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Grinspan Syndrome: Does it Really Exist? – An Opinion Article

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During daily clinical practice and through the many articles in the scientific literature, sometimes it pops up the so called Grinspan syndrome. This condition, which at a first glance may appear as a well-affirmed clinical entity, actually still today represents a controversial topic among physicians. The first publication about this syndrome dates back to 1963, when Grinspan and colleagues analyzed 23 patients diagnosed with oral lichen planus (OLP) and diabetes mellitus (DM), 7 of which were affected by hypertension (HTN) [1]. They believed that there was a link between OLP, DM, and HTN, although the correlation was not assessed statistically.

In this opinion article, we analyze some features that could help to get an idea of what Grinspan syndrome may represent. In addition, we present one of our clinical experiences and finally we express an opinion on how Grinspan syndrome should be considered today.

Grinspan syndrome refers to the association of OLP, DM and HTN [2]. Lichen planus is an autoimmune chronic inflammatory disease of unknown etiology that can affect skin, including appendages, and mucous membranes [3]. Oral mucosa gets involved in about 50% of cases and a variable percentage of patients (13%-53%) develops isolated oral lesions, most frequently in cheeks, tongue, lips and gums [2]. Prevalence of OLP as oral disease is around 1%–2%, while the prevalence of the Grinspan syndrome is referred to be about 0.4%–0.23% [4].

Since the first time Grinspan syndrome was described, many authors wondered if it really existed. The immune dysregulation in diabetes is supposed to be a pathogenic mechanism in the development of OLP [5]. Some authors linked the occurrence of OLP lesions with the intake of drugs for diabetes and hypertension, assuming Grinspan syndrome may be an Oral Lichenoid Lesion (OLL) due to drugs intake [6]. OLL, first described by Almeyda and Levantine in 1971, are a group of oral inflammatory lesions similar to OLP, typically due to an etiological factor. OLL includes contact lesions, drug reactions and graft versus host disease [7].

Some features can help to distinguish between OLL and classic OLP: lichenoid lesions often occur unilaterally and involve the lip [8]. Medical history reveals a topical treatment or a systemic drug relatable to OLL. Some histopathological features like a perivascular inflammation with neutrophils, eosinophils and plasma cells are mainly found in OLL (instead of the classic band-like pattern of OLP).

Furthermore, discontinuation of the granular layer of epidermis, focal parakeratosis, scattered apoptotic keratinocytes have been reported in OLL [9]. Indirect immunofluorescence shows a typical "string of pearls" pattern of antibodies in drug-induced lesions [2]. Removing the potential causal factor is key to manage lichenoid lesions and the remission within few months is highly suggestive for diagnosis [6].

Here we present a clinical case of our dermatological unit that could be useful to assess a final opinion about this clinical entity. A 62-years old man developed hyperkeratotic leukoplakia. He had a medical history of hypertension and hypercholesteremia, in therapy with olmesartan, rosuvastatin and aspirin. Laboratory tests revealed a condition of diabetes, which was probably pre-existing, and the patient started to assume metformin. After a few weeks, oral lesions got worse and the patient finally came to our dermatological unit. Clinically, hyperkeratotic lesions on the right superior hemiarch and on the inferior arch were visible. The patient was initially treated with oral betamethasone and topical tacrolimus on the mucosal lesions. We performed a biopsy, one week after discontinuation of betamethasone and tacrolimus, that confirmed the diagnosis of OLP. After one year treatment with clobetasol 0.05% ointment, periodic intramuscular injections of triamcinolone acetonide and oral fluconazole, the disease was stable. All the therapies for OLP have been discontinued.

Finally, Grinspan syndrome still remains an unclear phenomenon. Many authors agree on considering it as a stochastic effect of different drugs used to treat diabetes and hypertension [4,6]. Worsening of oral lesions after the introduction of metformin in our case-report could suggest an etiopathogenetic role of drugs. On the other hand, clinical remission without removing any anti-diabetic or anti-hypertensive therapy may exclude drugs as the only pathogenic factor. The question is: does Grinspan syndrome really exist? Do we need to consider it as a separate clinical entity still today although the existence of OLL and OLP?

From our point of view, this "syndrome" is mostly like a consequence of different circumstances. First of all, diabetes and HTN are really frequent in the general population and a correlation between them is well established today [10]. So, it is not unexpected that many patients with OLP or OLL are previously diagnosed with diabetes and HTN. Diabetes may play a role in the onset of both OLP and OLL, due to the related immunological dysregulation. In addition, drugs used to treat hypertension and diabetes are probably responsible for the development of such oral lesions [5]. Garpalati et al, moreover, carried out a metanalysis with a negative result about the association of these three clinical entities [4]. Since it has never been proved any statistical correlation between OLP, diabetes and HTN, and given the existence of OLP and OLL as clinical entities, we should begin to consider that "Grinspan syndrome" may assume just a historical significance.

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