrent disease after a year. However, the largest study done to date of serum SCCA in IP patients, suggested that in patients with a serum SCCA level

Table 1 Demographic data and serum squamous cell carcinoma antigen (SCCA) levels.

Characteristics	IP ($n = 30$)	NP ($n = 30$)	Rhinitis ($n = 28$)	*P* value
Gender (%)				
Male	18 (60.0)	23 (76.7)	17 (60.7)	0.350[a]
Female	12 (40.0)	7 (23.3)	11 (39.3)	
Age (Mean, years (SD))	55 (11.6)	42.9 (15.8)	42.7 (20.6)	0.005[b]
SCCA level				
>1.5 ng/ml, *n* (%)	24 (80.0)	2 (6.7)	4 (14.3)	<0.001[a]
Median, ng/ml (IQR)	3.9 (2.3, 7.9)	0.8 (0.6, 1.2)	1.1 (0.7, 1.4)	<0.001[c]

[a] Chi–Square test.
[b] ANOVA F-test.
[c] Kruskal–Wallis test, IP: inverted papilloma, NP: nasal polyps.

Table 2 Pre-operative squamous cell carcinoma antigen (SCCA) levels according to Krouse Staging.

Krouse Staging	*n*	Median (IQR) of pre-op SCCA (ng/ml)	*P* value
1	3	1.1 (1.1, 1.7)	0.108[a]
2	7	5.9 (2.5, 7.8)	
3	20	4.8 (2.8, 8.4)	
4	0	–	

[a] Kruskal–Wallis test.

Table 3 Pre- and post-operative serum squamous cell carcinoma antigen (SCCA) levels.

Group	Serum SCCA (ng/ml), Median (IQR)		*P* value
	Pre-operative	Post-operative	
Inverted papilloma	3.9 (2.3,7.9)	0.8 (0.7,1.2)	<0.001[a]
Nasal polyps	0.8 (0.6,1.2)	1.0 (0.7,1.2)	0.072[a]

[a] Wilcoxon signed rank test.

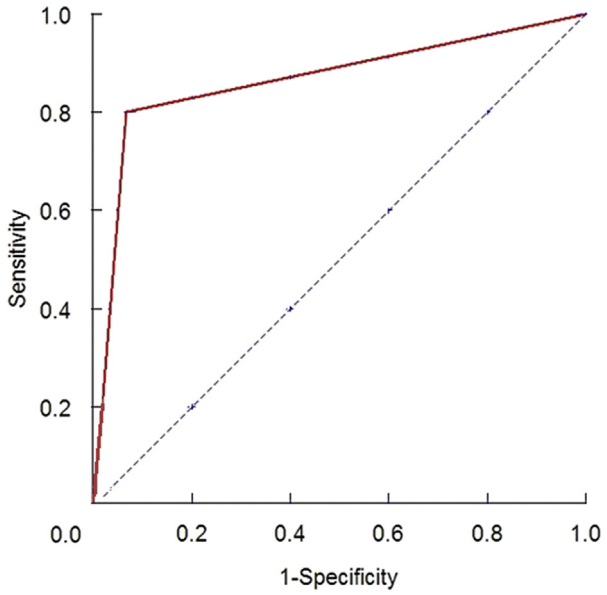

Fig. 1 Receiver operating characteristic (ROC) curve analysis for squamous cell carcinoma antigen (SCCA) levels in the inverted papillomas (IP) and nasal polyps (NP) groups. ROC curve analysis yielded an area under the curve of 0.905.

Table 4 Review serum squamous cell carcinoma antigen (SCCA) levels series of inverted papilloma patients.

First author	Country	Year	*n*	SCCA>1.5 ng/ml (%)	Min	Median	Max
Yasumatsu[12]	Japan	2002	11	90.9	0.8	3.6	8.9
Yasumatsu[13]	Japan	2005	28	89.3	1.1	3.6	6.1
Suzuki[14]	Japan	2012	22	81.8	0	4	8.4
Peter[15]	Czech Republic	2014	20	85	0.7	3.9	7.6
Yamashita[16]	Japan	2016	30	83.3	N/A	2.4	N/A
Chakapan[a]	Thailand	2018	30	80	0.8	3.9	20.3

[a] This study.

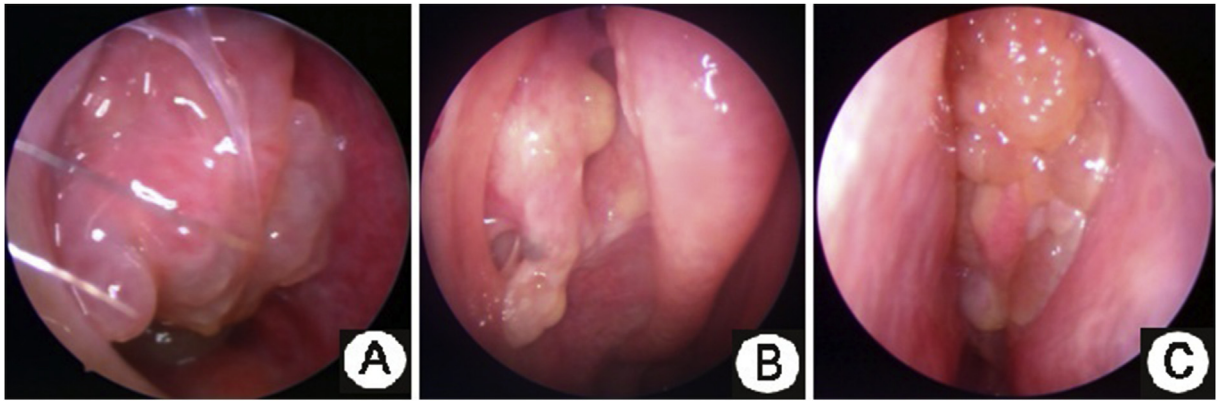

Fig. 2 Endoscopic view of inverted papillomas (IP)'s patient. A: Typical IP opaque and rugged polypous appearance. B,C: IP coexist with nasal polyps.

of 1.6 ng/ml or higher had an imminent chance of developing recurrent disease in the future and recommended frequent follow-ups for this group.[17]

IPs are sinonasal tumors that typically present in the fifth and sixth decades of life and with male dominance.[3] The findings in our series are consistent with those data, as the male to female ratio was 2:1. The average age was 55 years, significantly older than those in both the NP and rhinitis groups. The clinical presentation of IP depends upon the site or sites of involvement, including unilateral nasal obstruction, nasal polyps, epistaxis, rhinorrhoea, hyposmia, and frontal headache. The commonest symptom is progressive unilateral nasal obstruction.[20] The examination usually detects unilateral masses with polypous appearance, more opaque and rugged than inflammatory polyps. Regarding useful preoperative diagnostic procedures for IP, endoscopic studies, imaging, and pathologic examinations are usually recommended. However, inflammatory polyps can coexist with papillomas in 3.7%—10% of cases (Fig. 2) and biopsy of the nasal lesion cannot always detect an IP lesion.[5,6] For this reason, sometimes on clinical examination, it's difficult to distinguish IP from NP patients. Moreover, because the treatment options and disease prognosis are different, it is important that IP patients are identified promptly and are treated with complete surgical removal of the papilloma, but the NP group can be initially treated medically and with less aggressive surgical options.

In recent years several studies have found SCCA levels to be clinically helpful as tumor markers in various malignant neoplasms, including several benign skin and lung diseases.[8—11] There have also been reports that serum SCCA levels were found to be elevated in IP patients, and then decreased following treatment,[12—16] indicating that serum SCCA levels can be useful in the diagnosis of IP, and also in monitoring disease status. In this study, we investigated whether serum SCCA levels correlated with disease status and also compared these levels in similar common sinonasal diseases, NP and rhinitis.

Conclusion

The serum SCCA level could be a diagnostic marker for distinguishing IP patients from NP patients in condition that the clinical and initial tissue biopsy could not get the definite pathologic confirm diagnosis for appropriated treatment planning. The decreasing serum SCCA levels correlates with the treatment status also.

Limitation

In the present study, we could not evaluate the smoking habits of the patients, which may have been a confounding factor for serum SCCA level. According to the Yamashita et al[16] study noted earlier, 2.0 and 1.5 ng/ml might be suitable cutoff levels for smokers and never-smokers, respectively. The power and sample size calculations for evaluating the mean difference of three groups for the primary objective of this study, then it's not to validate for sensitivity and specificity. Finally, IP is known to have a

tendency to recur, and may progress into SCC, and the role serum SCCA in recurrence and transformation to malignancy needs further study.

Statement of ethics

The Ethic Committee at Faculty of Medicine, Prince of Songkla University approved the study protocol. The reference number of the study approval was EC58-109-13-1. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants whose data were included in the study.

Funding sources

The research was supported by a Grant from the Faculty of Medicine, Prince of Songkla University, Thailand.

Author contributions

CP was a major contributor in writing the manuscript. SS drafted the manuscript and designed the figures. PK was measured SCCA level. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Chakapan Promsopa: Conceptualization, Methodology, Writing - original draft. **Supakan Suwansri:** Writing - original draft, Writing - review & editing. **Paiwon Khuntikij:** Visualization, Investigation.

Acknowledgement

This research was supported by the research fund of the Faculty of Medicine, Prince of Songkla University. Sincere thanks to Virat Kirtsreesakul for suggestions.

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Edited by Yi Fang