A RARE ASSOCIATION BETWEEN LAUGIER-HUNZIKER, SJOGREN SYNDROMES AND OTHER AUTOIMMUNE DISORDERS- CASE REPORT AND LITERATURE REVIEW

O ASOCIERE RARĂ ÎNTRE SINDROAMELE LAUGIER-HUNZIKER, SJOGREN ȘI ALTE AFECȚIUNI AUTOIMUNE- PREZENTARE DE CAZ ȘI REVIZUIRE A LITERATURII

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A rare association between Laugier-Hunziker, Sjogren syndromes and other autoimmune disorders - case report and literature review

Abstract

Laugier-Hunziker-Baran syndrome is an aquired hypermelanosis of the oral mucosa, nails and other cutaneous sites of unknown etiology that affects middle aged individuals of all races. Up to date, less than 200 cases have been reported in the literature. So far, no association has been found between Laugier-Hunziker and genetic predisposition, malignancies, connective tissue and autoimmune disorders, even though these comorbidities have been mentioned in the literature over the years. We present the case of a 58 years old caucasian female diagnosed with Laugier-Hunziker, Sjogren syndrome and autoimmune thyroid disease, completed with a literature review. To our knowledge, this is the second case report regarding the association between Laugier-Hunziker and Sjogren syndrome presented in the literature and the first report regarding the association with autoimmune thyroid disease. The informations available so far do not conclude whether these are coincidental associations, therefore we reccomend screening patients with Laugier-Hunziker syndrome for autoimmune disorders in order to facilitate a better understanding of this relative recently described condition.
Introduction

Laugier-Hunziker disease is a rare, acquired condition whose main features are represented by oral/mucosal hyperpigmentation and, sometimes, longitudinal melanonychia. This syndrome was first described in 1970 by Laugier and Hunziker who reported five cases of adult-onset macular pigmentation of the oral mucosa, followed nine years later by Baran who noted that, in some patients, longitudinal melanonychia is associated with the mucosal lesions. Later on, lesions with similar histopathological aspect have been described in other areas of the body and the term “idiopathic lenticular mucocutaneous pigmentation” has been proposed for them. Up to date, less than 200 cases have been reported in the literature, but the syndrome seems to be more frequent. Laugier-Hunziker syndrome is a diagnosis of exclusion, confirmed only after other diseases associated with hyperpigmentation, mainly Addison’s disease and Peutz-Jeghers syndrome, have been ruled out. It’s etiology still remains unknown and scientists have failed to find any familial predisposition, malignant and connective tissue or autoimmune association linked to it.

Case report

A 58 years old Caucasian woman was referred to our dermatology clinic for the evaluation of asymptomatic nail hyperpigmentations, condition which had been present for at least 4 years. She denied any local trauma, hemorrhage, topical or systemic medication prior to the appearance of the lesions. The family history revealed neurological and metabolic disorders (Alzheimer’s disease, Parkinson disease and type II diabetes mellitus) without any history of abnormal mucocutaneous pigmentation. The patient reported previous exposure to toxic chemicals in the work environment for about 10 years (but not to any known substances that might induce hyperpigmentations) and a smoking habit suspended for 5 years. She had also been diagnosed with chronic lymphocytic thyroiditis having oral substitution (50 μg levothyroxine/day), Sjogren syndrome, for which she has been treated with hydroxychloroquine (400 mg/day), and osteoporosis treated with cholecalciferol (1000 UI/day). Sjogren syndrome was diagnosed based on clinical signs (xerostomia and xerophthalmia), positive Schirmer’s test and specific positive serology (anti SSA antibody > 2000 U/ml and anti SSb antibody > 2000 U/ml).

Physical examination revealed an alert, orientated, overweight white female (Fitzpatrick III skin type), with no acute distress and stable vital signs, xerostomia and xerophthalmia. Dermatological exam showed brownish, well defined, homogenous pigmentation in longitudinal stripes on the nails of the first finger of her right hand and the second and third fingers of her left hand (fig.1).

Figure 1. Homogenous pigmentation in longitudinal stripes on the nails
This longitudinal melanonychia was associated with poorly defined pigmentation of the periungual skin (Hutchinson sign). Similar hyperpigmented bands were also present on the nails of the first, second and fourth right toes and first and second left toes (fig. 2). No nail dystrophy was found. Brown, ovoid shaped, well-defined, asymptomatic macules (7 millimeters), in a lentiginous pattern, were symmetrically disposed on the hard palate mucosa (fig. 3). There were no other hyperpigmented macules in the conjunctiva or genital mucosa and the rest of the skin was normal except the hands, which showed typical signs of phytophotodermatitis.

Laboratory tests revealed mild leucopenia and neutrophilia, a positive rheumatoid factor and an elevated ESR (21 mm/hour). Other blood tests values were all within the normal limits. They included complete blood count, biochemistry, coagulogram, ionogram, urine analysis, lipid status, renal and hepatic function, nasal and tonsillar exudate. Additional biochemical assessment did not show any abnormalities regarding the levels of cortisol, ACTH, sodium, potassium, magnesium, thereby excluding Addison disease. Several other blood tests (anti double stranded DNA antibody, anti Sm antibody, C3 and C4 complement levels, LKM1 antibody, ASMA, Ig M and IgG antiphospholipid antibody, lupic cells) have also been performed in order to exclude potential autoimmune diseases and their results were negative.

Dermoscopic examination of the nail unit revealed pseudo Hutchinson sign with homogenous brownish and grayish longitudinal band and lines, with ill-defined margins on the nail plate (fig. 4). The mucosal lesions on the hard palate were not accessible for dermoscopy due to their localization. Nail fold capillaroscopy revealed a normal pattern, but described the presence of pigment deposits similar to those of hemosiderin, without capillary involvement. Chest X-ray showed discrete pulmonary fibrosis and no pathological changes were found in the abdominal ultrasound.
Upper gastrointestinal endoscopy and colonoscopy were also considered but the patient refused these investigations. In addition, she did not have any suggestive family history, nor clinical manifestations of a gastro-intestinal disorder, which made the diagnosis of Peutz-Jeghers syndrome very unlikely. Considering the clinical manifestations, laboratory findings, the lack of systemic involvement, and by excluding other disorders with similar mucocutaneous lesions, a final diagnosis of Laugier-Hunziker syndrome was made.

**Dermoscopy**
The dermoscopic features of Laugier-Hunziker syndrome have recently been described and they include the following criteria depending on localization: parallel pattern with light to dark brown streaks and, occasionally, globules for mucosal lesions (oral, genital); longitudinal, bandlike pigmentation with poorly defined margins and micro-Hutchinson sign on the nails; parallel, furrowed pigmented lesions on acral lesions (palmo-plantar)\(^{5,12,13}\).

**Histopathology**
The main histopathological features of Laugier-Hunziker syndrome have been studied using biopsy specimens from mucosal lesions or keratinized skin. Nail changes have not been described histopathologically because nail biopsies are rarely necessary and difficult to perform in the context of multiple nail involvement. The hiperpigmented macules of Laugier-Hunziker usually disclose dense hypermelanosis with melanin deposits in the basal layer with no cell atypia, accumulation of melanophages in the papillary dermis, intact basement membrane and occasionally, incontinentia pigmenti. Recently, immunohistochemical studies using S100 and L-3,4 have documented an increase of non-nested melanocytes in some areas of hyperpigmentation\(^{10}\).

**Differential diagnosis**
Laugier-Hunziker syndrome is a diagnosis of exclusion. Other pathologies similar in respect of clinical presentation are listed in table 1\(^{14,15,16,17}\).

### Table 1. Differential diagnosis of Laugier-Hunziker syndrome

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Peutz Jeghers Syndrome</td>
<td>- family history – autosomal dominant transmission</td>
</tr>
<tr>
<td></td>
<td>- hamartomatous gastro-intestinal polyposis</td>
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<td></td>
<td>- onset age usually in infancy or early childhood</td>
</tr>
<tr>
<td></td>
<td>- pigmented macules over perioral region, the oral mucosa, eyes, nose, hands; rarely on nails</td>
</tr>
<tr>
<td>Addison Disease</td>
<td>- endocrine disease</td>
</tr>
<tr>
<td></td>
<td>- hyperpigmentations on the pressure exposed areas, but pigmentation of the oral mucosa may be the first sign</td>
</tr>
<tr>
<td></td>
<td>- decreased pubic and axillary hair in women</td>
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<tr>
<td>McCune Albright Syndrome</td>
<td>- café-au-lait macules</td>
</tr>
<tr>
<td></td>
<td>- onset age usually in infancy</td>
</tr>
<tr>
<td></td>
<td>- bony modifications</td>
</tr>
<tr>
<td>Posttraumatic melanosis</td>
<td>- history of trauma</td>
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<tr>
<td></td>
<td>- leukomichotic area over the hematoma</td>
</tr>
<tr>
<td></td>
<td>- gradually fading with nail growing</td>
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<tr>
<td>Smoker melanosis</td>
<td>- hyperpigmentation over the anterior attached gingiva</td>
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<tr>
<td></td>
<td>- no other pigmentation of the body</td>
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<tr>
<td>Racial pigmentation</td>
<td>- the principal cause of longitudinal melanonychia</td>
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<td></td>
<td>- usually occurs in 2 to 5 nails</td>
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<tr>
<td>Leopard Syndrome</td>
<td>- lentigines present in early infancy/childhood</td>
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<tr>
<td></td>
<td>- EKG modifications, ocular hypertelorism, abnormal genitalia, growth retardation, deafness</td>
</tr>
</tbody>
</table>
**Discussion**

Laugier-Hunziker syndrome is an acquired benign condition of unknown etiology that affects mainly middle-aged patients with no racial predilection and a slightly predominance in women\(^{(3)}\), characterized by asymptomatic hyperpigmented brown macules located on the oral mucosa (lips, tongue, gingiva, soft and hard palate). The macules can be round, lenticular, linear in shape, solitary or multiple, with distinct or poorly defined borders, they appear gradually and are considered to be permanent\(^{(3)}\). Longitudinal melanonychia occurs in more than 60% of cases, it is present in more than one nail, affecting both the fingers and the toes, but it is not associated with dystrophic changes. Pseudo-Hutchinson sign has been described in patients with Laugier-Hunziker syndrome, often present in multiple nails on the same patient\(^{(3)}\), which is a very useful criteria in separating this condition from nail malignant melanoma.

Lately, similar pigmented changes have been reported in other areas of the body, such as fingers, thorax, abdomen, arms, eyebrows and legs but also on other mucosal surfaces, like the genitalia, conjunctiva and esophagus\(^{(2,3)}\).

While most authors consider that there is no genetic predisposition associated with the syndrome, Makhoul et al reported the presence of Laugier-Hunziker syndrome in 3 members of the same family (a mother and two daughters)\(^{(6)}\).

The condition is caused by a melanocytic functional alteration with increased synthesis of melanosomes, which are subsequently transported to the basel cell layer\(^{(3)}\). The exact etiologic mechanism that induces all these changes still remains unknown.

Laugier-Hunziker syndrome is a diagnosis of exclusion, stated only after other serious pathologies, mainly Addison’s disease and Peutz-Jegers syndrome have been ruled out. In order to achieve that, the following tests should be performed: complete physical examination and history, corticotropin level, morning corti-
Currently unknown the exact significance of their association is cur-
rently known (5). The literature reports one case of Laugier-Hunziker associated with actinic lichen planus (11). So far, there is no known association between Laugier-Hunziker syndrome and malignancies, but there has been one report of ovarian cancer and another one of pancreatic carcinoma and Laugier-Hunziker syndrome. While in the first case, the pigmented lesions appeared during chemotherapy, in the latter the onset of mucosal lesions was contemporary with the first symptoms of carcinoma. Therefore, Wondratsch et al believe that the possibility of an underlying malignancy should be considered in Laugier-Hunziker syndrome (8).

Laugier-Hunziker syndrome does not require treatment, unless esthetic concerns bother the patients, in which case Q-switched Nd:Yag, Q-switched alexandrite laser therapy or cryosurgery seem to be good alternatives, even though recurrences after treatment are frequent (8, 10).

Our patient has also been diagnosed with Sjogren syndrome and autoimmune thyroiditis. To our knowledge, only one case regarding the association between Laugier-Hunziker and Sjogren syndrome has been presented in the literature (7) and we could not find any report regarding the association with autoimmune thyroid disease. In the absence of compelling evidence that link Laugier-Hunziker syndrome with autoimmune diseases, these associations might be regarded as coincidental. Nevertheless, we recommed screening the patients with Laugier-Hunziker syndrome for connective tissue and other autoimmune disorders with subsequent reports in the literature. This conduct might stimulate researchers to develop new prospective randomised studies, which might shade a light on this subject.

Bibliography