ORIGINAL RESEARCH PAPER

Microbiology

CONNECTING THE DOTS:, HYPERTENSION, DIABETES AND ORAL LICHEN PLANUS. THE GRINSPANS SYNDROME REVISITED

KEY WORDS:

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Grinspan's syndrome has been an area of inquisitiveness since its discovery in 1963 by Grinspsan. The associated ambiguity with this syndrome is what makes this syndrome an enigma for most clinicians.

Grinspan's syndrome is a triad of hypertension, diabetes mellitus and oral lichen planus.

Drug therapy for diabetes mellitus and hypertension is capable of producing lichenoid reactions of the oral mucosa. It is often a topic of discussion amongst researchers whether Grinspan's syndrome is a drug induced phenomenon.

Oral lichen planus sit occurs predominantly in older adults, and many drugs used in the treatment of systemic diseases trigger the development of oral lichenoid lesions as an adverse effect.

Oral lichen planus affects all racial groups, with a female-to-male ratio of 1.4:1. The skin lesions of lichen planus appear as small, angular, flat-topped papules only a few millimeter in diameter. These may be discrete or gradually coalesce into larger plaques, each of which is covered by a fine, glistening scale. The papules are sharply demarcated from the surrounding skin. develops. The center of the papule may be slightly umbilicated. Its surface is covered by characteristic, very fine grayish-white lines, called Wickham's striae. and classically is characterized by lesions consisting of radiating white or gray, velvety, thread-like papules in a linear, annular or retiform arrangement forming typical lacy, reticular patches, rings and streaks over the buccal mucosa and to a lesser extent on the lips, tongue and palate. When plaque-like lesions occur, radiating striae may often be seen on their periphery. Vesicle and bulla formation has been reported in oral lesions of lichen planus, but this is not a common finding, and the diagnosis of lichen planus from the clinical appearance of the lesions is extremely difficult. This bullous form of lichen planus has been discussed by Shklar and Andreasen. Still another type, the so-called erosive form of lichen planus, usually begins as such and not as a progressive process from 'nonerosive 'lichen planus. An atrophic form of lichen planus occurs with some frequency and appears clinically as smooth, red, poorly defined areas, often but not always with peripheral striae evident. A hypertrophic form of lichen planus may also occur on the oral mucosa, generally appearing as a well-circumscribed, elevated white lesion resembling leukoplakia. In such cases biopsy is usually necessary to establish the diagnosis. Histopathologic examination of lesional tissue is the most relevant investigation in cases of OLP. Typical findings include hyperparakeratosis or hyperorthokeratosis with thickening of the granular layer, acanthosis with intracellular edema of the spinous cells in some instances, the development of a 'saw tooth 'appearance of the rete pegs. Band-like subepithelial mononuclear infiltrate consisting of T-cells and histiocytes; increased numbers of intraepithelial T-cells; and degenerating basal keratinocytes that form colloid(Civatte, hyaline, cytoid) bodies, which appear as homogenous eosinophilic globules are consistently seen. Degeneration of the basal keratinocytes and disruption of the anchoring elements of the epithelial basement membrane and basal keratinocytes (e.g. hemidesmosomes, filaments, fibrils) weakens the epithelial-connective tissue interface. As a result, histologic clefts (i.e. Max-Joseph spaces) may form, and blisters on the oral mucosa (bullous lichen planus) maybe seen at clinical examination. B cells and plasma cells are uncommon findingsTreatment. At present there is no cure, although various agents have been tried. Due to its minimal potential for malignant transformation, these patients used to be kept on long-term follow-up. Medical treatment of OLP is essential for the management of painful, erythematous, erosive, or bullous lesions. The principal aims of current OLP therapy are the resolution of painful symptoms, the resolution of oral mucosal lesions, the reduction of the risk of oral cancer, and the maintenance of good oral hygiene. As it is an autoimmune mediated condition, corticosteroids are recommended. In patients with recurrent painful disease, another goal is the prolongation of their symptom free intervals.

Diabetes mellitus is a group of diverse illnesses that often show hyperglycemia and glucose intolerance via insulin shortage, insulin impairment or both (Sicree et al., 2006) . Diabetes mellitus is thus divided into four sorts or classes: type 1 diabetes, type 2 diabetes, gestational diabetes, and other subtypes (Sicree et al., 2006) Although type 1 diabetes is noted to be the most common form of diabetes in younger age groups in most developed counteries, it constitutes a modest percentage of the overall burden of diabetes in a community. Type 1 diabetes in both developed and developing countries is becoming more common. An increased tendacy has also been noted in youngsters to type 1 diabetes is predicted at an earlier age (Sicree et al., 2006)

Lifelong treatment is often necessary to prevent unwanted complications. Ideally, glucose levels should be maintained at 90 to 130 mg/dL and HbA1c at less than 7%. While glucose control is very important, outrageous management may lead to hypoglycemia, which is fatal.. Since T1DM is a disease primarily due to the absence of insulin, insulin administration using a daily injection or an insulin pump, is the recommended. However in T2DM, diet and exercise may be adequate treatments, at times in milder cases or at the start of the treatment. Other modules of treagment aims at insulin

sensitivity or increase insulin secretion by the pancreas. The specific subclasses for drugs include biguanides (metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagonlike-peptide-1 agonist, dipeptidyl peptidase IV inhibitors (DPP-4), selective, amylinomimetics, and sodium-glucose transporter-2 (SGLT-2) inhibitors. Metformin is the first line of drugs prescribed to the patient. It acts by lowering basal and postprandial plasma glucose. Insulin administration at times might be necessary for T2DM patients. These patients are the ones who have not been able to manage their glucose levels in the later stages of the disease.. In morbidly obese patients, bariatric surgery is also a treatment module in order to normalize glucose levels. But it should only be done for patients who have been unresponsive to other treatments and who have significant comorbidities.

Systemic arterial hypertension is said to be the most important versatile risk factor for all-cause morbidity and mortality all over the world and is associated with increased risk of cardiovascular disease (CVD).

Systemic arterial hypertension (also known as hypertension) is characterized by persistently high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of the systolic BP (that is, the pressure that the blood exerts on the arterial walls when the heart contracts) and the diastolic BP (the pressure when the heart relaxes).

Low-dose pharmacological therapy has also been shown to be effective in lowering BP and preventing hypertension. Targeted dietary approaches can reduce the systolic BP in individuals with hypertension.

Other modalities also include Reduced salt intake and increased potassium intake alcohol consumption in moderation: intake of 4.7 g/day

Physical activity also reduces BP in individuals with hypertension when done regularly. Endurance training reduces BP more in persons with hypertension than in individuals with normal BP.

when there is excess adipose tissue in the body it raises the BP in susceptible patients , and patients with hypertension who also have obesity require more antihypertensive medications to control their BP and are more likely to be treatment resistant.

Antihypertensive therapy has advanced over the past few years. So much so that clinicians now have a wide variety of antihypertensive medications of different drug classes and a variety of fixed dose combinations.

first-line antihypertensive medications are usually given single drug administration or sometimes a combination of drugs. Combination therapy may be preferable in patients with higher levels of pretreatment BP. First-line antihypertensive medications include ACE inhibitors, angiotensin II receptor blockers (also known as sartans), dihydropyridine calcium channel blockers, and thiazide diuretics Beta-blockers are also indicated in patients with low left ventricular ejection fraction or post myocardial infarction. The choice should be based on individual efficacy and tolerability. Ethnicity affects the response to antihypertensive medications, and it has been suggested that calcium channel blockers and diuretics may be the first choice in people of African descent. In cases of hypertension in pregnant women, other medications such as alpha-methyldopa (an agonist of alpha adrenoreceptors in the central nervous system that inhibits the sympathetic nervous system) or labetalol (a beta adrenoreceptor blocker) are preferable, whereas some first line antihypertensives.

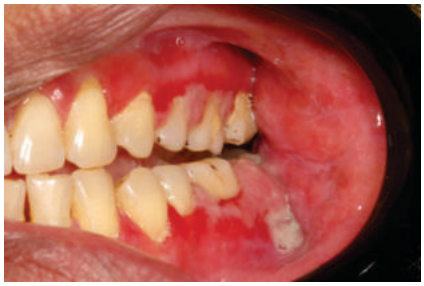
Certain patients with severe hypertension, BP remains uncontrolled with single drug therapy. It's always important to consider all risk factors such as whether patient has comorbidities and whether the combination of drugs will be helpful in lower BP or in tune create adverse effects for the patient.

ACE inhibitors or angiotensin II receptor blockers, thiazide diuretics and dihydropyridine calcium channel blockers are helpful in lowering BP and can be combined as double or triple combination therapies. However, combining ACE inhibitors and angiotensin II receptor blockers does little to lower BP but instead increases risk of renal dysfunction and hyperkalemia (high blood potassium levels, which can lead to cardiac arrhythmias.

Dihydropyridine calcium channel blockers elicit vasodilation by blocking vascular smooth muscle L-type calcium channels. A very important advantage of this drug is that it can be combined with all other first-line antihypertensives.

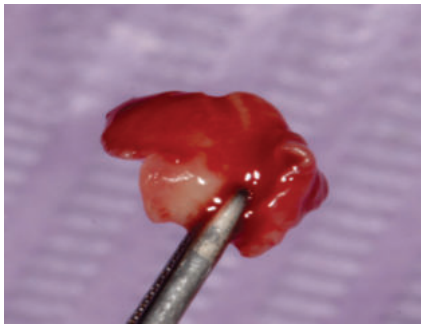
A female in her mid-fifties came to the dental office with the chief complaint of ulcers in the cheek region for past 3 months.

On examination white lesions were observed in the left buccal mucosa extending till the ramus region. The surface of the lesion showed grey-whitish lines. (Figure 1)



Medical history of the patient was also taken. She had been undergoing drug therapy for hypertension as well as diabetes mellitus.

The patient was advised a biopsy and the same was done at the dental office and the specimen (fig2)



was sent to the pathology department of a private hospital in New Delhi. According to which it was an inflammatory Leision (fig 3)

Histo Biopsy Small

Histopathology Number:
S-9245/23

Specimen Type:
Left buccal mucosa biopsy

Clinical Data / Impression:
Not submitted

Gross Description:
Two grey brown soft tissue bits together measure 0.8 x 0.5 x 0.5 cm (ETP).

Microscopic Examination & Impression:
Inflammatory granulation tissue.
Negative for granuloma, atypia or malignancy.

A second biopsy was done at the oral pathology department

at I.T.S. Dental college, Ghaziabad.

According to this report H & E stained section shows fibrocellular connective tissue stroma showing mixed inflammatory infiltrate chiefly composed of neutrophils, lymphocytes and plasma cells. Few areas show cells undergoing ballooning degeneration with pale eosinophilic cytoplasm and large vesicular nuclei. Focal areas show presence of inclusion bodies. Presence of a few giant cells is appreciated. Thick and thin bundles of collagen fibers interspersed with spindle shaped fibroblasts are seen. Varying calibers of endothelial cells lined blood vessels with engorged RBCs are also appreciated, which is indicative of oral lichen planus. (Figure, 4A\ and 4B and Figure 5)

BIOPSY REPORT

Submitted H & E stained section shows fibrocellular connective tissue stroma showing mixed inflammatory infiltrate chiefly composed of neutrophils, lymphocytes and plasma cells. Few areas show cells undergoing ballooning degeneration with pale eosinophilic cytoplasm and large vesicular nuclei. Focal areas show presence of inclusion bodies. Presence of few giant cells is appreciated. Thick and thin bundles of collagen fibers interspersed with spindle shaped fibroblasts are seen. Varying calibers of endothelial cells lined blood vessels with engorged RBCs are also appreciated.

Impression: Vesiculobullous lesion

Note: Advice biopsy from intact mucosal surface and immunofluorescence for confirmatory diagnosis.

Histological Diagnosis:

Section -A (Right Buccal Mucosa)

Submitted H & E-stained section shows ulcerated epithelium overlying the fibrocellular connective tissue stroma. The epithelium shows basal cell degeneration and basement membrane duplication. Subepithelial area shows band of inflammatory infiltrate chiefly composed of lymphocytes, plasma cells and few mast cells. The underlying stroma is composed of thick and thin bundles of collagen fibers interspersed with spindle shaped fibroblasts. Numerous proliferating blood vessels engorged with RBSs are also appreciated. Deeper stroma shows intact muscle bundles. Hemorrhagic areas are also appreciated focally.

Section -B (Left Buccal Mucosa)

Submitted H & E-stained section shows ulcerated epithelium overlying the fibrocellular connective tissue stroma. The epithelium shows elongated rete pegs and acanthosis with features such as basilar hyperplasia and nuclear hyperchromatism. Focal areas show basement membrane duplication. Subepithelial area shows chronic inflammatory infiltrate chiefly composed of lymphocytes, and plasma cells. The underlying stroma is composed of thick and thin bundles of collagen fibers interspersed with spindle shaped fibroblasts. Numerous proliferating blood vessels engorged with RBSs are also appreciated. Hemorrhagic areas are also appreciated focally.

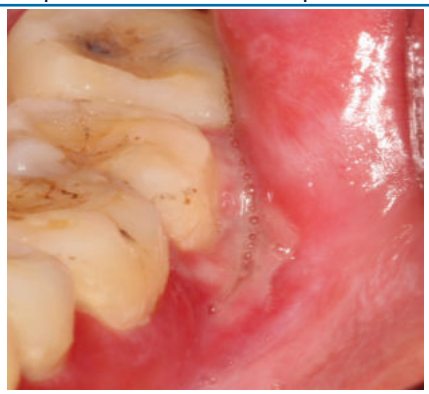
Impression: Oral Lichen Planus

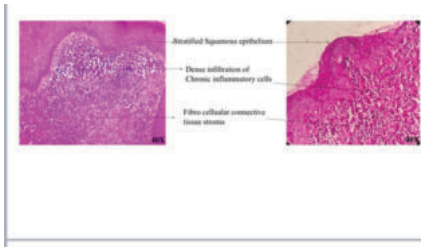
Treatment

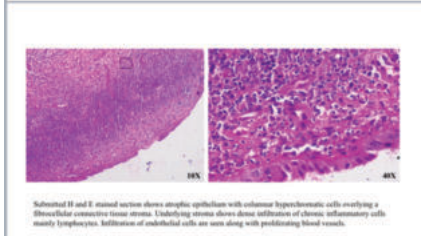
Patient was referred to in office internal medicine senior consultant for systemic disease management. Patient was asked to get blood tests done. HBA1c was found to be 7.8% which is suggestive of uncontrolled diabetes. Patient was prescribed suitable medication to control diabetes mellitus as well as hypertension.

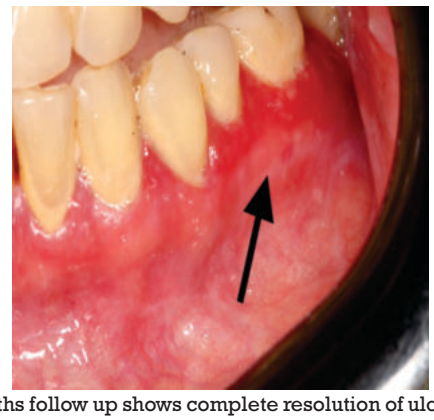
Oral lichenoid lesions were treated with corticosteroid therapy. Initially the patient was treated with topical corticosteroids (Powercort cream 0.05%) which is applied to the mucosa 3-4 times a day after meals. Patient was advised not to eat or drink for 30 minutes after application. Topical retinoids (Retino A (0.05% tretinoin) once a day for 1 month) were also prescribed for their non keratinizing and immunomodulating effects.

2 weeks follow up showed uneventful healing of the biopsy wound. (Figure 6)









18 months follow up shows complete resolution of ulcers with generalised marginal gingivitis. (Figure 7)

Glycemic levels and hypertension was under control, an oral prophylaxis was performed and the patient was advised to take measures to maintain proper oral hygiene.

CONCLUSION

It is mandatory for all suspicious lesions to be sent for histopathologic examination ,at times more than once, to reach a correct diagnosis.

The role of the oral pathologist and physician is crucial in management of lesions such as the one mentioned above .

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