J Oral Pathol Med (2007) 36: 528–32

doi: 10.1111/j.1600-0714.2007.00572.x

www.blackwellmunksgaard.com/jopm

Oral manifestation of chronic mucocutaneous candidiasis: seven case reports

Xiaosong Liu, Hong Hua

Department of Oral Medicine, School and Hospital of Stomatology, Peking University, Beijing, China

BACKGROUND: Chronic mucocutaneous candidiasis (CMC) is a rare disorder characterized by persistent or recurrent candidal infections of the skin, nails and mucous membranes or by a variable combination of endocrine failure as well as immunodeficiency. Oral clinicopathological features of CMC have seldom been described in detail.

METHODS: Seven patients with CMC were reported in the study. The clinical and histological findings, etiological *Candida* species, immunological evaluation, and therapeutic pattern of oral lesions, were analyzed.

RESULTS: Long-standing whitish hyperplastic and nodule-like lesions with exaggerated deep fissure were the typical and characteristic oral manifestations presented by all patients. The tongue was the most common site affected. Histologically, no obvious distinction was found between CMC and other forms of candidal infection. Abnormal proportions of T-lymphocyte subsets and positive titers of autoantibody were observed in three subjects (42.9%) and one patient (14.3%) respectively. Meanwhile, four subjects (57.1%) showed decreased albumin and increased globulin, three cases (42.9%) had high levels of ESR. But no iron deficiency was found. *Candida albicans* was the microorganism isolated from these patients.

CONCLUSIONS: Multiple and widespread candidal infectious lesions can be observed on the oral cavity of CMC patients. Hyperplastic and nodule-like lesion with irremovable whitish patches and deep fissure are the most common oral manifestations of these patients. Dentists, otolaryngologists and pediatricians should be familiar with the clinical appearances of CMC to make an accurate diagnosis. Potential systemic disorders should be concerned to avoid the reoccurrence of oral candidiasis.

J Oral Pathol Med (2007) **36:** 528–32

Keywords: *Candida;* chronic mucocutaneous candidiasis; clinicopathology; oral manifestation; oral mucosa

Correspondence: Hong Hua, Department of Oral Medicine, School and Hospital of Stomatology, Peking University, 22 Zhongguancun Nandajie, Beijing 100081, China. Tel: +86 10 62179977 ext. 2349, Fax: +86 10 62173402, E-mail: honghua1968@yahoo.com.cn
Accepted for publication April 29, 2007

Introduction

Chronic mucocutaneous candidiasis (CMC) is a heterogeneous disorder characterized by persistent or recurrent candidal infection of the skin, nails and mucosa. It can be familial or sporadic, early or adult onset, and may or may not be accompanied by endocrinopathy. The mechanism of CMC is unclear. In general, CMC with endocrinopathy refers to APECED (autoimmune polyendocrinopathy candidiasis ectodermal dysplasia) syndrome, a familial recessive inheritance gene defect associated with the autoimmune regulator, *AIRE* found on locus 21q22.3 (1, 2). Iron deficiency (3, 4) and/or a selective defect in the ability of the cellular immune response to clear *Candida albicans* infection is usually thought to be associated with CMC (5–7). However, the oral clinicopathological features of CMC have not been described in detail. The aim of this study was to examine clinical and histopathological features in the oral mucosa of CMC patients to help clinicians make a rapid and accurate diagnosis.

Subjects and methods

Subjects

Seven patients with CMC aged 5–57 (the median age was 35 years), who visited the outpatient clinic of the Department of Oral Medicine in the School and Hospital of Stomatology, Peking University, China, from 2003 to 2006, were reported in this study. All the patients complained of burning pain and sensitivity of their oral mucosa, as well as their deep-fissured tongue. None of the patients had taken antibiotics prior to the study.

Among these patients, F1 and his father F2, M1 and his father M2 came from two different families. The others were sporadic. S2, a six-year-old girl, appeared with right eyeball-atrophy resulting from purulent keratitis, and has suffered from recurrent oral thrush and urethral candidiasis since the age of 6 months. She was particularly susceptible to colds. Another patient S3, a 57-year-old male, had been diagnosed with diabetes mellitus and

Table 1 Summary of general status of patients

	F1	*F2*	*M1*	*M2*	*S1*	*S2*	*S3*
Age (years)	23	47	8	35	53	5	57
Period of infected (years)	10	19	1	0.5	50	5	0.5
Oral sites infected	LD, P, BM, AC	LD, P, BM	LD, P, BM	LD, P, BM	LD, P, BM, A, PC, AC	LD, P, BM, A	LD, P, BM, A
Onychomycosis	–	–	–	+	+	+	+
Cutaneous lesions	–	–	–	–	–	–	–
Others	RAU	–	RAU	RAU	RAU	Urethral candidiasis, acute laryngitis, susceptible to cold, atrophy of the right eyeball from keratitis	Diabetes mellitus, rheumatoid arthritis

RAU, recurrent aphthous ulcer; A, angle of mouth; P, palate; PC, palate mucosa contacting to denture; BM, buccal mucosa; AC, alveolar mucosa contacting to denture; LD, lingual dorsum.

rheumatoid arthritis for almost 10 years. Clinical details of each subject are documented in Table 1.

Histological procedures
Biopsy specimens from the oral lesions of all subjects were formalin fixed and processed according to routine histological procedures. Hematoxylin–eosin (H&E) and periodic acid-Schiff (PAS)-stained sections were evaluated by light microscopy.

Microbiological procedures
Scrapes from oral lesions were prepared using potassium hydroxide (KOH). Unstimulated whole saliva from each patient was incubated on a Sabouraud Dextrose Agar plate (Jinzhang Medical New Technology Institute, Tianjin, China). CHROMagar plates (Biocell Institute, Zhengzhou, China) were used to identify the yeast species. The API system (bioMerieux, France), the germ-tube formation assay, and the 45°C growth assay were used for species confirmation.

Basic and immunological investigations
Full blood count, erythrocyte sedimentation rate (ESR), liver function, fasting glucose, anti-HIV antibody, serum iron (SI), serum ferrin (SF), total iron binding capacity (TIBC), T-lymphocyte subsets, anti-ENA antibodies and immunoglobulin (Ig), thyroid-stimulating hormone (TSH), complements (C), free triiodothyronine (FT3), free thyroxine (FT4) and serum electrophoresis were examined.

Diagnosis criterion of CMC
Diagnosis of CMC was established based on persistent or recurrent candidiasis of the oral cavity skin and other structures such as fingernails. In addition to this, it can also happen as familial or sporadic, early or adult onset, and with or without association with other generalized disease processes (8).

Saliva culture, histological observation and PAS staining were performed for each case when diagnosis was established. For those seven patients, diagnosis was made on recognition of oral or dermatological manifestations and confirmed by pathological analysis.

Results

Clinical features
There were two females and five males, who are all Han nationalities. All patients fulfilled the diagnostic criterion of CMC based on the evidence of history review, clinical and pathological and laboratory investigations. Seven patients (100%) had long-standing and refractory oral candidiasis (the median period of infection is 5 years), and four (57.1%) had thickened and grey nails which were diagnosed with onychomycosis (Fig. 1).

In oral cavity, the hyperplastic and nodule-like lesions with exaggerated deep fissure and the large scale of irremovable whitish patches were remarkably noticed. The lesions were observed on palate mucosa and lingual dorsum of all subjects (Fig. 2). Moreover, denture-induced stomatitis with hyperplastic lesions, papillae atrophy of the tongue, angular cheilitis with erythema, and *Candida* infection-associated rhomboid glossitis could also be found.

Histopathological features
The most important histological findings showed: (1) epithelial hyperplasia (acanthosis) with thick layer of keratinization; (2) superficial micro-abscesses, intraepithelial; (3) inflammatory cells (mainly neutrophils)

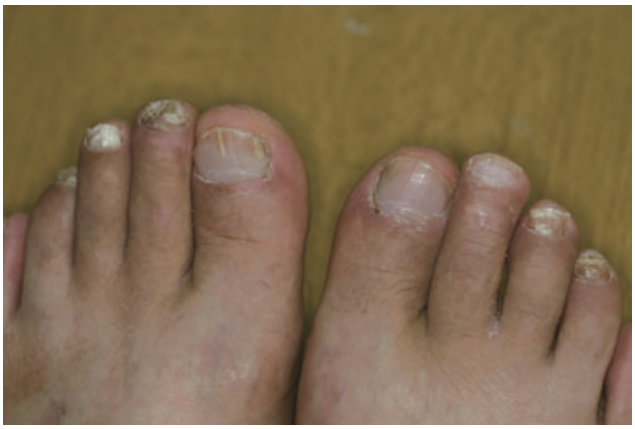

Figure 1 Thickened and grey nails were noted on the toes of patients with CMC.

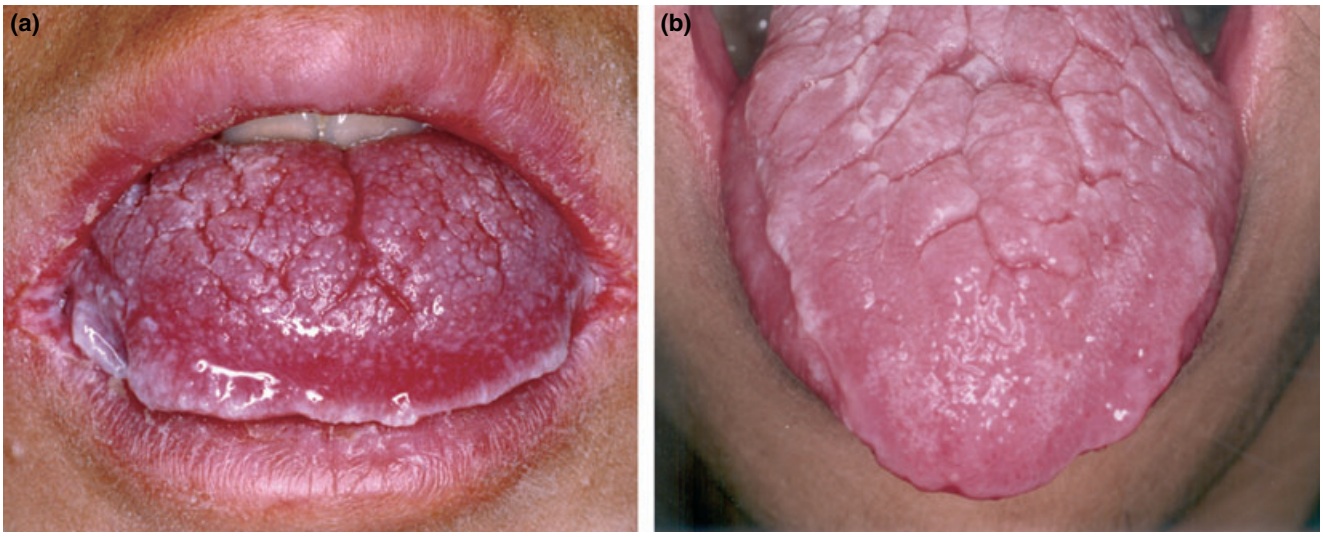

Figure 2 Oral manifestation of CMC. (a) Whitish patches on the reddish surface of lingual dorsum and the edge of tongue of CMC patient, accompanied by angular cheilitis. (b) Nodule-like lesions on the enlarged and deep-fissured tongue of CMC patient.

throughout the layer of the epithelium; (4) intracellular edema adjacent to the micro-abscesses; and (5) large amounts of hyphae of *Candida albicans* in the upper layer of the epithelium under the PAS staining. There was also atrophy in the red area of the mucosa (Fig. 3).

Laboratory investigations

The laboratory details of each subject are documented in Table 2. All subjects were infected with *Candida albicans*. Among them, three patients (42.9%), two children and one adult, showed lower $CD4^+$ T-lymphocyte proportion and/or higher $CD8^+$ T-lymphocyte proportion. One patient (14.3%) had positive titers of autoantibody against α-fodrin (AaFA). Four subjects (57.1%) presented with low albumin and high globulin levels. Three subjects (42.9%) had increased ESR, and only one subject had mild reduction in SI, which could not be identified as iron deficiency because of her normal levels of SF and TIBC. All patients were HIV negative.

Subject S3, one of the patients with changed T-lymphocyte subsets, was diagnosed with megaloblastic anemia for his decreased vitamin B12, increased mean cell volume (MCV) and mean concentration of hemoglobin (MCH). On the basis of diabetes mellitus and reduced serum FT3 and FT4, low T3 syndrome was also identified.

A daily dose of 100 mg of fluconazole was prescribed to all adult patients, but nystatin tablets to children instead. Three percent liquid sodium bicarbonate was used both as a mouthwash and a cleaning agent for dentures. By antimycotic treatment of 3 months, the whitish plaques, burning pain and sensitivity of oral mucosa were resolved completely, but the widespread nodule-like lesions of tongue still remained. No *Candida*

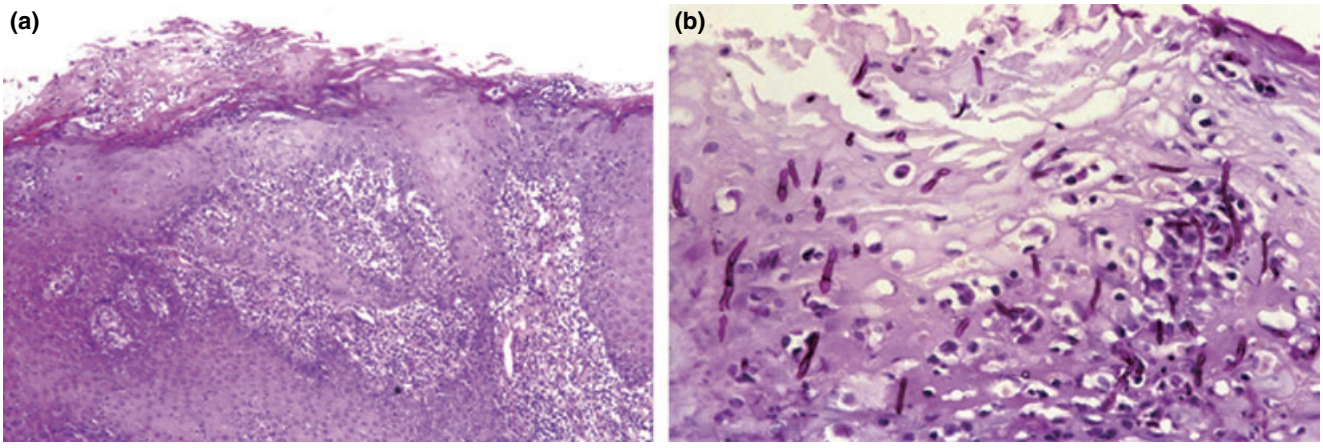

Figure 3 Histopathological features of patient with CMC in microscopy. (a) parakeratinized epithelia and acanthosis; epithelial edema and inflammatory cell especially neutrophil were found in the epithelium (×40 scale, H&E stained). (b) Subepithelial invasion of candidial hyphae and intracellular edema were found adjacent to microabscesses in the subepithelium (×100 scale, PAS stained).

Table 2 Summary of physical investigations and results

	Full blood count, ESR	*T-lymphocyte subpopulation*	*Autoantibody levels*	*TSH, FT3 and FT4*	*SI, SF, TIBC*	*Ig, C, serum electrophoresis*
F1*	ESR: 34 (H)	Normal	Normal	ND	ND	Albumin: 56.9% (L) α1: 3.5% (H) α2: 12.8% (H) γ: 17.6% (H)
F2*	Normal	Normal	AaFA (+)	ND	ND	Albumin: 59.9% (L) α2: 11.4% (H)
M1*	Normal	CD4: 24% (L) CD4/CD8 ratio: 0.67(L)	Normal	ND	ND	Normal
M2	ND	ND	ND	ND	ND	ND
S1*	ESR: 53 (H)	Normal	Normal	Normal	Normal	Albumin: 54.8% (L) α1: 3.5% (H) α2: 11.2% (H) γ: 20.1% (H) IgA: 5.28 (H) IgG: 17.4 (H)
S2**	ESR: 20 (H)	CD8: 35% (H) CD4/CD8 ratio: 0.94 (L)	Normal	Normal	SI: 43 (L)	A/G: 1.35 (L)
S3*	VitB12: 205.8 (L) MCV: 99.7 (H) MCH: 33.4 (H)	CD4: 5.33% (L) CD8: 75.84% (H)	Normal	FT3: 3.42 (L) FT4: 11.25 (L)	SF: 434 (H)	Albumin: 50.4% (L) γ: 29.4% (H) IgG: 27.67 (H) A/G: 0.93 (L)

Some normal parameters are as follows: ESR: male <15 mm/h, female <20 mm/h and children <10 mm/h; albumin: 60.0–71.0%; α1: 1.4–2.9%; α2: 7.0–11.0%; γ: 9.0–16.0%. Albumin/globulin (A/G): 1.49; IgG: 6.94–16.18 g/L; IgA: 0.68–3.78 g/L. VitB12: 240–900 pg/ml; FT3: 3.5–6.5 pmol/L; FT4: 11.45–23.17 pmol/L. SI: 50–120 μg/dl, SF: 13–400 μg/ml; MCV: 80–95 fl. MCH: 27–32 pg. *CD4: 27–51%; CD8: 15–44%; CD4/CD8 ratio: 0.7–2.8. **CD4: 27–57%; CD8: 4–34%; CD4/CD8 ratio: 1.1–2.0. * and ** were normal parameters used in different clinical laboratories.

species were isolated from these patients by KOH smear and saliva culture after 6–12 months follow-up.

Discussion

Chronic mucocutaneous candidiasis is a rare disorder characterized by persistent or recurrent candidiasis of the mucosa, skin and nails. Several classifications of CMC have been proposed. Based on familial or sporadic occurrence, early or adult onset, and the presence or absence of endocrinopathy, CMC was classified as follows: (1) familial CMC without endocrinopathy, either autosomal recessive or autosomal dominant inheritance, early onset; (2) with hypothyroidism, autosomal dominant, early onset; (3) APECED syndrome; (4) chronic localized candidiasis, early onset; (5) candidiasis with the hyper-IgE syndrome, autosomal recessive inheritance, early onset; (6) CMC with thymoma, adult onset; (7) candidiasis with chronic keratitis, early onset; (8) chronic oral candidiasis, adult onset (9). All patients involved in the study were diagnosed with CMC for their recurrent and refractory candidal infection that mainly occurred on oral mucosa and occasionally on nails. According to this, F1, F2, and M1, M2 could be classified as the type of familial CMC without endocrinopathy, and subjects S1 and S3 as the type of chronic oral candidiasis. Subject S2 could be classified as the type of candidiasis with chronic keratitis. However, without the gene mutational analysis, subject S2 could not be excluded completely from the type of APECED syndrome, which is characterized by the presence of two of three major symptoms: Addison's disease, hypoparathyroidism and CMC. In most cases, CMC is the first clinical manifestation of APECED syndrome, and usually appears before the age of 5 years, followed by hypoparathyroidism (usually before the age of 10 years), and later by Addison disease (usually before the age of 15 years) (10).

Differing from the report of a large family of CMC with thyroid disease and inherited in the form of autosomal dominant (5), no sufficient evidence of hypothyroidism was found in this study, although subject S3 showed low levels of FT3 and FT4. The reduced FT3 and FT4 were thought to be secondary to his diabetes mellitus because of his normal TSH, and resulted in vitamin B12 absorption defect and subsequent megaloblastic anemia.

Generally, the defensive mechanism against local candidiasis mainly depends on cellular immunity. Thus, CMC can be secondary to some cellular immunodeficiency diseases, such as HIV infection, Di George syndrome and severe combined immunodeficiency (11). Not only the quantity of T lymphocytes, but the selective dysfunction of T lymphocytes to *Candida* antigens was proved to be related to CMC as well (5–7). In this study, subjects M1, S2 and S3 showed a decreased proportion of $CD4^+$ T lymphocytes and/or increased $CD8^+$ T lymphocytes, and the reduction in CD4/CD8 ratio. Similar to the patients in our study, CMC patients were always with normal humoral immunity to prevent themselves from systemic candidal infection (11).

Previous studies had detected high levels of antibody against adrenal cortex, parathyroid glands and thyroid

glands in APECED patients (12), as well as antibody against thyroid microsomal and antiparietal cell in some family members of CMC without any disorder of thyroid and other endocrine glands (4). Similarly, one patient in our study was observed to have positive titers of AaFA autoantibody, but without clinical manifestation. The correlation of AaFA autoantibody with CMC cannot be concluded immediately; follow-up visits are needed.

With regard to oral manifestation of CMC, no obvious distinction was reported from other forms of candidiasis such as pseudomembranous candidiasis, erythematous candidiasis, hyperplastic candidiasis, and angular cheilitis. Clinically, hyperplastic lesion is seldom seen when compared with other forms of oral candidiasis. However, in our study, multiple and widespread lesions were observed, and meanwhile, hyperplastic and nodule-like lesions with irremovable whitish patches and exaggerated deep fissure were the main manifestations of these patients. Lingual dorsum and upper palate mucosa were the most often affected sites. The oral mucosa underlying dentures also presented with hyperplastic lesions. Reichart *et al*. (13) hypothesized that hyperplastic but not pseudomembranous or erythematous candidiasis was a superficial cellular reaction to *Candida*, that could not be entirely eradicated by systemic or local immune responses. Therefore, the hyperplastic lesions mainly observed in our study might be the result of host reaction to persistent stimulation of hyphae that could not be readily cleared, as these patients were infected with *Candida* for more than 6 months.

Candida albicans was the etiological microorganism. Fluconazole and nystatin were effective treatments for those CMC patients. The whitish plaques, burning pain, and sensitivity were resolved after 3 months of treatment, which is longer than the normal treatment for *Candida*. Longer time is required to recover from the fissured and nodule-like appearances of oral mucosa.

In summary, CMC is not a common disease affecting the oral mucosa, skin and nails. Lesions of oral mucosa may be the initial observation, which could be followed by endocrinopathy or secondary to some rare diseases, such as HIV infection, Di George syndrome, high IgE syndrome and severe combined immunodeficiency. Dentists, otolaryngologists and pediatricians may be visited first by CMC patients. Therefore, it is important to be familiar with the clinical appearances of CMC to make an accurate diagnosis and to prompt the doctors to look for systemic disorders. Furthermore, their potential systemic disorders should be concerned to avoid the reoccurrence of *Candida* infection.

References

1. Nagamine K, Peterson P, Scott HS, *et al*. Positional cloning of the APECED gene. *Nat Genet* 1997; **17**: 393–8.
2. The Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger mutations. *Nat Genet* 1997; **17**: 399–403.
3. Wells RS, Higgs JM, Mcdonald A, *et al*. Familial chronic muco-cutaneous candidiasis. *J Med Genet* 1972; **9**: 302–10.
4. Ee HL, Tan HH, Ng SK. Autosomal dominant familial chronic mucocutaneous candidiasis associated with acne rosacea. *Ann Acad Med Singapore* 2005; **34**: 571–4.
5. Atkinson TP, Schaffer AA, Grimbacher B, *et al*. An immune defect causing dominant chronic mucocutaneous candidiasis and thyroid disease maps to chromosome 2p in a single family. *Am J Hum Genet* 2001; **69**: 791–803.
6. Shih-Jung Chiu, Ching-Hsoung Tsao, Li-Chen Chen, *et al*. Chronic mucocutaneous candidiasis in a 6-year-old boy. *J Microbiol Immunol Infect* 2004; **37**: 196–9.
7. Germain M, Gourdeau M, Hebert J. Familial chronic mucocutaneous candidiasis complicated by deep Candida infection. *Am J Med Sci* 1994; **307**: 282–3.
8. Tyldesley WR, Field EA. *Oral medicine*, 4th edn. Oxfrod: Oxfrod Medical Publications, 1995.
9. Zuccarello D, Salpietro DC, Grangerni S, *et al*. Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis. *J Med Genet* 2002; **39**: 671–5.
10. Betterle C, Greggio NA, Volpato M. Autoimmune polyglandular syndrome type 1. *J Clin Endocr Metab* 1998; **83**: 1049–55.
11. International Union of Immunological Societies. Primary immunodeficiency diseases: report of an IUIS Scientific Committee. *Clin Exp Immunol* 1999; **118**(Suppl. 1): S1–28.
12. Peterson P, Pitkanen J, Sillanpaa N, Krohn K. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): a model disease to study molecular aspects of endocrine autoimmunity. *Clin Expt Immunol* 2004; **135**: 348–57.
13. Reichart PA, Samaranayake LP, Philipsen HP. Pathology and clinical correlates in oral candidiasis and its variants: a review. *Oral Dis* 2000; **6**: 85–91.

Acknowledgements

The authors would like to thank Professor Yan Gao from Peking University and Professor Yanying Xu from NSFC of China for their critical review of the manuscript.