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Original Article

Significantly higher serum tumor marker levels in patients with oral submucous fibrosis

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Background/purpose: Our previous study showed that carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC–Ag), and ferritin are significantly higher in patients with oral potentially malignant disorders (OPMDs including oral leukoplakia, oral erythroleukoplakia, and oral verrucous hyperplasia) than in healthy controls (HCs). Oral submucous fibrosis (OSF) is also recognized as an OPMD. This study evaluated whether these three serum tumor marker levels were also significantly higher in OSF patients than in HCs.

Materials and methods: The serum CEA, SCC-Ag, and ferritin levels in 41 OSF patients and 164 HCs were measured and compared. Patients with serum CEA level $\geq$3 ng/mL, SCC-Ag level $\geq$2 ng/mL, and ferritin level $\geq$250 ng/mL were scored as serum positive for CEA, SCC-Ag, and ferritin, respectively.

Results: We found significantly higher mean serum CEA, SCC-Ag, and ferritin levels in 41 OSF patients than in 164 HCs (all *P*-values $<$ 0.05). Moreover, 41 OSF patients had significantly

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higher serum positive rates of CEA (39.0%), SCC-Ag (19.5%), and ferritin (53.7%) than 164 HCs (all *P*-values < 0.05). Of the 41 OSF patients, 26 (63.4%), 7 (17.1%), and 2 (4.9%) had serum positivities of one, two, or three tumor markers including CEA, SCC-Ag, and ferritin, respectively. *Conclusion:* There are significantly higher mean serum CEA, SCC-Ag, and ferritin levels and significantly higher serum positive rates of CEA, SCC-Ag, and ferritin in OSF patients than in HCs. The serum CEA, SCC-Ag, and ferritin levels may be served as tumor markers for evaluation of malignant potential of OSF lesions.

Introduction

An estimation of 354,864 new cases of lip and oral cavity cancers was reported in 2018 worldwide, and 177,384 deaths from lip and oral cavity cancers occurred in the same year. However, the global new cases of lip and oral cavity cancers emerging in 2012 were about 300,400, and there were 145,400 deaths from lip and oral cavity cancers in the same year.[1,2] In Taiwan, the data of the Ministry of Health and Welfare show that oral cancer is the fifth leading cause of cancer death in the total population and ranks fourth leading cause of cancer death in males in 2019.[3] The growing number of the newly-diagnosed oral cancers and the increased number of death from oral cancers highlight the importance of early diagnosis and treatment for oral cancers.

Oral squamous cell carcinoma (OSCC) is the most common oral cancers.[4] Oral leukoplakia (OL), oral erythroleukoplakia (OEL), oral verrucous hyperplasia (OVH) and oral submucous fibrosis (OSF) are considered to be common oral potentially malignant disorders (OPMDs).[5—10] The malignant transformation rates of OPMDs are reported to be 1—7% for homogeneous thick OL, 4—15% for granular or verruciform OL, 18—47% (mean 28%) for OEL, 3—17% for OVH, and 7—13% for OSF lesions.[6—9] The high malignant transformation rates of OPMDs also indicate the importance of early diagnosis and treatment for OPMDs.

OSF is a chronic inflammatory disease with deposition of excessive collagen in the subepithelial connective tissue or superficial muscle layer.[10] The onset of OFS is relatively insidious and often lasts for several years. Though OSF patients may complain of stiffness of oral mucosa, difficulty in tongue movements, and limitation of mouth opening in the later phase, the initial symptoms of OSF include burning sensation of oral mucosa and sensitivity to spicy and irritating foods. Several treatment modalities for OSF have been proposed, including surgical intervention, medical treatments, and physiotherapy but there is lack of an effective way for treatment of OSF so far.[11—15] Thus, early diagnosis of OSF is pivotal for prevention of occurrence of OSF.

Biomarkers are the substances that can be detected or measured in some biological or pathogenic processes.[16,17] Many biomarkers have been recognized in human cancers and some of them can even be applied as tools to detect cancers or to predict treatment outcomes; for instance, prostate specific antigen (PSA) for screening prostate cancers,[18] CA15-3 for monitoring breast cancers,[19] and carcinoembryonic antigen (CEA) for detecting colorectal adenocarcinomas.[20] In recent years, more and more associated biomarkers have been proved to be related to OSF.[21—30] The biomarkers involved in OSF can be further categorized into solid tissue markers, serum markers, and saliva markers. Tissue markers associated with OSF include proliferating cell nuclear antigen (PCNA), Ki67, hypoxia-inducible factor 1-alpha (HIF-1α), E-cadherin, Shh, Gli-1, CD1a, CD207, bax, and p53, which are involved in cell proliferation, hypoxia, epithelial—mesenchymal transition, immunity, tumor suppressor genes, cell apoptosis, and angiogenesis.[21—25] Serum markers consist of beta-carotene, copper, malondialdehyde (MDA), and lactate dehydrogenase (LDH). Moreover, LDH can be detected in saliva of OSF patients as well. These markers are involved in antioxidant activity, oxidative stress, and cell metabolism, respectively.[26—30] The number of serum and saliva markers is lower than the number of the solid tissue markers. However, for clinical use, the acquisition of the sera or saliva for marker detection is relatively convenient and accepted by the patients.

Squamous cell carcinoma antigen (SCC—Ag) is the tumor-associated protein and is found to be associated with the uterine cervical carcinomas.[31,32] Elevated serum SCC-Ag level and high serum SCC-Ag-positive rates in OSCC patients have been reported in several studies.[33—36] Also, the serum SCC-Ag level has been proved to have potential to detect the recurrence and metastasis during the follow-up period in post-operative SCC patients.[31—36] A more recent study has demonstrated that the serum SCC-Ag, ferritin, and CEA levels in OSCC patients are significantly increased, when comparing to those in patients with benign oral tumors or healthy control subjects.[37] Our recent study has assessed the serum CEA, SCC-Ag, and ferritin levels in OL, OEL and OVH patients and found significantly higher mean serum CEA, SCC-Ag, and ferritin levels and significantly higher serum positive rates of CEA, SCC-Ag, and ferritin in these OL, OEL and OVH patients than in healthy control subjects.[38] Thus, the serum CEA, SCC-Ag, and ferritin levels are tumor markers for evaluation of malignant potential of OL, OEL and OVH lesions.[38]

Oral risk habits including betel quid chewing, cigarette smoking, and alcohol consumption are involved in the multistate progression of the OPMDs in Taiwan.[39] The betel quid chewing habit is a major risk factor of OSF and the concurrent use of cigarette and alcohol results in synergistic

effects on malignant transformation of OSF.[40,41] Taken together, the main purpose of this study was to assess whether OSF patients may have significantly higher mean serum CEA, SCC-Ag, and ferritin levels and significantly higher serum positive rates of CEA, SCC-Ag, and ferritin than healthy control subjects. In addition, the relations between these serum markers and oral risk habits in OSF patients were further evaluated as well.

Materials and methods

Study participants

The study subjects in this study consisted of 41 OSF patients (39 men and 2 women; age range, 23—69 years; mean 43.9 ± 11.9 years). All the OSF patients were seen consecutively, diagnosed, and treated in the Department of Dentistry, Far Eastern Memorial Hospital, New Taipei City, Taiwan from 2019 to 2020. This study was reviewed and approved by the Institutional Review Board at the Far Eastern Memorial Hospital (FEMH No.: 107116-E).

The diagnosis of OSF was made when patients exhibited characteristic manifestations of OSF, including paleness of the oral mucosa, prominent fibrous bands or stiffness of the buccal mucosa, and limitation of mouth opening.[42] Because OSF is a clinically-apparent disease, biopsy is usually not performed for the characteristic cases of OSF. However, when OPMD lesions such as OL, OEL, OVH lesions occurred in OSF patients, biopsy was often performed to rule out epithelial dysplasia and oral malignancy. Three OPMD lesions in three OSF patients were further biopsied in this study and the histopathological results showed epithelial hyperplasia in two lesions and severe dysplasia in one lesion.

The exclusion criteria included patients with autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, pemphigus vulgaris, and cicatricial pemphigoid), other inflammatory diseases, malignancy, serum creatinine concentrations indicative of renal dysfunction (men, > 131 mM; women, > 115 mM), and with a past medical history of stroke, heavy alcohol use, or diseases of the liver, kidney, or coronary arteries. For each OSF patient, four age- (within 3 years of the age of OSF patient) and sex-matched healthy control subjects were recruited from dental patients with dental caries, pulpal disease, malocclusion, or missing of teeth but without any oral mucosal or systemic diseases. Thus, a total of 164 healthy control subjects were included in this study. In addition, none of our participated OSF patients and healthy control subjects had taken any prescription medication for their corresponding oral diseases at least 3 months before entering the study.[43,44]

Patients' oral habits including details of daily/weekly consumption of betel quid, cigarette, and alcohol as well as the duration of these oral habits were recorded. OSF patients were defined as betel quid chewers when they chewed 2 or more betel quids daily for at least one year, as cigarette smokers when they smoked every day for at least one year and consumed more than 50 packs of cigarettes per year, and as alcohol drinkers when they drank more than three days and consumed more than 20 g of pure alcohol per week for at least one year.[43,44] By these definitions, all the 41 OSF patients were betel quid chewers, but the data of cigarette smoking habit were available for 38 OSF patients and the data of alcohol drinking habit were available for 30 OSF patients. We further divided our OSF patients into current chewers and ex-chewers. In addition, the chewers or smokers were further stratified into different groups by their daily consumption of betel quids or cigarettes and duration of these chewing or smoking habit.[43—45]

Determination of serum CEA, SCC-Ag, and ferritin concentrations

After obtaining the signed consent form, the blood samples were drawn from the 41 OSF patients and 164 healthy control subjects for measurement of serum CEA, SCC-Ag, and ferritin concentrations. The serum CEA, SCC-Ag, and ferritin concentrations were determined by the routine tests performed in the Department of Laboratory Medicine, Far Eastern Memorial Hospital. Based on previous associated studies, patients with serum CEA level ≥3 ng/mL, SCC-Ag level ≥2 ng/mL, and ferritin level ≥250 ng/mL were scored as positive for serum CEA, SCC-Ag, and ferritin, respectively.[33—36,46—52]

Statistical analysis

The mean serum levels of CEA, SCC-Ag, and ferritin were compared between 41 OSF patients and 164 healthy control subjects by the Student's *t*-test. The serum positive rates of CEA, SCC-Ag, and ferritin between 41 OSF patients and 164 healthy control subjects were compared by chi-square or Fisher's exact test, where appropriate. Pearson correlation was used to test whether there were significant correlations between any two of these three markers in OSF patients. The mean serum CEA, SCC-Ag, and ferritin levels between two groups of 41 OSF patients with or without alcohol drinking or cigarette smoking habit as well as between two groups of chewers or smokers consuming different amounts or durations of betel quids or cigarettes, respectively, were compared by the Student's *t*-test. The result was considered to be significant if the *P*-value was less than 0.05.

Results

The mean serum levels of CEA, SCC-Ag, and ferritin in 41 OSF patients and in 164 healthy control subjects are shown in Table 1. The mean serum CEA, SCC-Ag, and ferritin levels were 3.0 ± 1.7 ng/ml, 1.4 ± 1.2 ng/ml, and 282.6 ± 159.8 ng/ml in 41 OSF patients and 1.4 ± 0.7 ng/ml, 0.9 ± 0.3 ng/ml, and 59.9 ± 72.7 ng/ml in 164 healthy control subjects, respectively. There were significantly higher mean serum CEA, SCC-Ag, and ferritin levels in 41 OSF patients than in 164 healthy control subjects (all *P*-values < 0.05, Table 1).

As mentioned previously, patients with serum CEA level ≥3 ng/mL, SCC-Ag level ≥2 ng/mL, and ferritin level ≥250 ng/mL were scored as serum-positive for CEA, SCC-Ag, and ferritin.[33—36,46—52] We found that 39%, 19.5%, and

Table 1 Comparisons of mean serum levels of carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC–Ag) and ferritin between 41 patients with oral submucous fibrosis (OSF) and 164 age- and sex-matched healthy control subjects.

Group	CEA (ng/mL)	SCC-Ag (ng/mL)	Ferritin (ng/mL)
OSF patients (n = 41)	3.0 ± 1.7	1.4 ± 1.2	282.6 ± 159.8
P-value[a]	<0.001	0.01	<0.001
Healthy control subjects (n = 164)	1.4 ± 0.7	0.9 ± 0.3	59.9 ± 72.7

[a] Comparisons of means of parameters between 41 OSF patients and 164 healthy control subjects by Student's *t*-test.

53.7% of 41 OSF patients were serum-positive for CEA, SCC-Ag, and ferritin, respectively (Table 2). The serum CEA, SCC-Ag and ferritin positive rates were significantly higher in 41 OSF patients than in 164 healthy control subjects (all *P*-values < 0.005) (Table 2).

We also discovered that parts of OSF patients had the serum positivities of one, two or three tumor markers such as CEA, SCC-Ag, and ferritin. Of the 41 OSF patients, 26 (63.4%), 7 (17.1%), and 2 (4.9%) had serum positivities of one, two, or three tumor markers including CEA, SCC-Ag, and ferritin, respectively (Table 3). Besides, 6 OSF patients had none of serum positivities of CEA, SCC-Ag, or ferritin (Table 3). Moreover, Pearson correlation coefficient demonstrated no significant correlations between any two of these markers in OSF patients (data not shown).

We further investigated whether the oral risk habits might influence the serum tumor marker levels in 41 OSF patients. In this study, all 41 OSF patients were betel quid chewers including 19 current chewers and 22 ex-chewers. The data of cigarette smoking habit were available for 38 OSF patients including 30 smokers and 8 non-smokers. The data of alcohol drinking habit were available for 30 OSF patients including 17 drinkers and 13 non-drinkers. Comparisons of mean serum CEA, SCC-Ag, and ferritin levels between two groups of OSF patients with or without alcohol drinking or cigarette smoking habit as well as between two groups of chewers or smokers consuming different amounts or durations of betel quids or cigarettes, respectively, are shown in Table 4. In general, there were no significant correlations between alcohol drinking, betel quid chewing, or cigarette smoking habit and the serum tumor marker levels in two different groups of OSF patients (Table 4). However, the mean serum SCC-Ag level was found to be higher in betel quid chewers consuming more than 20 quids per day than those consuming less than or equal to 20 quids per day (marginal significant, $P = 0.09$) (Table 4).

Table 2 Comparisons of frequencies of higher carcinoembryonic antigen (CEA ≥ 3 ng/mL), squamous cell carcinoma antigen (SCC–Ag ≥ 2 ng/mL), and ferritin levels (≥250 ng/mL) between 41 patients with oral submucous fibrosis (OSF) and 164 age- and sex-matched healthy control subjects.

Group	Patient number (%)		
	CEA	SCC-Ag	Ferritin
OSF patients (n = 41)	16 (39.0)	8 (19.5)	22 (53.7)
P-value[a]	<0.001	0.001	0.001
Healthy control subjects (n = 164)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Comparisons of frequencies of parameters between 41 OSF patients and 164 healthy control subjects by chi-square or Fisher's exact test, where appropriate.

Table 3 The number and frequencies of patients with one, two or three positivities of serum tumor markers including carcinoembryonic antigen (CEA ≥ 3 ng/mL), squamous cell carcinoma antigen (SCC–Ag ≥ 2 ng/mL), and ferritin (≥250 ng/mL) in 41 patients with oral submucous fibrosis (OSF).

Positivity for serum tumor marker	Patient number (%)
	OSF patients (n = 41)
CEA + SCC-Ag + ferritin	2 (4.9)
CEA + SCC-Ag	2 (4.9)
CEA + ferritin	5 (12.2)
SCC-Ag + ferritin	0 (0.0)
CEA only	7 (17.1)
SCC-Ag only	4 (9.8)
Ferritin only	15 (36.6)
none	6 (14.6)

Discussion

In the past decade, various biomarkers have been discovered to be associated with OSF. These biomarkers may be involved in certain physiological processes or pathological alterations. Hosthor et al. found that the serum copper level is significantly increased in OSF and OSCC patients when compared to that of healthy control subjects.[26] Besides, both OSF and OSCC patients have the betel quid chewing habit, while the healthy control subjects do not have this habit. Because copper ions may damage proteins, RNA or DNA by generation of superoxide radicals that can initiate the malignant transformation process, they concluded that the serum copper ions and the betel quid ingredients may be associated with the pathogenesis and progression of OSF and OSCC.[26] Beta-carotene can reduce free radical damage and probably hamper the development of malignancy. Rathod et al. discovered that 40 OSF patients have decreased serum beta-carotene levels as compared to the 40 healthy control subjects.[27] Moreover, there is the lowest serum beta-carotene level in the most serious OSF patients (with the mouth opening < 10 mm), suggesting the possible protective function of beta-carotene in OSF patients.[27] DNA adducts with malondialdehyde (MDA) detected in oral mucosal cells have been regarded as a risk oral cancer marker. Paulose et al. showed higher serum MDA levels and DNA damages in 30 OSF patients than in 30 healthy control subjects.[28] Hence, MDA, an oxidative biomarker, together with comet assay analysis to

Table 4 Comparisons of mean serum carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC—Ag), and ferritin levels between two groups of oral submucous fibrosis (OSF) patients with or without alcohol drinking or cigarette smoking habit as well as between two groups of chewers or smokers consuming different amounts or durations of betel quids or cigarettes, respectively.

Group	Mean serum tumor marker level ± standard deviation (ng/mL)		
	CEA	SCC-Ag	Ferritin
Alcohol drinking (n = 30)			
Drinker (n = 17)	2.84 ± 1.68	1.39 ± 1.09	294.46 ± 135.15
Non-drinker (n = 13)	3.45 ± 2.19	1.55 ± 1.69	242.88 ± 171.83
P-value[a]	0.39	0.75	0.36
Betel quid chewing (n = 41)			
Current Chewer (n = 19)	2.67 ± 1.49	1.63 ± 1.64	254.25 ± 133.44
Ex-chewer (n = 22)	3.26 ± 1.88	1.18 ± 0.61	307.09 ± 178.87
P-value[a]	0.28	0.23	0.30
Daily consumption (n = 19)			
> 20 quids (n = 9)	3.14 ± 1.64	2.30 ± 2.19	237.48 ± 158.48
≤ 20 quids (n = 10)	2.25 ± 1.29	1.03 ± 0.53	269.35 ± 112.93
P-value[a]	0.20	0.09	0.62
Duration (n = 19)			
> 10 years (n = 9)	2.76 ± 1.76	1.23 ± 0.64	274.31 ± 168.15
≤ 10 years (n = 10)	2.60 ± 1.30	1.99 ± 2.17	236.20 ± 98.57
P-value[a]	0.83	0.33	0.55
Cigarette smoking (n = 38)			
Smoker (n = 30)	3.24 ± 1.91	1.51 ± 1.37	287.38 ± 173.28
Non-smoker (n = 8)	2.26 ± 0.80	1.09 ± 0.57	270.22 ± 128.08
P-value[a]	0.17	0.40	0.80
Daily consumption (n = 30)			
> 20 cigarettes (n = 10)	3.05 ± 1.97	1.62 ± 1.97	316.01 ± 190.79
≤ 20 cigarettes (n = 20)	3.33 ± 1.93	1.46 ± 1.00	273.07 ± 167.16
P-value[a]	0.72	0.76	0.53
Duration (n = 30)			
> 10 years (n = 27)	3.33 ± 2.00	1.58 ± 1.42	290.01 ± 182.72
≤ 10 years (n = 3)	2.37 ± 0.38	0.87 ± 0.06	263.77 ± 21.0
P-value[a]	0.42	0.40	0.81

[a] Comparisons of mean serum tumor marker levels between two groups of OSF patients by Student's *t*-test.

detect DNA damage may be of diagnostic value to identify OSF patients with high risk of malignant potential.[28]

The lactate dehydrogenase (LDH) is a cytoplasmic enzyme in human cells, and its increase in the serum or saliva may reflect the alteration from normal tissue to premalignant lesions or even to oral cancers via glycolysis. Mishra et al. demonstrated significantly higher serum and salivary LDH levels in OSF patients than in the age-matched healthy control subjects.[29] The serum LDH is further shown to be correlated with the frequency of areca nut chewing habit and mouth opening in OSF patients, whereas saliva LDH level was not. Therefore, the serum LDH level may be a good biological marker in evaluation of malignant potential of OSF lesions.[29]

In this study, we found significantly higher mean serum CEA, SCC-Ag, and ferritin levels as well as significantly higher serum positive rates of CEA (39.0%), SCC-Ag (19.5%), and ferritin (53.7%) in 41 OSF patients than in 164 healthy control subjects. These findings indicate that the serum CEA, SCC-Ag, and ferritin levels may be served as important biomarkers for evaluation of malignant potential of OSF lesions.

SCC-Ag is a tumor-associated protein that involves in the pathogenesis and progression of several human SCCs by inhibiting cell apoptosis and promoting tumor cell migration.[53] Although it was first recognized in cervical SCC, several studies have demonstrated the higher serum SCC-Ag levels and serum SCC-Ag positive rates in OSCC patients.[36,46—48,54] Yoshimura et al. have reported a positive correlation between serum SCC-Ag level and clinical stages, lymph node status or recurrence in oromaxillary cancer patients.[36] Yoshida et al. have also proved the close relations between serum SCC-Ag level and the tumor sizes, tumor sites, clinical stages or recurrence in OSCC patients.[47] Similarly, Lin et al. found the elevated serum SCC-Ag levels in OSCC patients and their significant associations with the tumor status and lymph node status. Besides, the serum SCC-Ag positivity is also found to be associated with some prognostic parameters, including disease-free survival, overall survival, and distant metastasis.[48] Thus, significantly higher serum SCC-Ag levels in OSF patients than in healthy controls in this study may suggest the increased malignant transformation potential in OSF patients. However, Travassos et al. did a meta-analysis on

1901 head and neck SCC cases and discovered that the elevated serum SCC-Ag level is significantly correlated to male and advanced TNM stages, but is not significantly associated with overall survival and disease-free survival.[52]

Ferritin is an iron storage protein and elevation of serum ferritin has been found in patients with different cancers. It is generally considered that its elevation in cancer patients is most possibly induced by an inflammatory status. Besides, ferritin can provide abundant iron for DNA synthesis, which is necessary for maintaining the high proliferation potential of cancer cells. Extracellular ferritin may also cause immunosuppressive effects on immune cells, making the cancer immunotherapy more difficult.[55,56] Stevens et al. showed that the increase of ferritin and decrease of transferrin levels may be utilized to predict for the presence of hepatocellular carcinoma.[57] Baharvand et al. found a significantly higher serum ferritin level in 60 oral cancer patients than in healthy control subjects.[51] Therefore, the significantly higher serum ferritin levels in OSF patients than in healthy controls indicate the OSF oral mucosa is under a higher inflammatory status and also has a relatively higher malignant potential.

The CEA is a cell surface glycoprotein and functions as an intercellular adhesion molecule. Dysregulation of CEA inhibits terminal differentiation of epithelial cells and anoikis, and in turn cells maintain a proliferative potential, consequently resulting in tumorigenesis.[58—60] Elevation of serum CEA has been reported to show a close association with colorectal cancers clinically.[20,61] Because the high serum CEA has been also reported in OSCC patients, the significantly higher serum CEA levels in OSF patients than in healthy controls may also suggest the augmented malignant potential for OSF lesions.[33,34,37]

Combination of SCC-Ag and other tumor markers can be applied together for detection of OSCC or head and neck SCC and for prediction of T status, N status, clinical or pathological stages, recurrence, and/or overall or disease-free survival in OSCC or head and neck SCC patients. Kurokawa et al. have shown significantly higher serum positive rates of CEA, SCC-Ag, and immunosuppressive acidic protein (IAP) in OSCC patients than in control patients.[33,34] Kimura et al. also assessed the serum SCC-Ag, CEA, and ferritin levels in a group of head and neck SCC patients.[50] They discovered that serum SCC-Ag levels are correlated with tumor size, lymph node metastasis, clinical stages, and survival rates. However, there are no significant associations between the serum CEA or ferritin levels and the clinicopathological parameters of head and neck SCC patients in their study.[50]

Most previous studies assessed the serum SCC-Ag, CEA, and ferritin levels in OSCC and head and neck SCC patients and only few studies measured the serum SCC-Ag, CEA, and ferritin levels in OPMD patients. Thakur and Guttikonda showed the decreased levels of blood hemoglobin and serum iron and ferritin levels in OSF patients compared with normal control subjects.[30] There is also an inverse correlation between these markers and the severity of OSF, suggesting that blood hemoglobin and serum iron and ferritin levels are reliable biomarkers in OSF patients.[30] Our previous studies have assessed the CEA, SCC-Ag, and ferritin levels in OL, OEL and OVH patients. Significantly higher mean serum CEA, SCC-Ag, and ferritin levels as well as significantly higher serum positive rates of CEA, SCC-Ag, and ferritin were found in OL, OE and OVH patients than in healthy control subjects.[38] Therefore, based on the results of above-mentioned studies, the serum CEA, SCC-Ag, and ferritin levels seem to be potential markers for OPMDs including OL, OEL, OVH, and OSF, and may serve as clinical tools to evaluate the malignant potential of these OPMD lesions.

In regard to the relations between oral risk habits and serum CEA, SCC-Ag, and ferritin levels, in general we found no significant associations of alcohol drinking, betel quid chewing, and cigarette smoking habits with the serum CEA, SCC-Ag, and ferritin levels in OSF patients except a marginally significantly higher mean serum SCC-Ag level in betel quid chewers consuming more than 20 quids per day than in those consuming less than or equal to 20 quids per day (Table 4). Furthermore, although there was no significant difference, the mean serum CEA, SCC-Ag and ferritin levels were higher in smokers than in non-smokers (Table 4); these results were similar to those reported previously in our OL, OEL, and OVH patients.[38] Because the sample size of this study was relatively small, further studies with a large sample size of OSF patients are needed to clarify the exact relations between the serum CEA, SCC-Ag and ferritin levels in OSF patients and the oral risk habits such as betel quid chewing, cigarette smoking, and alcohol drinking.

We conclude that there are significantly higher mean serum CEA, SCC-Ag, and ferritin levels and significantly higher serum positive rates of CEA, SCC-Ag, and ferritin in OSF patients than in healthy control subjects. The serum SCC-Ag, CEA, and ferritin levels may be served as tumor markers for evaluation of malignant potential of OSF lesions.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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