

Milestone of Oral Medicine in Thailand: Faculty of Dentistry, Chulalongkorn University Perspective

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Abstract

Dentist is the first person who has the opportunity to detect abnormal changes in the oral cavity. As oral diseases are frequently associated with systemic diseases, this is important for the patients because early detection and correct diagnosis can save the patients' life. Many oral diseases can cause burning sensation, severe pain and difficulty in speaking, swallowing, and/or eating. These symptoms can tremendously affect the patients' general health as well as their quality-of-life. With the emerging new diseases/infections and the increase in autoimmune disease related oral lesions, achieving accurate diagnosis and effective treatment has been a challenge. Hence, knowledge in oral diagnosis and oral medicine are very important for the dental practitioners. Topical steroid such as fluocinolone acetonide was established in the Faculty of Dentistry, Chulalongkorn University since 1985. Treatment and management of Oral Lichen Planus (OLP), Oral Lichenoid Drug Reaction (OLDR), Recurrent Oral Ulceration (ROU), Glossitis, Pemphigus, Mucous Membrane Pemphigoid (MMP) and research in oral medicine have been discussed. This review presented the interesting oral diseases in Thai patients and milestone of oral medicine in Thailand.

Key words: Fluocinolone acetonide; Lichen planus; Lichenoid; Mucous membrane pemphigoid; Oral; Pemphigus

Received Date: Oct 24, 2014, Accepted Date: Jan 12, 2015

Introduction

Although oral medicine was not an official course at that time of the establishment of the Faculty of Dentistry, Chulalongkorn University in 1940, there were various related courses in the dental curriculum. For examples, General Medicine provided the dental students the knowledge of signs and symptoms in the body that could be related to oral health. Oral diagnosis was documented as an important course in dental curriculum because the accurate diagnosis led to effective treatment of the diseases. Therefore, dental students were required to take the oral diagnosis course. Apart from participating in the out-patient department, oral diagnosis was also a part of the Operative Dentistry department, which comprised the Periodontology, Oral Medicine and Oral Diagnosis led by Professor Issara Yuktanan since 1963. In 1974, Periodontology department was established as individual entity and subsequently was Oral Medicine department. Oral examination and oral diagnosis have been in the curriculum of Oral Medicine course ever since.

Various patients were enrolled to the Oral Diagnosis and Oral Medicine clinic, Faculty of Dentistry, Chulalongkorn University for oral examination, diagnosis and treatment of dental problem or oral mucosal diseases. In Thailand 0.1 % triamcinolone acetonide in orabase was the only commercially available topical steroid, but it was not effective in the treatment of severe oral ulceration. In 1985, Assistant Professor Punni Soomsawasdi, Head of Oral Medicine Department, introduced a new high potency topical steroid named 0.1 % fluocinolone acetonide to the Pharmacology Department, Faculty of Dentistry, Chulalongkorn University. Assistant Professor Somsri Rassamithat, Head of Pharmacology Department and Associate Professor Wanee Taweessap prepared 0.1 % fluocinolone acetonide in the solution (FAS) form first and then in the orabase form (FAO) later.

Research on topical steroids – Fluocinolone Acetonide

Since 1988, the research on topical steroid in the topic of “0.1 % fluocinolone acetonide in orabase in the treatment of oral lichen planus” was supported by Ratchadapiseksoompooch Grant, Chulalongkorn University. Oral Lichen Planus (OLP) is the most common oral lesion in the Oral Medicine clinic and it is a chronic inflammatory disease of unknown etiology characterized by white striae with or without erythematous or erosive/ulcerative area. Patients usually come to Oral Medicine clinic with the chief complaint of burning sensation or pain when eating hot and spicy food. Most of the patients with OLP are middle-aged women.¹ In recalcitrant OLP, control of oral hygiene with topical treatment the OLP lesion with 0.1 % FAO can enhance healing of the lesions without serious side-effects (Fig. 1). Only *pseudomembranous candidiasis* during treatment with FAO may occur, but could be easily resolved with antifungals. There was no adrenal suppression found in all cases after treatment with FAO for 6 months. This study confirmed that this drug was safe for long-term use in chronic lesions such as OLP. Moreover, FAS has been found to be effective, low cost and safe in the treatment of OLP in the long-term follow-up (Fig. 2). The patients from various parts of Thailand, particularly the poor patients, benefitted greatly from these drugs. This resulted in reduced treatment cost and travel expenses of the patients. This research was also published in the Journal Oral Pathology and Medicine in 1992 by the title of “Relative efficacy of fluocinolone acetonide compared with triamcinolone acetonide in treatment of oral lichen planus”.² From this research, Thongprasom *et al.* Clinical Scoring Criteria has been widely used to assess the treatment outcomes, clinical response and the severity OLP lesion in the researches of many International Medical and Dental Journals as follows:³⁻⁹

Score 1 = mild white striae

Score 2 = white striae with atrophic area < 1 cm²

Score 3 = white striae with atrophic area > 1 cm²

Score 4 = white striae with erosive area < 1 cm²
Score 5 = white striae with erosive area > 1 cm²

In 1992, the technology of the preparation of 0.1 % FAO was transferred to the Government Pharmaceutical Organization of Thailand. However, as it was not cost effective for industrial production at that time, this drug had only been prepared in the Faculty of Dentistry, Chulalongkorn University. Nowadays, this drug is widely used by dental practitioners in many universities, hospitals and private clinics in Thailand. Recently, fluocinolone acetonide has been accepted into the National List of Essential Medicines in Thailand. Since fluocinolone acetonide has been widely used and

has been found to be effective with no serious side-effect in long-term follow-up,¹⁰ more topical steroids have been prepared in the Faculty of Dentistry, Chulalongkorn University such as 0.05 % clobetasol propionate, 0.1 % fluocinolone + 1 % clotrimazole gel, 0.05 % dexamethasone mouthwash, 0.01 % triamcinolone acetonide mouthwash and etc. to treat the widespread lesions of oral autoimmune diseases such as pemphigus, mucous membrane pemphigoid, recurrent aphthous ulceration. Not only Thai patients, but also foreign patients with oral lesions referred from various countries, have been treated with these topical steroids.



Figure 1 Poor oral hygiene in a 60-year-old male with OLP, the lesions persisted more than 10 years and no response to any medications. Heavy calculus deposition, furcation involvement on tooth 26, generalized abrasion and deep caries under gingival margin on tooth 37 were seen (mirror image). The left marginal and attached gingiva showed erythematous and ulcerative areas with white striae.
A. Atrophic/ulcerative lichen planus in a patient with poor oral hygiene before treatment
B. After control of oral hygiene and treatment with 0.1 % FAO, gingiva returned to normal after 4-year follow-up.



Figure 2 White striae with erythematous and ulcerative areas on the left buccal mucosa in a 49-year-old female
A. Erythematous and ulcerative areas of OLP on the left buccal mucosa before treatment
B. The OLP lesion showed remission after treatment with 0.1 % FAS in one month. This is after 8-year follow-up.

Recurrent aphthous ulceration, stomatitis and glossitis

Apart from OLP, recurrent aphthous ulceration, glossitis or stomatitis are also commonly found in Thai patients. Recurrent aphthous ulceration defined as a common condition which is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors typically present first in childhood or adolescence. The etiology of this disease is not entirely clear. Stomatitis defined as generalized inflammation of the oral mucosa, whereas glossitis defined as inflammation of the tongue. These disorders affect the quality-of-life of the patients because of chronic pain and burning sensation to hot and spicy food. In 1998, the Government Budget Fund supported us to conduct the applied research in the topic of “Hematological abnormalities in oral lichen planus, recurrent aphthous

ulceration and stomatitis or glossitis”. Our studies were the first to explain the abnormalities of folate and vitamin B₁₂ levels in Thai patients with those diseases.^{11,12} From these results, we found that folate levels should be investigated in patients with symptomatic oral lesions, especially those with risk factors of age, poor nutrition or systemic diseases. Correction of folate and vitamin B₁₂ deficiencies have been found to be useful in the treatment of such lesions (Fig. 3). The recalcitrant oral lesions/ulceration with the underlying diseases showed significant improvement. In addition, patients who had suffered from more than 10 years of painful recurrent oral ulceration or glossitis displayed complete remission of the oral lesions and symptoms. There were no longer food restriction for these patients and their health and quality-of-life had improved tremendously.



A



B

Figure 3 Recurrent oral ulceration and glossitis on fiery red tongue from vitamin B₁₂ deficiency more than 10 years in a 52-year-old female

A. Multiple round and oval oral shape ulceration size 2 - 4 mm on the right lateral surface of the tongue, before treatment

B. After treatment with 1,000 µg hydroxocobalamin injection for 3 months, the tongue returned to normal.

Potentially malignant disorders

OLP is one of the potentially malignant disorders that carry an increased risk of Oral Squamous Cell Carcinoma (OSCC). In 1999, the research entitled “Telomerase activity in oral lichen planus” supported by Government Budget Fund was conducted. The novel research of this kind has

never been reported before in Thailand. New data of OLP in Thai patients suggested that telomerase activity might not be particularly associated with the premalignant phenotype in OLP.¹³ Furthermore, multicenter study of OLP in Thai patients from the North, Northeastern and central parts showed low malignant transformation.¹⁴

Oral lichenoid lesions

Middle-aged or elderly patients with systemic diseases usually take multiple medications, some of which can induce lesions such as oral ulceration, Oral Lichenoid Drug Reaction (OLDR), gingival overgrowth, xerostomia, hyperpigmentation etc. Non Steroids Anti-Inflammatory Drugs (NSAIDs) are commonly used in the elderly patients with arthritis. “Adverse oral reactions associated with the COX-2 inhibitor-Rofecoxib” was the first case report that showed severe oral lesions as the side-effect of this drug. The patient had developed severe oral ulceration that was not responsive to treatment for more than 1 year. Cessation of the suspected drug and replacement with alternative drugs resulted in complete remission of the lesion. Collaboration and good communication between oral medicine specialist and physician were important in the management of drug induced oral lesions. Interestingly, the side-effect presented in oral cavity in this case had

been reported before the Federal of Drug Administration (FDA) withdrew Rofecoxib from commercial use because of its cardiac toxicity.¹⁵ Dental materials such as amalgam can also induce Oral Lichenoid Contact Lesion (OLCL), which is similar to OLP clinically and histopathologically. Removal of amalgam filling followed by resin composite filling replacement usually results in lesion remission.

Immunopathogenesis of OLP

“Expression of TNF- α in oral lichen planus treated with 0.1 % fluocinolone acetonide” was one of the researches conducting in Thailand and showed that cytokine (TNF- α) was involved in the immunopathogenesis in Thai patients with OLP (Fig. 4). Moreover, it was the first study that demonstrated the effectiveness of topical steroid - 0.1 % FAO in inhibiting TNF- α in the OLP lesion.¹⁶ This finding may lead to a new target therapy of chronic oral lesion of OLP.

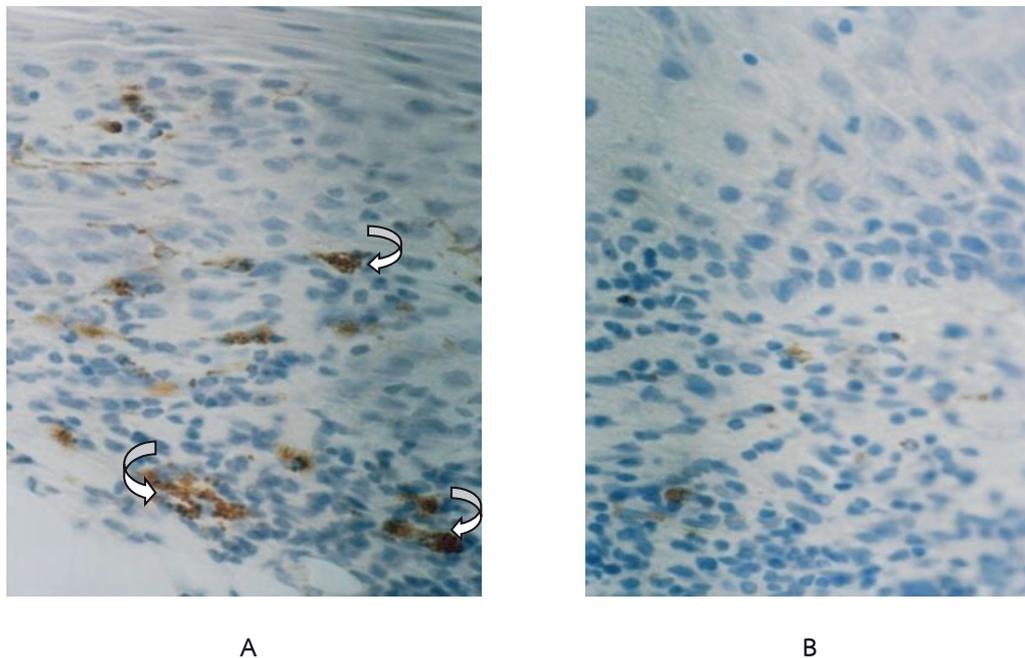


Figure 4 A study of immunopathogenesis of OLP in Thai patients. The immunohistochemical staining for TNF- α in tissue sections of OLP. Proinflammatory cytokine, TNF- α has been implicated in the pathogenesis of OLP.

A. Tumor necrosis factor- α (TNF- α) expression (arrows) in OLP lesion

B. After treatment OLP lesion with 0.1 % fluocinolone acetonide orabase (FAO) for 1 month, 0.1 % FAO can inhibit TNF- α expression.

International collaboration in Oral Medicine and Oral Diseases Group of Thailand (ODGT)

In 2006, Asian Oral Lichen Planus Group, led by the National Medical Research of Singapore in collaboration with the research groups from Thailand, India and Korea, conducted a research entitled “A randomized controlled trial to compare steroid with cyclosporine for the topical treatment of Oral Lichen Planus”. Unfortunately, the result showed that cyclosporine was not as effective in the treatment of OLP as the topical steroid, 0.1 % triamcinolone acetonide in orabase. Furthermore, side-effects such as burning sensation, swelling lips, itching had been observed in some patients treated with cyclosporine. As a result, cyclosporine could not be launched in worldwide commercial market.^{17,18}

Oral lesions of autoimmune diseases such as Mucous Membrane Pemphigoid (MMP) may precede the development of lesions in other mucous membranes of the body such as oropharynx, nasal mucosa, eyes etc, and the progression of the disease may cause blindness in some patients. One interesting case was a patient who presented with a palatal ulceration with the diagnosis of MMP and was initially treated by an oral medicine specialist. The lesion subsequently progressed to involve the oropharynx and eye, at which point the patient was under the care of the physicians. Unfortunately, the physicians treated other non-oral lesions in this patient symptomatically without knowing the original oral diagnosis. This patient developed airway problem during treatment, and finally developed blindness. This case was brought to the court of justice for the inappropriate treatment of the patient. Oral medicine specialists from various parts of Thailand tried to find document to support that the blindness was definitely by the progression of MMP itself not by the malpractice of oral medicine specialist or physicians. This case showed the significant association between oral lesions and patient’s life. Many medical professionals were also affected from this case. In 2004, the Oral Diseases Group of Thailand (ODGT) was founded to disseminate the

updated knowledge and to emphasize the importance of oral medicine subject to dental and general practitioners. Moreover, ODGT has been accepted as one of the world group of oral medicine associations during World Workshop in Oral Medicine IV in San Juan, Puerto Rico since 2006.

Research unit in oral diseases has been set up at the Faculty of Dentistry, Chulalongkorn University in 2006. The objectives of research unit were to elucidate the pathogenesis of oral diseases, side-effects of drugs and to form collaborative networks both at the national and international levels.^{14,17,19} The interesting research was the first comparative study of OLP between Thai and Croatian which was the first study to compare characteristics of OLP between Asian and Caucasian ethnic groups.¹⁹

In 2008, the Cochrane Oral Health Group updated the Cochrane review “Interventions for treating oral lichen planus”. From Meta-analysis of systematic review, more than 850 articles were reviewed and 28 randomized controlled trials were extracted for analysis. This update review analyzed the effectiveness of drugs used in the treatment of symptomatic OLP that would be useful for clinicians in making the decision even before treating this disease. This was the first time that Thai dentists had the opportunity to participate in the international research with the Cochrane collaboration which is an independent, non-profit, non-governmental organization consisting of more than 31,000 volunteers from more than 120 countries. The collaboration was formed to organize medical research information in a systematic way to facilitate the choices that health professionals, patients, policy makers and others face in health interventions according to the principles of evidence-based medicine.^{7,8,20}

Pemphigus

Regarding serious oral autoimmune diseases, pemphigus is also commonly found in Thai patients. Gingiva is the most common site of the lesion of pemphigus in Thai patients.²¹ Actually, oral lesions usually precede skin lesion and the dentist plays an important role in

the diagnosis and management. Control of oral hygiene and long-term follow-up are very important. Cooperation with the physician and topical steroids have been found to be useful in treatment and management of the lesions.²² Interestingly, cooperation with the dermatologist, metallurgical engineer, oral pathologist and oral medicine specialists resulted in the new finding that nickel in the metal fused to porcelain crowns can induce pemphigus-like lesion (Fig. 5).²³ A patient presented with oral pemphigus lesion that was not responsive to any treatment for more than 2 years. We removed all old porcelain crowns and bridges to porcelain fused to

precious metal and treated the lesions with potent topical steroids- 0.1 % FAS and 0.05 % clobetasol propionate in orabase. Finally, those treatment and management were found to be effective and resulted in complete remission (Fig. 6). Interestingly, rare oral autoimmune diseases with long-term follow-up was presented in a patient with pemphigus, discoid lupus erythematosus and dermatomyositis. This unusual case presented with gingival lesions that might be useful for general dentist to aware of autoimmune diseases which commonly appear on the gingiva at the first site.²²



Figure 5 The porcelain fused to metal crowns and bridges on the left permanent maxillary second premolar to the left permanent maxillary second molar (tooth 25 - 27), and the left permanent mandibular second premolar to the left permanent mandibular second molar (tooth 35 - 37), the left permanent mandibular canine to the right permanent mandibular first molar (tooth 33 - 46) persisted in the oral cavity more than 15 years induced pemphigus-like lesion. A. Gingival erosion and desquamative epithelium at the mandibular anterior teeth area of crowns and bridges B. After replacement crowns with precious metal with porcelain and treat with 0.1% FAS, the gingiva showed complete remission. (Acknowledge to Dr. Adirek S. Wongsa for his kind reconstruction of all new PFM)

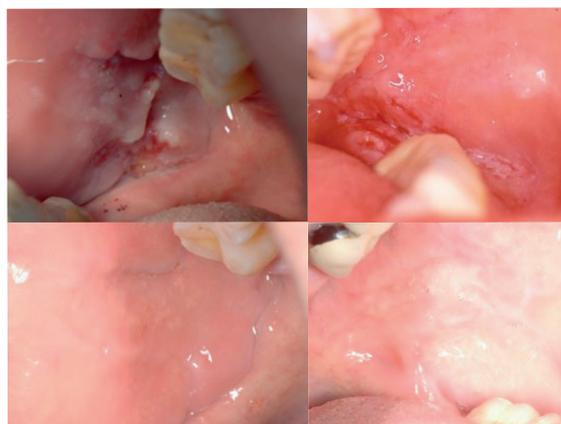


Figure 6 Deep oral ulceration on the right and the left buccal mucosa in patient in Fig. 6 before treatment (upper) and complete remission 3 years after treatment with 0.1 % FAS and 0.05 % clobetasone propionate in orabase (lower)

Topical steroids such as FAO, FAS, 0.05 % clobetasone propionate, 0.05 % dexamethasone mouth-wash have been found to be effective and safe in the treatment of OLDR patients with many systemic diseases during 7-year follow-up.²⁴ Recently, a study of “Oral lichenoid lesions and serum antinuclear antibodies in Thai patients” has been presented. The number of serum-ANA-positive OLP and OLDR patients was significantly higher than the control group. Our first findings in Thai patients would be clarified about the relationship and/or overlapping OLP, OLDR and lupus erythematosus lesions in a near future.²⁵

Discussion

Over the past decades, the need for oral health care professionals to understand basic principles of diagnosis and oral medicine has grown exponentially. Increasing number of patients seeking oral health services are taking multiple medications, so untoward effects of drugs to the oral mucosa will be increased. Oral health is an important part of general health, so dentists and dental specialists should be aware of medical status of their patients in order to provide a high level of oral health care.²⁶ Oral medicine in Thailand has been progressing in diagnosis, treatment and management of oral diseases for the past 25 years. Various patients with oral lesions including autoimmune, fatal, life-threatening, chronic and unusual diseases have been referred to the department of Oral Medicine, Faculty of Dentistry, Chulalongkorn University and other universities in many regions of Thailand for the definite diagnosis and treatment. Cooperation between dentists and physicians has been found to be useful during management of problems related to oral diseases.

Conclusion

It is incumbent upon the oral medicine specialists and general dentists to provide the most accurate diagnosis and effective treatment to the patients as

these can at least improve their quality-of-life and at most save their life. Thus, knowledge in oral diagnosis and oral medicine are essential subjects for dentists to provide appropriate oral health care in Thai patients.

Acknowledgement

I would like to express my sincere gratitude to Chulalongkorn University and Research Unit in Oral Diseases, Faculty of Dentistry, Chulalongkorn University for long-term support on all researches. My thanks will go to the staff of General Medicine, Faculty of Medicine, Chulalongkorn University, Saraburi and Lumphun hospitals for kind cooperation.

All patients, postgraduate students, staffs of Oral Medicine, Oral Pathology, Pharmacology, Oral Surgery, Periodontology, Radiology and Microbiology Departments, Faculty of Dentistry, Chulalongkorn University are acknowledged for their cooperation and support. Oral Diseases Group of Thailand (ODGT) is acknowledged for providing oral medicine knowledge to our community.

Special thanks will go to Assoc. Prof. Kittipong Dhanuthai for his kind editing this review and support.

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