



## Interferon and Ribavirin-Induced Oral Hyperpigmentation in Two Taiwanese Patients: Case Report and Literature Review

Yu-Jong Weng<sup>1,2\*</sup> and Min-Fu Tsan<sup>3</sup>

<sup>1</sup>Department of Medicine, Taichung Veterans General Hospital, Republic of China

<sup>2</sup>Department of Applied Chemistry, National Chia-Yi University, Republic of China

<sup>3</sup>McGuire Research Institute and Veterans Affairs Medical Center, USA

**\*Corresponding author:** Yu-Jong Weng, Division of Gastroenterology, Department of Medicine, Taichung Veterans General Hospital, 600, Section 2, Shixian Road, West District, Chia-Yi Branch, Chia-Yi, Taiwan 60090, Republic of China, Tel: +886-(0)5-2359630 x 1002, Fax: +886-(0)5-2369676, E-mail: [yujong3495@gmail.com](mailto:yujong3495@gmail.com)

### Abstract

Hyperpigmentation of the tongue and oral mucosa is a rare adverse event of the combination therapy with either interferon  $\alpha$  (IFN) or polyethylene glycol-conjugated IFN (PEG-IFN) and ribavirin (RBV) in patients with hepatitis C virus (HCV) infection. The majority of these lesions either improves or resolves completely after completion of the therapy. It occurs more frequently in patients with dark skins and in female patients. While most patients have tongue hyperpigmentation alone, others also have hyperpigmentation involving gum, hard palate and/or buccal mucosa. It is not clear whether the hyperpigmentation of tongue and/or oral mucosa is associated with similar lesions in the gastrointestinal mucosa. We reported the first two cases of PEG-IFN and RBV combination therapy-induced oral hyperpigmentation in Taiwanese patients with hepatitis C, one in the tongue and the other in the buccal mucosa. Upper gastrointestinal (UGI) endoscopic exams revealed that none of these two patients had similar hyper-pigmented lesions in the esophageal, gastric, and duodenal mucosa. Since none of the previous reports mentioned any UGI endoscopic findings, further studies are necessary to determine whether the IFN or PEG-IFN and RBV-induced hyperpigmentation may also involve UGI mucosa. The mechanism of IFN and RBV-induced oral hyperpigmentation remains unclear. While most authors attributed oral hyperpigmentation to IFN or PEG-IFN, there has been no reported case of oral hyperpigmentation in patients treated with IFN, PEG-IFN or RBV alone. Therefore, it is more appropriate to call it IFN or PEG-IFN and RBV-induced oral hyperpigmentation.

### Keywords

Oral hyperpigmentation, Interferon, Polyethylene glycol-conjugated interferon, Ribavirin, and Hepatitis C

### Introduction

A variety of medications such as non-steroidal anti-inflammatory drugs, anti-malarials, amiodarone, cytotoxic drugs, tetracyclines, heavy metals, and psychotropic drugs, may cause cutaneous hyperpigmentation [1]. Recently, hyperpigmentation of the tongue and oral mucosa have also been reported in patients with hepatitis

C virus (HCV) infection who were being treated with either short acting IFN or long acting polyethylene glycol-conjugated IFN (PEG-IFN) combined with ribavirin (RBV) [1,2]. The IFN or PEG-IFN and RBV-induced oral hyperpigmentation appears to be more common in patients with dark skin, even though it has been reported in both Caucasian as well as non-Caucasian patients [3-5]. It is not clear whether IFN and ribavirin-induced oral hyperpigmentation is associated with similar lesions in the gastrointestinal mucosa in the affected patients. Here we report oral hyperpigmentation developed during the PEG-IFN and RBV combination therapy in two Taiwanese patients with hepatitis C. Upper gastrointestinal (UGI) endoscopic exams revealed that no similar hyper-pigmented lesions were noted in the esophageal, gastric, and duodenal mucosa.

### Case report

#### Case 1

A 33-year-old Taiwanese male patient with HCV infection developed hyperpigmentation of his tongue 18 weeks after the initiation of PEG-IFN  $\alpha$ -2b (180  $\mu$ g weekly) plus RBV (1,200 mg daily) therapy. On physical examination, irregular brown, macular, pigmented patches were noted on ventral and dorsolateral aspects of his tongue (Figure 1A). No hyper-pigmented lesions were noted in his gum, hard palate, inner side of cheeks, nails or other cutaneous sites. There was no discomfort or altered taste associated with his tongue hyperpigmentation. His HCV genotype was 1a and his HCV ribonucleic acid (RNA) level before therapy was 3,357,596 IU/ml. He was not taking any medications or having any medical conditions that might cause hyperpigmentation [1,6,7]. He complained of acid regurgitation and substernal chest pain. An UGI endoscopic exam revealed esophageal mucosal break without evidence of mucosal hyperpigmentation in esophagus, stomach, and up to the 2<sup>nd</sup> portion of the duodenum. He was treated with proton pump inhibitor with prompt resolution of the chest pain. Six months after the completion of a 24-week PEG-IFN and RBV therapy, there was no improvement in his pigmented tongue lesions.

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**A**

**Figure 1A:** Case 1: Hyper-pigmented patches on the dorsolateral aspects of the tongue

**B**

**Figure 1B:** Case 2: Hyper-pigmented patches on inner side of bilateral cheeks

## Case 2

A 31-year-old Taiwanese male patient with HCV and human immunodeficiency virus (HIV) co-infection was treated with a combination of PEG-IFN  $\alpha$ -2b (180  $\mu$ g weekly) plus RBV (1,200 mg daily) for his hepatitis C. Twenty nine weeks after initiation of the therapy; he noted sensitive hyper-pigmented patches on his bilateral buccal mucosa (Figure 1B). On physical exam, no similar lesion was found in his tongue, gum, hard palate, nail or other cutaneous sites. His HCV genotype was 1a and his HCV RNA level was 3,679,809 IU/ml before therapy. He was not taking any medications or having any medical conditions that might cause hyperpigmentation [1,6,7]. An UGI endoscopic exam was performed due to complaint of acid regurgitation and heartburn. Antral gastritis was found, however, there was no similar mucosal hyperpigmentation in esophagus, stomach, and proximal duodenum. Two months after the completion of a 48-week PEG-IFN and RBV therapy, there was no improvement in his pigmented tongue lesions.

## Discussion

A total of 30 cases of IFN or PEG-IFN and RBV- induced oral hyperpigmentation have been reported in the literature since 2003 (summarized in table 1) [2-5, 8-21]. The incidence of this side effect is not clear. Three retrospective studies revealed an incidence of 2.9%, i.e., 5 out of 171 patients [3], 0.3%, i.e., 1 out of 286 patients [19], and 0.7%, i.e., 1 out of 152 patients [21]. However, a prospective study, which only included patients who had received the PEG-IFN/RBV therapy for more than 3 months, showed a much higher incidence of 9.9%, i.e., 7 out of 77 patients [4]. The incidence would be even higher, i.e., 21% or 16 out of 77 patients, if one included all patients with PEG-IFN/RBV-induced hyperpigmentation, i.e., tongue, oral mucosa, nail and skin [4]. The reason for the discrepancy in these studies is not clear.

Analysis of these 30 reported cases revealed that IFN or PEG-IFN and RBV-associated oral hyperpigmentation affected predominantly dark skinned patients (21 of 30 patients). Of the 23 patients whose sex was available in the reports, 15 patients were female with a female/male ratio of 1.9. Oral hyperpigmentation might occur as quickly as 1 month or as late as 12 months after the initiation of IFN or PEG-IFN and RBV therapy. The most frequent site of oral hyperpigmentation was the tongue (100%). While most patients had tongue hyperpigmentation alone (16 patients), others also had hyperpigmentation involving gum, hard palate and/or buccal mucosa. Eight patients also had lesions involving other parts of the body skin. Interestingly, in 5 of the 30 cases nails (melanonychia) were also involved [4], and 1 female patient also had vulvar mucosa hyperpigmentation [20]. The majority of these patients did not

have any symptoms associated with this IFN- or PEG-IFN and RBV-induced oral pigmentation. Only 7 patients reported tongue symptoms, such as pain, discomfort, burning sensation, or sensitivity to hot and spicy food. None of these patients required reduction in IFN dosages or discontinuation of the IFN therapy. The lesions disappeared in 3 patients, improved in 9 patients, and unchanged in 7 patients at various intervals, i.e., 2-24 months, after completion of the IFN or PEG-IFN and RBV therapy. In one patient the tongue lesion disappeared during the therapy. Whether these differences in outcomes were due to the different length of patient follow-up is not clear.

The mechanism for the IFN or PEG-IFN and RBV therapy-induced oral hyperpigmentation is not clear. Most authors attribute it to IFN or PEG-IFN, because it has been shown that IFN up-regulates the expression of  $\alpha$ -melanocyte stimulating hormone receptors in murine melanocytes, which may lead to an increased melanin production [22]. However, there has been no report of oral hyperpigmentation in patients who were treated with either IFN or RBV alone. Thus, until there is convincing evidence to demonstrate that IFN or PEG-IFN alone can induce oral hyperpigmentation, it is prudent to say that it is the combination of IFN or PEG-IFN and RBV that induced the oral hyperpigmentation.

Clinical diagnosis of IFN or PEG-IFN and RBV-induced oral hyperpigmentation appears straightforward, when hyperpigmentation of tongue and/or oral mucosa develops in a patient during the course of IFN or PEG-IFN and RBV combination therapy. However, it is necessary to rule out other concomitant medications or other medical conditions, such as melanoma, acanthosis nigricans, hemochromatosis and Addison's disease, that may cause systemic hyperpigmentation [1,6,7]. Immunohistochemical examination of these hyperpigmented lesions reveals an increased deposit of melanin, confirming the presence of hyperpigmentation [2]. However, biopsy of the lesion is usually not required for the clinical diagnosis of IFN or PEG-IFN and RBV-induced oral hyperpigmentation.

In the current report, we presented 2 additional cases of PEG-IFN and RBV-induced oral hyperpigmentation, one involving the tongue, while the other involving the buccal mucosa alone. Hyperpigmentation involving buccal mucosa without tongue involvement has not been described previously. In addition, we noted that no similar hyperpigmented lesions were noted in the esophageal, gastric, or duodenal mucosa upon UGI endoscopic exams in these 2 patients. Since none of the previously reported cases had mentioned any UGI endoscopic findings, it is not clear whether the IFN or PEG-IFN and RBV-induced hyperpigmentation may also involve UGI mucosa.

In summary, IFN or PEG-IFN and RBV-induced oral hyperpigmentation is a benign side effect requiring no need to reduce

**Table 1:** Characteristics of IFN or PEG-IFN and RBV-induced tongue and oral mucosa hyperpigmentation

Case #	Age	Sex	Skin Color	HCV GT*	Dosage IFN/RBV	Duration** of Tx (M)	Hyperpigmentation						Symptom	Outcome (M)	Ref
							Tongue	Gum	HP	BM	Nail	Skin			
1	47	F	Dark	5	IFN 3MU/d; RBV 1,200 mg/d	9	+	-	-	-	+	+	-	Disappear (24)	[2]
2	47	M	Dark	2a	***	12	+	-	-	-	-	+	-	Improved after dose reduction	[2]
3	41	F	Dark	2a	PEG-IFN 180 µg/w; RBV 400 mg/d	?	+	-	-	-	-	+	?	Improved (2)	[3]
4	46	M	Dark	4c	PEG-IFN 180 µg/w; RBV 1,200 mg/d	?	+	-	-	-	-	-	?	Unchanged (6)	[3]
5	49	F	Dark	1b	Same as #4	?	+	-	-	-	-	+	?	Improved (3)	[3]
6	46	M	Dark	1	Same as #4	?	+	-	-	-	-	-	?	Disappeared during treatment	[3]
7	40	M	Dark	4	PEG-IFN 180 µg/w; RBV 1,000 mg/d	?	+	-	-	-	-	+	?	Unchanged	[3]
8	45	M	Dark	3a	PEG-IFN 80 mg/w; RBV 800 mg/d	2	+	-	-	-	-	-	?	Improved (6)	[8]
9	54	F	Dark	1b	?	4	+	-	-	+	-	-	?	Unchanged (6)	[8]
10	53	F	White	?	?	1.5	+	-	+	-	-	-	+	Tx ongoing (Tongue Burning)	[5]
11	58	M	Dark	6	Same as #4	2	+	-	-	+	-	+	?	Improved (5)	[9]
12	33	F	Dark	1b	Same as #8	11	+	+	-	-	-	-	?	Gum disappeared (12) Tongue persisted	[10]
13	40	F	White	4	Same as #7	3	+	-	-	+	-	-	+	(Tongue discomfort)	[11]
14	66	F	Dark	?	Same as #7	8	+	-	-	-	-	-	-	Reduced (6)	[12]
15	54	F	White	1b	Same as #8	4	+	-	-	-	-	-	-	?	[13]
16	36	F	White	?	PEG-IFN 120 µg/w; RBV 800 mg/d	4	+	-	-	-	-	-	+	(Tongue sensitive)	[14]
17	54	F	Dark	?	PEG-IFN 1.5 µg/kg/w; RBV 1,000 mg/d	2	+	-	-	-	-	-	-	?	[15]
18	44	F	Dark	4	PEG-IFN 80 µg/w; RBV 1,000 mg/d	10.5	+	-	-	-	-	-	+	(Tongue discomfort)	[16]
19	47	F	Dark	4	?	2	+	-	-	-	-	-	-	?	[17]
20	43	M	Dark	1b	Same as #4	1	+	-	-	-	-	-	+	Disappeared (4) (Oral discomfort)	[18]
21-27	28-66	M, F	****	?	?	?	*****								[4]
28	47	M	White	?	?	11	+	-	-	-	-	-	?	Disappeared (3)	[19]
29	49	F	White	1	PEG-IFN 180 µg/w; RBV 1000 mg/d	1	+	-	-	+	-	-	+	(Tongue Burning)	[20]
30	63	F	White	?	?	6	+	-	-	+	-	-	?	Improved (14)	[21]

\* Abbreviations and Acronyms used: BM, buccal mucosa; d, day; F, female; HCV GT, hepatitis C virus genotype; HP, hard palate; IFN, interferon; M, male; (M), month; MU, million units; PEG-IFN, polyethylene glycol-conjugated IFN; RBV, ribavirin; Tx, treatment; w, week; ?, information not available.

\*\* Duration of treatment in months when hyperpigmentation was noted.

\*\*\* IFN: 10 MU/d x 2w, 5 MU/d x 2w, 3 MU/d x 11m, 3 MU 3x/w x 6m; RBV: 1,200 mg/d x 7m, 800 mg/d x 11m.

\*\*\*\* Skin color (Fitzpatrick Scale): 2 Type II, 3 Type III, and 2 Type IV.

\*\*\*\*\* Seven patients with oral hyperpigmentation involving tongue, hard palate, and/or buccal mucosa; only one patient had symptom (tongue discomfort). Of these seven patients, four also had melanonychia.

the dosage or to discontinue the therapy. The majority of these lesions will either improve or disappear after completion of the therapy. It occurs probably more common in patients with dark skins and female patients. HCV infection is a global health problem affecting 130 to 170 million individuals worldwide. The recent development of direct-acting antiviral agents may revolutionize the therapy of HCV infection [23]. However, due to the high cost of these newer agents, PEG-IFN and RBV will continue to be the main stay for the treatment of hepatitis C, particularly in resource-limited countries. Clinicians should be familiar with the possibility of PEG-IFN and RBV-induced oral hyperpigmentation.

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## Ethical Statement

This case report was not a research involving human subjects and no identifiable individual information was collected or reported, therefore no Institutional Review Board approval is required.

## Conflict of Interest Statement

The authors declare no real or perceived conflict of interest related to the content of this manuscript

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