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ORIGINAL ARTICLE

Oral Lichen Planus: Manifestation of Grinspan's Syndrome or a Lichenoid Reaction to Medications

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ABSTRACT

Introduction/Objectives: Oral lichen planus is a condition of chronic nature and has no defined etiology. Oral lichen planus has been linked to several disorders such as hepatitis, hypertension, hypothyroidism, and hypercholesterolemia. The objective was to determine the link between the mucosal variant of lichen planus and systemic diseases, namely hypertension and diabetes mellitus. This triad is named Grinspan's Syndrome. No previous studies have confirmed a true relation between the three diseases.

Material and methods: Almost 1100 patients presented to the dental diagnostics department, out of which 89 were diagnosed with oral lichen planus clinically. Both males and females were included in the study. Age was variable in all these patients. A detailed history proforma was used to record their history and clinical diagnosis.

Results: From the pool of patients that had lichen planus (n=89), almost half, 41.6% (n=37) had hypertension. Not all these patients had been prescribed, nor had been taking anti-hypertensives for their condition. 59.5% (n=22) of these 89 individuals were taking medicines for their hypertensive state. 24.7% (n=22) individuals had diabetes mellitus but not all were on oral or injectable hypoglycemics. Infact, 72.7% (n=16) out of these 22 diabetics had been taking medicines for hyperglycemia.

Conclusion: On account of obtained medical history, majority of the patients with either hypertension or diabetes had been taking medicines for their systemic condition. The list of drugs included oral hypoglycemics, beta-blockers, diuretics, and calcium-channel blockers. All these drugs are notorious for giving rise to the condition called lichenoid reactions. For determination of accurate results, it is necessary at both histopathological and molecular level to rule out the possibility of lichen planus before labelling the condition as lichenoid reactions caused by drugs. This can help in declaring such patients as truly having Grinspan's Syndrome.

Keywords: Grinspan's syndrome, hypertension, diabetes mellitus, oral lichen planus

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory condition of unknown cause, primarily affecting middle aged females (1). It was first described by Erasmus in 1869 as a flat tree-moss resembling lesion on the skin (2). Lichen planus is known to affect 0.1-5% of the worldwide population (3). It usually affects females more than males in the ratio of 2.5:1 with the average age of these females being 55 years at the time of diagnosis (4). Despite its aetiology being idiopathic, literature relates T-cell mediated response as a causal agent of lichen planus. Associations between lichen planus and various medical conditions such as hypertension, thyroid dysfunction, hepatitis C virus and hyperlipidaemia have been mentioned in literature (5-7). Another such association, termed Grinspan's syndrome is considered to be a link between oral lichen planus, namely erosive type, hypertension and diabetes mellitus (8). Grinspan's syndrome was first described by Grinspan in 1963 as a relatively rare clinical disease as a triad of hyperglycaemia, vascular hypertension and lichen planus occurring orally (9). Grinspan's syndrome is a clinical triad that usually affects the elderly.

Oral lichenoid reactions (OLR) may be subclassified as clinical variants of lichen planus. Lichenoid reactions are considered to occur because of drug reactions. Other causes of OLR are contact allergy or chronic graft versus host disease. Rare associations of atopic components have been reported in literature such as tobacco (10). although no time period has been established on how long it takes to develop OLR after drug use, some studies suggest it can develop as early as 3 months after starting a drug and resolve after a minimum of 9 months after discontinuing drug use or switching to an alternative drug therapy for a medical condition (11). clinically and histologically, it is difficult to differentiate between oral lichen planus and oral lichenoid reactions.

Some notable drugs known to cause lichenoid reactions include antihypertensives, diuretics and oral hypoglycaemics, which are all used in treating vascular hypertension and hyperglycaemia (12). Although the mechanism of these lesions as a consequence of drug use is not completely known, it is considered to be a delayed hypersensitivity reaction to these medications (8). Examples of antihypertensives more commonly implicated in causing OLRs include calcium channel blockers (amlodipine), ACE inhibitors, methyldopa, propranolol and statins (atorvastatin) (13). Oral hypoglycaemics that may induce oral lichenoid lesions are biguanides (Metformin) and sulfonylureas (Glibenclamide) (14). Moreover, no specific drug is documented to have caused lichenoid reactions more commonly than another and discontinuation of drug does not revert the mucosal condition back to normal immediately.

While the aetiology of OLP is not completely known, OLR is considered a Type 4 hypersensitivity reaction. Type 4 hypersensitivity reactions refer to delayed or cell-mediated reactions. These entail major histocompatibility complex presentation of drug molecules to T-cells with cytokine and inflammatory mediator release (15). OLR may occur at sites of the oral cavity where lichen planus lesions are rare, for instance, the palate, more commonly associated with chronic Graft Versus Host disease (cGVHD) (16). Additionally, OLR may also be seen on the labial mucosa as a consequence of plaque accumulation on the anterior teeth, albeit rarely (17). It is also difficult to differentiate the two conditions on histopathological grounds. Some changes, however, may be variable. OLP has a relatively superficial, mixed infiltrate at the subepithelial level compared to deeply distributed lymphocytic infiltrate in drug induced OLR. Drug-related OLR are less commonly encountered than skin reactions(18). Topographical criterion may also indicate a difference between OLP and OLR as the removal of causative agent from the site of lesion may result in the disappearance of the lesion (19). Both these conditions are equally associated with malignant transformation(20).

MATERIALS AND METHODS

This observational study was conducted in Department of Diagnostics and Oral Medicine, Fatima Memorial Hospital College

of Medicine and Dentistry, Lahore, Pakistan. A total of 89 (n=89) clinically diagnosed patients of oral lichen planus of both genders and all age groups were recruited and detailed history was recorded in the designed proformas.

Sampling was done using census to maintain a degree of precision. Approval was sought from the Institutional Review Board of Fatima Memorial Hospital and granted. The entire sample of patients signed a written consent prior to actively participating in the study.

Patients were evaluated for having hypertension and diabetes and the record of the drugs being used was made. It was noted that the patients had started taking medicines for either of the two conditions several years prior to presenting to our clinic. None of these patients developed hypertension nor diabetes during the study. It was determined if the medication was being used for either of the two pre-existing medical condition that the patient presented with i.e., hypertension and/or diabetes. These patients were divided into three groups based on the medications they were taking. The diagnosis was clinically established for lichen planus and lichenoid lesions by specialists in the field of Oral Medicine. These groups were designated as follows:

A. Patients clinically diagnosed with OLP taking medications for hypertension.

B. Patients clinically diagnosed with OLP also taking medications for diabetes.

C. Patients with OLP also taking medications for both hypertension and diabetes.

The data was recorded using proformas and was analysed using SPSS v.22 software.

RESULTS

A total of 89 patients were selected for this study. The age of the patients ranged from 10-74 years, mean age being 48.8 ± 13.8 years. The male to female ratio was 3:8 in which 24 were male and 65 females, owing to a higher predilection of oral lichen planus in females. Among all these patients suffering from oral lichen planus, n=37 (41.6%) had a positive history for hypertension prior to development of lichenoid lesions. Among these pre-diagnosed hypertensive patients, n=22 (59.5%) were taking different medication for their hypertensive state. Whereas lichen planus or lichenoid lesions were found in 22 (24.7%) patients with 16 (72.7%) of these patients using the hypoglycaemic drug (oral or injectable) to control their blood glucose levels. At the time of presentation, 19 people were taking medicines for both diabetes and hypertension. It was undetermined at this stage whether one or more drug contributed to lesions in the oral cavity. No specific, single drug was conclusive of creating these lesions alone or in conjunction with other drugs.

Amongst these n=89 lichen planus patients 19 (21.3%) had both hypertension and diabetes mellitus (fulfilling the criteria for Grinspan's Syndrome) all of whom were under treatment for both conditions.

Table 1: Frequency of patients using Hypertension and/or Diabetes Medication

Disease	Frequency (n)	Percentage
For both yes	10	11.2
Both no	60	67.4
One either one yes	18	20.2
Total	89	100.0

Table 2: There is an insignificant relation between the intake of medication for both hypertension and diabetes and the development of lichen planus, r(87) = 0.886, p= 0.005

Correlations			
		Hypertension+Diabetes Medication	disease
Hypertension+ Diabetes Medication	Pearson Correlation	1	.015
	Sig. (2-tailed)		.886
	N	89	89
disease	Pearson Correlation	.015	1
	Sig. (2-tailed)	.886	
	N	89	89

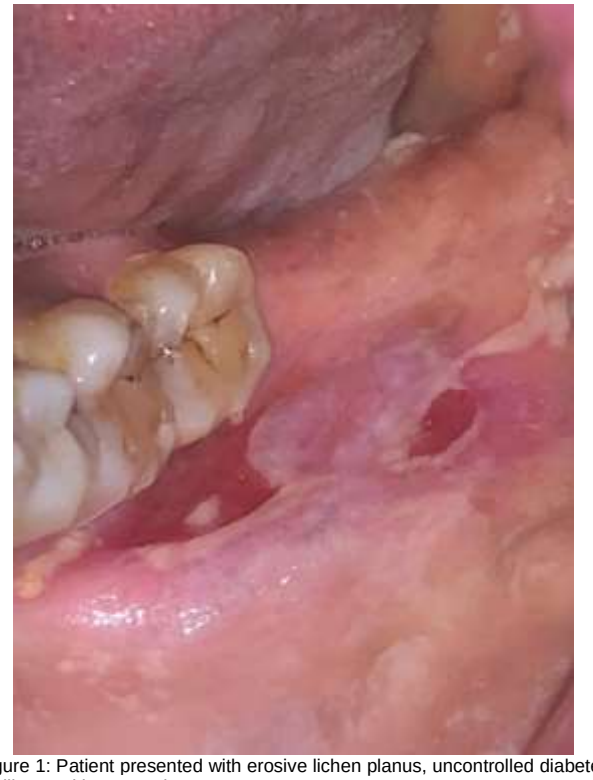

Figure 1: Patient presented with erosive lichen planus, uncontrolled diabetes mellitus and hypertension

Figure 2: Plaque like presentation of lichen planus on lateral border of tongue

DISCUSSION

Amongst a handful of diseases known to be associated with lichen planus, diabetes and hypertension remain two of the most commonly occurring. OLP may present in various forms which include reticular, ulcerative, erosive, bullous etc.(21, 22). Reticular in combination with other forms is more common than any other type alone, whereas, bullous type is amongst the rarest(23). Insulin, if unregulated in the body may lead to unwanted skin lesions due to altered skin temperature, slower blood flow and a thickened viscosity of blood plasma (24). These lesions include diabetic dermopathy, cutaneous bacterial and fungal infections,

xanthomas, lichen planus, pruritis, and skin tags in patients suffering from Diabetes Mellitus (25). In this study, patients were suffering from oral lesions which were present in some patients who had hypertension and diabetes irrespective of them taking medication for the medical conditions, diabetes and hypertension. A similar relation was seen in these conditions and periodontitis. In one such study a patient on medications for diabetes developed periodontitis in the absence of other medication use (26). Another case report indicated presence of intraoral lesions suggestive of oral lichen planus in a patient on insulin for diabetes mellitus (27), comparable to 24.7% of the patients in our study.

Lichenoid reactions may also be a result of contact or as a consequence of Graft versus Host Disease. The reactions to metal alloys used in dentistry is rare but still reported in literature, especially to amalgam (26). Patients in our study were evaluated and none had undergone treatment pertaining to metal fillings or replacement of teeth via cast metal dentures. These elements usually present in the oral cavity following the topographical criterion in which the site of contact is affected and resolves as soon as the allergen is removed, whereas, in our study, the lichenoid reactions were bilateral and present irrespective of dental restorations being present or not.

The most common form of lichen planus implicated in patients of Grinspan's syndrome is erosive type (26) which was seen in majority but not all of the patients in our study. Patients taking several medications including those for diabetes and hypertension may develop oral lichenoid reactions which are clinically and histopathologically indistinguishable from lichen planus lesions. Even after drug withdrawal, these oral lesions may persist for prolonged periods of time(16). Although topical corticosteroids are the mainstay therapy for OLP, stopping the use of predisposing agents such as medicines used in treating medical conditions may revert the lichenoid lesions (13).

Another study concluded that the presence of oral lesions resembling lichen planus in patients with Diabetes mellitus was seen irrespective of medicine intake (28). Prevalence of OLP in DM patients has been reported to be up to 10% in a previous study(29). In another study, there is contradictory evidence in the presence of lichenoid lesions and presence of diabetes mellitus (30), unlike the study conducted by us.

Some studies suggest that OLR may present as reticular form in patients taking antihypertensives which is not usually painful and unlike the erosive form commonly seen in OLP patients (31). Almost 60% individuals were taking anti-hypertensive medications for hypertension by the time they reported to the Oral Medicine clinic with oral lesions, compared to 4.5% individuals who presented with OLR after taking anti-hypertensive medications according to a study in India (32).

When either of these conditions are symptomatic and present with pain, it is seen that lichen planus lesions might regress without any treatment in 20% of the cases if individuals maintain better fitness and lifestyle (33). This does not true for lichenoid reactions as the patients need frequent intake of prescribed medicines for their medical conditions and the medications cannot be abruptly discontinued without a physician's approval.

CONCLUSION

According to medical history taken from the entire pool of the presenting patients, it was observed that majority of them were using oral hypoglycaemics to control their blood sugar levels for diabetes mellitus. Similarly, most of them were using beta blockers, diuretics and calcium channel blockers for treatment of diagnosed hypertension. All these drugs mentioned are notorious for causing lichenoid reactions. Therefore, it should be ruled out at histopathological/ immunological and molecular level whether these patients are suffering from lichen planus or lichenoid drug reactions to truly declare them as patients with Grinspan's Syndrome.

Ethics Statement and Conflict of Interest Disclosures: Human subjects: Consent was obtained or waived by all participants in this study. Institutional Review Board, Fatima Memorial Hospital, Lahore issued approval None. This study had been granted approval by the IRB of Fatima Memorial Hospital, Lahore, Pakistan. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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