Tongue Hyperpigmentation during Interferon and Ribavirin Therapy; A Case Report

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Abstract

Tongue hyperpigmentation during treatment of hepatitis C virus (HCV) with pegylated interferon (Peg INF) and ribavirin considered a rare finding, we report a case and review literature to disclose this side effect of HCV treatment. Twenty seven cases of tongue pigmentation during HCV treatment were reported (14 out of 27) cases included the response to HCV treatment in their reports,12 cases (12/14, 85.7%) had response to treatment and 8 cases (8/14, 57%) achieved sustained virological response (SVR); this may raise a question whether the appearance of tongue pigmentation is a marker of response to treatment?

There is no relation between tongue pigmentation and HCV genotype and duration of treatment. Dark skin may be a risk factor as 66.6% of the reported cases were in non-Caucasien. Sixty five percent (13/27) of patients with tongue pigmentation were females.

Gastroenterologists should be aware of this rare side effect, and probably under diagnosed, as an alteration in mucous membrane and/or skin pigmentation can be a source of significant emotional and psychological distress for some patients.

Keywords: Tongue hypespigmentation, Hepatitis C virus.

Introduction:

Cutaneous side effects of interferon (INF) include dry skin, pruritus, skin rashes, alopecia, and exacerbation of autoimmune dermatoses, such as psoriasis, lichen planus, or vitiligo.(1)

In HCV infected patients, skin reactions to IFN are uncommon and usually seen at the injection sites due to local inflammatory changes(2,3). Skin and/or mucosal hyperpigmentation on antiviral therapy for chronic hepatitis C is considered rare(4-17). One case series showed that hyperpigmentation of mucous membrane is not infrequent (9%)18.

We present this case because of rarity or under recognition of this side effect of HCV medications and to make physicians who prescribe such therapy for HCV infection aware of this mucosal pigmentation as an uncommon and slowly reversible complication.

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Case Report:
A 59-year old woman with chronic HCV infection (genotype 1b) presented to gastroenterology and hepatology clinic, Jordan University Hospital, Amman, Jordan with sore tongue and lingual pigmentation.

She was non-smoker with history of diabetes mellitus and hypertension. Physical and local abdominal examinations were normal.

Treatment with weekly injection of subcutaneous pegylated interferon α2a once weekly and daily oral ribavirin (1200 mg daily) started 8 weeks before the appearance of symptomatic bluish patches on the dorsum and the tip of her tongue as well as the oral mucosa (Figure 1), no other sites were involved. Laboratory examination showed normal liver function test, kidney function test, Complete Blood Count (Hb13.8 g/dl, WBC 11000/mm³, Neutrophils 57%, platelet 387/mm³), cortisol and thyroid stimulating hormone (TSH). HCV quantitative value was 1.4*10⁵ IU/ml (by real time PCR) at the initiation of therapy. At 4th week of HCV treatment she developed anemia with Hb 10.5 g/dl that was managed by reducing ribavirin dose. She achieved extended rapid, completed early virological response, end of treatment responses and sustained virological response.

Review of Literature
To the best of our knowledge, there were 27 cases described INF-induce mucosal hyperpigmentation, especially reported in non-Caucasian patients (67%) (Table 1).

The differential diagnosis of lingual hyperpigmentation includes Addison disease, Peutz-Jeghers syndrome, Laugier-Hunziker syndrome, amalgam tattoo, nevi, lichen planus pigmentosus, and adverse reactions to medications, such as oral contraceptives, cyclophosphamide, bleomycin, chloroquine(4).

Although the exact mechanism underlying oral hyperpigmentation in patients treated with peginterferon and ribavirin is still unknown, it has been postulated that increased melanin...
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production, which is regulated by the melanocyte expression of melanocyte stimulating hormone (MSH) receptors, has been shown to be up regulated by IFN(5,6). The increased expression of MSH receptors in the presence of possibly increased plasma levels of MSH in IFN-treated patients may lead to increased melanin production and deposition in the hyperpigmented mucocutaneous areas(2).

Willems et al.(5) described the first report of both skin and tongue pigmentation during combination therapy in two non-white patients with HCV infection. Gurguta et al.(10) described tongue pigmentation in five (2.9%) out of 171 patients; the authors did not notice any hyperpigmentation in the non-Caucasian. Tsilika K. et al.(18) published a new case series of mucocutaneous pigmentation during treatment of HCV, 9% (7/77) of patients developed pigmentation of oral mucosa, 4 patients were Caucasian.

Figure 2. Flow chart shows 27 patients and their response to HCV treatment.

RVR: rapid virological response, SVR: sustained virological response, EOT: end of treatment

Discussion:

We report the first case from Jordan with mucosal hyper- pigmentation associated with PEG-INF-α2a plus ribavirin therapy in a patient infected with HCV.

Our patient was not receiving any drug that can cause tongue discoloration apart from HCV treatment. The absence of an alternative explanation and the temporal relationship between the initiation of HCV therapy and the observed pigmentedary changes suggested that antiviral therapy induced this abnormality. Our patient declined to do tongue biopsy.
Majority of studies mentioned the rarity of this condition, the last published series noted that tongue pigmentation during HCV treatment occurred at higher incidence rate (9%); This discrepancy in the incidence of oral mucosal hyperpigmentation may be explained by the symptomatology, 19/27 cases reported symptomatology and the rest (8/27) did not mention whether their patients had symptoms or not, 63% (12/19) of cases had no symptom and just 37% (7/19) presented with tongue pain, discomfort or mouth soreness (Table 1). Lack of symptoms may make this condition pass unrecognized by the patient.

Out of 27 patients, just 14 cases included their response to treatment, 12/14 (85.7%) case had some form of response including rapid virological response (RVR), SVR and end of treatment (EOT), 57% (8/14) achieved SVR (Figure 2); this may raise a question if the occurrence of tongue and/or skin pigmentation is a marker of response to treatment?

Nine cases (9/27) of oral pigmentation resulting from PEG-INF and ribavirin therapy were found in Caucasian patients. These findings suggest that dark skin color, which is found in 18/27 (66.6%) of patients, may be a relevant clinical risk factor for this therapy's complication.

Although it had been reported that gender was not considered as a risk factor for this condition, 20 studies included the gender of their patients; 13/20 (65%) were females.

Regarding the relationship between the genotype of HCV and tongue pigmentation, no predominance of one genotype over the other; 16/27 cases reported their HCV genotype, there were 6 cases with genotype 1 (which is the most prevalent genotype worldwide 46.2%), 5 cases with genotype 4 and the remaining cases were genotypes 2, 3, 5 and 6.

No association with treatment's duration as hyperpigmentation occurred after 1-10 months of starting HCV therapy and resolved partially over time with discontinuation of treatment.

It is also impossible to exclude a role for ribavirin, because all the patients received interferon associated with ribavirin. Combination therapy with INF and ribavirin induces more skin reactions than INF alone, suggesting a synergistic effect between INF and ribavirin.

Alterations in mucous membrane pigmentation can be a source of significant emotional distress for patients. Physicians should be aware of this adverse effect of interferon and ribavirin treatment, especially in dark skinned patients. Till now, nobody reported hyperpigmentation of skin and/or mucous membrane with the introduction of new direct acting antiviral therapy.
Table 1. 27 reported cases of tongue pigmentation during interferon and ribavirin treatment

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>Genotype</th>
<th>Time of appearance in months</th>
<th>Response to treatment</th>
<th>Race</th>
<th>Symptom***</th>
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<tbody>
<tr>
<td>Claude B et al. 4</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>RVR*</td>
<td>Non Caucasian</td>
<td></td>
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<tr>
<td>Willems et al. 5</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>RVR +SVR**</td>
<td>Non Caucasian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2a</td>
<td>12</td>
<td>RVR +SVR</td>
<td>Non Caucasian</td>
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<tr>
<td>Torres HA et al. 6</td>
<td>1</td>
<td>#</td>
<td>1.5</td>
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<td>Caucasian female</td>
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</tr>
<tr>
<td>Fernandez A et al. 7</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>Treatment discontinued</td>
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<td>Dell’Isola S. et al. 8</td>
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<td>1</td>
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<tr>
<td>Farshidi D. et al. 9</td>
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<td>#</td>
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<td>Gurguta C, et al 10</td>
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<td>4</td>
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<td>Oguz Karabay et al. 12</td>
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<td>2</td>
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<td>Radha krishna y et al. 13</td>
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<td>Mlika RB et al. 14</td>
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<tr>
<td>S. Ghosh et al. 15</td>
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<td>de Moraes PC et al. 16</td>
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<td>Katerina Tsilika et al. 18</td>
<td>7</td>
<td>#</td>
<td>#</td>
<td>#</td>
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<td>3 non Caucasian</td>
<td>-6</td>
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</tbody>
</table>

RVR*: rapid virological response, SVR**: sustained virological response, Symptoms***: tongue pain, discomfort or soreness, NR$: none responder, EOT$: end of treatment, +: occurred, -: not occurred, #: not mentioned.
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References

فُط تصبغ اللسان أثناء استعمال علاج الإنترفيرون والريبافيرين

عبد الله اليوزيكي 1، عامر الخطيب 2، مصطفى الشناف 2، وحبيبي أبو سهيب 2
1- مركز فاروق الطب السليماني، كردستان، العراق.
2- قسم أمراض الجهاز الهضمي والكبد، مستشفى الجامعة الأردنية، وكلية الطب، الجامعة الأردنية.

الملخص

بعد فُط تصبغ اللسان أثناء العلاج بالإنترفيرون من فيروس التهاب الكبد الوبائي نوع سي والريبافيرين حالة نادرة. ونحن نسجل الحالة ونراجع الأدبيات للكشف عن هذه الآثار الجانبية لعلاج التهاب الكبد الفايروس نوع (سي).

تم تسجيل سبعة وعشرون حالة تصبغ اللسان خلال استعمال علاج التهاب الكبد الفايروس نوع سي، تم الإبلاغ عن 14 من أصل 27 حالة تضمنت الاستجابة لعلاج فيروس (سي). في تقريرهم، 12 حالة (12/14، 85.7%) استجابت للعلاج، 8 حالات (8/14، 57%) حققت الاستجابة الفيروسية المستدامة. هذا قد يثير السؤال عن إذا كان تصبغ اللسان هو نعمة من علامات الاستجابة للعلاج 

(SVR) لا توجد علاقة بين تصبغ اللسان والطراز الغنبي للفايروس سي ودرجة العلاج. البشعة الداكنة عامل خطير، إذ كانت 66.6% من الحالات التي تم استعراضها في غير القوافرزين. حسب وسن بالمئة (13/27) من المرضى كانوا من النساء.

يجب أن يكون أطباء الجهاز الهضمي على بينة من هذه الآثار الجانبية النادرة، وربما دون التشخيص، حيث إن تصبغ الغشاء المخاطي /أو الجلد يمكن أن تكون مصدراً لاضطرابات عاطفية ونفسية كبيرة بالنسبة لبعض المرضى.

الكلمات الدالة: تصبغ اللسان، فيروس التهاب الكبد الوبائي.