Simultaneous detection of IFN-gamma in whole unstimulated saliva and lesional tissues from oral lichen planus patients

Thesis

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بسم الله الرحمن الرحيم

رب اشرح لي صدري
و يسر لي امري

صدق الله العظيم

Contents

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Oral lichen planus (OLP) is a chronic mucocutaneous inflammatory disease that appears in about 1–2% of the general population, very frequently showing oral manifestations **(Pindborg et al., 1997; Miller et al., 2001)** and is characterized by a clinical course with periodic remissions and reactivations **(Eisen, 1993; Lozada-Nur and Miranda, 1997; Scully et al., 1998; Chainani-Wu et al., 2001).**

As T cell-mediated autoimmunity is considered to be involved in the pathogenesis of this disease **(Sugerman et al., 2002)**, the roles of a line of T cell associated-cytokines and chemokines have been investigated in the past decades.

Cytokines are the major immunomodulators, determining the pathophysiologic outcome of infectious disease and systemic inflammatory responses, with either inhibitory or stimulatory effects on cellular growth, differentiation and function (**Tracey and Cermi, 1994).**

Among these cytokines ,interferon (IFN)-gamma and interleukin (IL)-4 have been studied more extensively because IFN-gamma and IL-4 are regarded as the characteristic cytokines of T helper 1) Th1) cells and T helper 2 (Th2), respectively (**Sugerman et al.; 2002, Neurath et al.; 2002).**

To date, the results on both cytokines in OLP have been inconsistent. **Khan et al. (2003)** found that IFN-gamma expression increased strongly in

OLP lesions which were secreted by lesional T cells in vitro culture, but **Yamamoto et al., (1991)** observed that IFN-gamma was significantly decreased in the peripheral blood of patients with OLP.

IFN-γ exerts profound effects on inflammation as it upregulates major histocompatibility class II molecules on most cells (**Steiniger et al., 1988, Chang and Flavell, 1995)**, activates macrophages and enhances expression of adhesion molecules on endothelial cells **(Issekutz, 1995)**.

IFN-γ has also, in an animal model, been found to preferentially mediate lymphocyte extravasation compared with neutrophils into inflammatory lesions **(Colditz and Watson, 1992)**.

Great numbers of unstimulated cells producing IFN-γ were detected in OLP lesions **(Yamamoto and Osaki, 1995)**.

Currently, the protein composition of human saliva has been initially investigated by proteome techniques, and a large number of unrevealed proteins in saliva were identified and further demonstrated as possible biomarkers in oral diseases, such as dental caries, periodontitis, and oral squamous cell carcinomas. However, few studies have utilized simultaneous detection of cytokines in local tissues and saliva to determine whether salivary cytokines could reflect the facts of local lesions **(Vitorino et al., 2004; Ghafouri et al., 2004; Tao et al., 2008).**

Consequently it was found of interest to study the simultaneous prevalence of IFN gamma in tissues and saliva of OLP.

REVIEW OF LITERATURE

Lichen planus (LP) is a chronic inflammatory disorder of cutaneous and mucosal tissues that is considered by some authors to be an autoimmune disease of unknown aetiology in which epithelial cells are recognized as foreign due to changes in cell surface antigenicity (**Edwards & Kelsch, 2002**).

The prevalence of lichen planus is unknown, but it is estimated to occur in one to two percent of the general adult population. Estimates of the prevalence vary among different populations, but the condition does not appear to exhibit a racial predilection and it is the most common non-infectious oral mucosal disease in patients referred to Oral Medicine and Oral Pathology clinics (**Axéll and Rundqvist, 1987; Boyd and Neldner, 1991; Bowers et al., 2000**).

An epidemiological study demonstrated that women suffer from oral lichen planus (OLP) more frequently (75%) than men (25%), and that the disease is more frequent in people over 40 years of age, although younger adults and children may be affected (**Vincent et al., 1990; Chainani-Wu et al., 2001; Eisen, 2002**).

Lichen planus often occurs on cutaneous surfaces and also may involve the oral mucosa, the genital mucosa, the nails and the scalp. Moreover, these areas may be exclusively involved. On the other hand laryngeal,

oesophageal and conjunctival involvement is uncommon (**Katta, 2000; Ismail et al., 2007**).

As a sole manifestation of LP, oral lesions make up to 15-35% of the patient's group, but up to 65% of patients with classical cutaneous LP have concomitant oral disease (**Boyd and Neldner, 1991**).

The classic appearance of skin lesions includes violaceous polygonal flat-topped papules and plaques. Close examination reveals a reticulated pattern of white scales known as Wickham's striae. Early cutaneous lesions appear as scattered erythametous papules. The flexor surfaces of extremities, particularly the wrists, are common locations for lichen planus (**Katta, 2000**).

Cutaneous lesions may occur in areas exposed to trauma, such as lacerations and this tendency is known as an isomorphic response or Koebner's phenomenon. Lesions often resolve with intense hyperpigmentation (**Katta, 2000**).

Some physicians describe lichen planus with the six "Ps"; pruritic, polygonal, planar (flat-topped), purple papules and plaques. While some patients may be asymptomatic, most of them experience intense pruritus, a hallmark of lichen planus (**Katta, 2000**).

Other variants of LP do exist and exhibit various morphologies. Patients with hypertrophic lichen planus present with thick hyperkeratotic plaques, commonly found on the anterior surface of the legs. In vesiculobullous

lichen planus, patients exhibit blisters within the plaques, while the actinic type of lichen planus occurs in sun-exposed areas of skin (**Katta, 2000**).

Nail involvement results in pitting, pterygium formation, and permanent nail loss. Scalp involvement results in scarring alopecia (**Sugerman et al., 2000b**).

The oral form of lichen planus seems more common, chronic, and recalcitrant than the cutaneous type, persisting up to more than 20 years without spontaneous remission (**Scully et al., 2000**).

The clinical presentation of OLP varies. In many patients, the onset of OLP is insidious, and patients are unaware of their oral condition. Some patients report roughness of the lining of the mouth, sensitivity of the oral mucosa to hot or spicy food, painful oral mucosa, red or white patches on the oral mucosa, or oral ulcerations (**Eisen, 1999**).

Six clinical forms of OLP have been described which are white forms namely reticular, papular, plaque-like and the red forms namely the erosive (ulcerated), atrophic (erythematous), and bullous (**Andreasen, 1968; Pindborg et al., 1997**).

The most common type is the reticular pattern which presents as fine white striae known as Wickham's striae. The striae are typically bilateral and symmetrical. The buccal mucosa is the most commonly affected, although any site can be affected. Patients with reticular lesions are often asymptomatic (**Eisen, 2002; Ingafou et al., 2006**).

Atrophic OLP presents as a diffuse red lesion. The lesions may appear as a mixture of clinical subtypes. For example, white and gray streaks may form linear or reticular pattern on erythematous background. Alternatively, a central area of shallow ulceration (erosion) may have a yellowish surface (fibrinous exudates) surrounded by an area of erythema (**Silverman et al., 1985**).

Erosive OLP presents as irregular erosion or ulceration covered with a fibrinous plaque or pseudomembrane. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae. Atrophic (erythematous) or erosive (ulcerated) OLP are often associated with burning sensation and pain (**Eisen, 2002**).

Plaque type OLP appears as homogenous white patches which resemble leukoplakia. However, the presence of white striations and histologic confirmation will allow for the definitive diagnosis of OLP to be made. This type commonly affects the dorsum of the tongue and buccal mucosa and is more common among tobacco smokers,it may range from a slightly elevated and smooth to a slightly irregular form (**Thorn et al., 1988**).

Bullous OLP is the least common type. The bullae range from few millimeters to several centimeters in diameter. They tend to rupture leaving ulcerated and painful surfaces. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae (**Zegarelli, 1993**).

The papular type can coexist with any of the previously described types (**Bricker, 1994**).