

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-Caucasian. 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 hyperpigmentation, Hepatitis C virus.

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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 $\alpha 2a$ once weekly and daily oral ribavirin(1200mg 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 (Hb13.8g/dl, WBC 11000/mm³, Neutrophils57%, platelet 387/mm³), cortisol and thyroid stimulating hormone (TSH). HCV quantitative value was 1.4×10^5 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 .



Figure 1. tongue pigmentation of HCV patient treated with interferon plus ribavirin

Review of Literature

To the best of our knowledge, there were 27 cases described INF-induced 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

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.

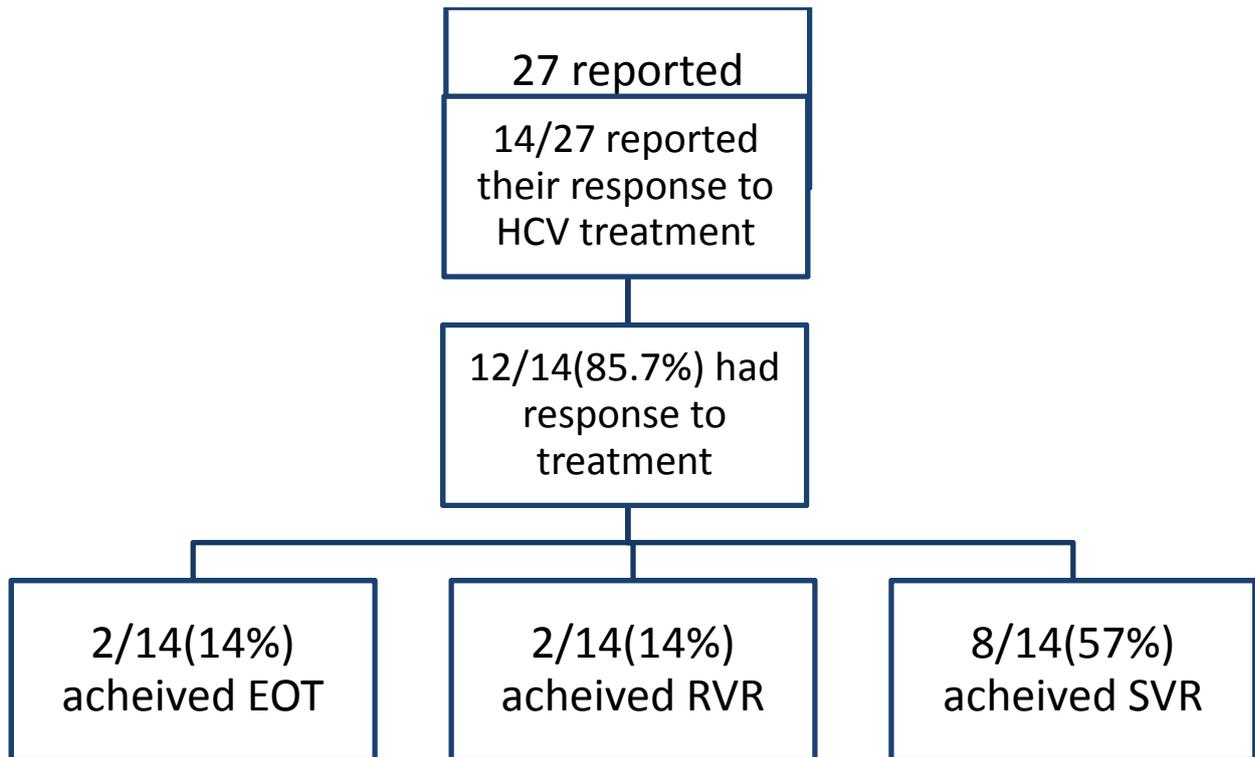


Figure 2. Flow chart shows 27 patients and their response to HCV treatemnt.

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- α 2a 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 pigmentary changes suggested that antiviral therapy induced this abnormality. Our patient declined to do tongue biopsy.

Majority of studies⁽⁴⁻¹⁷⁾ mentioned the rarity of this condition, the last published series⁽¹⁸⁾ 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^(6,7,8,9,17,18). 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^(5,6,10), 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%⁽¹⁹⁾), 5 cases with genotype 4 and the remaining cases were genotypes 2,3,5 and 6.

No association with treatment's duration (Table 1) as hyperpigmentation occurred after 1-10 months of starting HCV therapy and resolved partially over time with discontinuation of treatment^(5,10).

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

<i>References</i>	<i>No. of patients</i>	<i>Genot ype</i>	<i>Time of appearance in months</i>	<i>Response to treatment</i>	<i>Race</i>	<i>Symptom***</i>
Claude B et al. 4	1	4	2	RVR*	Non Caucasian	-
Willems et al. 5	2	5 2a	9 12	RVR +SVR** RVR +SVR	Non Caucasian Non Caucasian	- -
Torres HA et al. 6	1	#	1.5	RVR	Caucasian female	+
Fernandez A et al. 7	1	4	3	Treatment discontinued	Caucasian female	+
Dell'Isola S. et al. 8	1	1	#	SVR	Caucasian female	#
Farshidi D. et al. 9	1		4	#	Caucasian	+
Gurguta C,etal10	5	2a 4b 1b 1 4	8 10 3 1 1	SVR SVR NR ^s EOT ^{ss} EOT	Non Caucasian Non Caucasian Non Caucasian Non Caucasian Non Caucasian	# # # # #
Sood A. et al. 11	2	3a 1b	2 4	SVR SVR	Non Caucasian Non Caucasian	# #
Oguz Karabay et al. 12	1	#	2	#	Non Caucasian	+
Radha krishna y et al. 13	1	6	6	RVR +SVR	Non Caucasian	-
Mlika RB et al. 14	1	1	1	#	Non Caucasian	+
S. Ghosh et al. 15	1	4	10	#	Non Caucasian	+
de Moraes PC et al. 16	1	#	8	#	Non Caucasian	-
Ingrid A. et al. 17	1	1b	4	#	Caucasian	-
Katerina Tsilika et al. 18	7	#	#	#	4 Caucasian 3 non Caucasian	+1 -6

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

References

1. Chang LW, Liranzo M, Bergfeld WF. Cutaneous side effects associated with interferon-alpha therapy: A review. *Cutis* 1995; 56:144.
2. Christian MM, Diven DG, Sanchez RL, Soloway RD. Injection site vasculitis in a patient receiving interferon alpha for chronic hepatitis C. *J Am Acad Dermatol* 1997; 37: 118-20.
3. Kurzen H, Petzoldt D, Hartschuh W, Jappe U. Cutaneous necrosis after subcutaneous injection of polyethyleneglycol-modified interferon alpha. *Acta Derm Venereol* 2002; 82: 310-2.
4. Claude Bachmeyer MD, Jean-Charles Pellen MD. Tongue hyperpigmentation during hepatitis C treatment. *CMAJ* 2012;184: 1498.
5. Willems M, Munte K, Vrolijk JM, Den Hollander JC, Böhm M, Kemmeren MH et al. hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; 149:390-4.
6. Torres HA, Bull L, Arduino RC, Barnett BJ. Tongue hyperpigmentation in a Caucasian patient coinfectd with HIV and hepatitis C during peg interferon alfa-2b and ribavirin therapy. *Am J Gastroenterol* 2007;102:1334-5.
7. Fernández A, Vazquez S, Rodriguez-Gonzalez L. Tongue hyperpigmentation resulting from peg interferon alfa-2a and ribavirin treatment in a Caucasian patient with chronic hepatitis C. *J Eur Acad Dermatol Venereol* 2008;22: 1389-91.
8. Dell'Isola S, Lalungo AM, Starnini G, et al. A surprising hyperpigmentation of the gums and tongue. *Gut* 2008; 57: 1697.
9. Farshidi Dina, and Melvin W. Chiu. Lingual hyperpigmentation from pegylated interferon and ribavirin treatment of hepatitis C. *J AM ACAD DERMATOL* 2010; 62: 164-5.
10. Gurguta C, Kauer C, Bergholz U, et al. Tongue and skin hyperpigmentation during PEG-interferon-alpha/ribavirin therapy in dark-skinned non-Caucasian patients with chronic hepatitis C. *Am J Gastroenterol* 2006; 101: 197-8.
11. Sood A, Midha V, Bansal M. et al. Lingual hyperpigmentation with pegylated interferon and ribavirin therapy in patients with chronic hepatitis C. *Indian J Gastroenterol* 2006; 25: 324.
12. Oguz Karabay, Nadir Goksugur, Aziz Ogutlu. Tongue hyperpigmentation during interferon therapy. *Journal of Dermatology* 2011; 38: 290-1.
13. Radha Krishna Y, Itha S. What caused this lingual hyperpigmentation in a patient with chronic hepatitis. *Liver Int* 2010; 30: 416.
14. Mlika RB, Kerkeni N, Marrak H. Et al. Tongue hyperpigmentation during PEG-interferon-alfa/ribavirin therapy in a non-Caucasian patient with chronic hepatitis C: a case report and review of the literature. *Int J Dermatol* 2013; 52: 643-4.
15. Ghosh S, Duseja A, Dhiman RK, Chawla YK. Tongue hyperpigmentation resulting from peginterferon alfa-2b and ribavirin treatment in a patient with chronic hepatitis C. *Dig Dis Sci.* 2012; 57 (3): 820-1.
16. de Moraes PC, Noce CW, Thomaz LA, Mautoni MC, Correia ME. Tongue hyperpigmentation resulting from peginterferon alfa and ribavirin combination therapy: a case report. *J Am Dent Assoc.* 2009; 140 (11): 1377-9.
17. Ingrid Aguayo-Leiva, Bibiana Pérez, Irene Salguero, Pedro Jaén. Tongue hyperpigmentation during interferon-alpha and ribavirin therapy. *E J Dermatol* 2009; 19: 291-2.
18. Tsilika K, Tran A, Trucchi R., Pop S., Anty R., Cardot-Leccia N, et al. Secondary hyperpigmentation during Interferon Alfa Treatment for Chronic Hepatitis C Virus Infection. *JAMA Dermatol.* 2013; 149 (6): 675-7.
19. Jane P. Messina, Isla Humphreys, Abraham Flaxman, Anthony Brown, Graham S. Cooke, Oliver G. Pybus, et al. Global Distribution and Prevalence of Hepatitis C Virus Genotypes. *Hepatology.* 2015; 61: 77-87.

فرط تصبغ اللسان أثناء استعمال علاج الإنترفيرون والريبافيرين

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الملخص

يعد فرط 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 الفيروسي نوع (سي).

تم تسجيل سبعة وعشرون حالة تصبغ اللسان خلال استعمال علاج التهاب الكبد الفيروسي نوع سي، تم الإبلاغ عن 14 من أصل 27 حالة تضمنت الاستجابة لعلاج فيروس (سي) في تقاريرها، 12 حالة (14/12، 85.7%) استجابت للعلاج، 8 حالات (14/8، 57%) حققت الاستجابة الفيروسية المستدامة. هذا قد يثير السؤال عما إذا كان ظهور تصبغ اللسان هو علامة من علامات الاستجابة للعلاج (SVR). لا توجد علاقة بين تصبغ اللسان والطرز العرقي لفيروس سي ومدة العلاج.

البشرة الداكنة عامل خطر، إذ كانت 66.6% من الحالات التي تم استعراضها في غير القوقازيين. خمسة وستون بالمئة (27/13) 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 و/أو الجلد يمكن أن تكون مصدراً لاضطرابات عاطفية ونفسية كبيرة بالنسبة لبعض المرضى.

الكلمات الدالة: تصبغ اللسان، فيروس التهاب الكبد الوبائي.