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Vitiligo at Injection Site of PEG-IFN- α 2a in Two Patients with Chronic Hepatitis C: Case Report and Literature Review

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Key Words

Vitiligo · Injection site · PEG-IFN- α 2a · Chronic hepatitis C

Abstract

A 72-year-old female and a 57-year-old male with chronic hepatitis C were treated with a combination therapy of pegylated interferon (PEG-IFN)- α 2a (180 μ g s.c. once a week) and ribavirin (1,000 mg orally daily). This resulted in the destruction of melanocytes at the injection site in both patients. In the male patient, the depigmentation progressed to the surrounding skin area. The dermatologist concurred with vitiligo as the diagnosis in both patients. Injection and surrounding site vitiligo associated with PEG-IFN- α 2b treatment for hepatitis C was noticed in previous case studies. For the first time, the case reports below highlight the same immunological adverse event secondary to PEG IFN- α 2a/ribavirin combination therapy and explain, in part, the complex interaction between host immune response and viral genotype. In addition, we systematically review drug-induced vitiligo and autoimmune diseases associated with the depigmentation disorder.

Introduction

Hepatitis C virus (HCV) is second only to non-alcoholic steatohepatitis (NASH) as the most common cause of chronic hepatitis [1]. Since 2001, the most widely accepted viral clearance therapy is pegylated interferon (PEG-IFN)- α 2b/2a in combination with ribavirin. Adverse effects of this combination therapy are variable and mainly include flu-like illness, neuropsychiatric symptoms such as depression, and thyroid, dermatological and hematological abnormalities. Existing literature attributes all major side effects of the combination therapy to PEG-IFN except hemolytic anemia, which is a side effect of ribavirin [2]. Patients should be monitored for further evaluation of additional adverse effects of PEG-IFN.

Few cases of interferon-associated vitiligo have been reported in the past [3–8]. Vitiligo, an idiopathic acquired form of skin disease, is caused by destruction of epidermal melanocytes. The worldwide prevalence is 1–2%, with no race or gender predilection. The presence of serum autoantibodies targeting the surface of melanocytes [9] and of a large number of T cells specific for melanocyte antigens in vitiliginous lesions [10] suggests an autoimmune etiology; however, the exact pathogenesis remains unclear. PEG-IFN- α 2b injection site vitiligo has been reported once [8]. However, PEG-IFN- α 2a injection site and surrounding site vitiligo has never been reported; the following case reports highlight this potential treatment-related complication.

Case Presentation

Case 1

A 72-year-old Hispanic female was referred for chronic hepatitis C evaluation. Physical examination was normal. She denied any exposure to hepatitis-C-related risk factors. Her laboratory workup was negative except for raised liver enzymes, viral load log 5.5, and genotype 1a. She was started on combination therapy of PEG-IFN- α 2a (Pegasys®; Roche Pharmaceuticals, Nutley, N.J., USA) 180 μ g once a week and ribavirin 1,000 mg daily. Apart from flu-like symptoms after the first few injections, she tolerated the combination therapy well. After 12 weeks of therapy, her HCV RNA was undetectable. During the fourth month of therapy, the patient developed white macular skin lesions around PEG-IFN- α 2a injection sites on both upper arms ([fig. 1a, b](#)). These lesions increased in diameter during therapy and remained the same after discontinuation of therapy. Her HCV RNA (PCR) was undetectable after 48 weeks of treatment, but after 6 months, it returned positive.

Case 2

A 57-year-old Hispanic male was referred (to an internist) for complete workup for hepatitis C. He denied any exposure to hepatitis-C-related risk factors. He had abnormal liver enzyme values, but other laboratory values were within normal limits. His hepatitis C workup showed genotype 2b and viral load log 7. He was started on PEG-IFN- α 2a 180 μ g weekly and ribavirin 800 mg daily. In the fifth month of therapy, he developed white macular lesions on both thighs around PEG-IFN- α 2a injection sites ([fig. 2](#)). The vitiligo spread throughout the whole body except his face. His HCV RNA was undetectable after 12- and 24-week intervals of therapy, and 6 months after discontinuation of therapy.

Both patients agreed to continue with the antiviral treatment. There was no past medical or family history of any autoimmune disorder or especially vitiligo. Autoimmune markers were also negative in both patients. Diagnosis of vitiligo has been confirmed by dermatologist consultation in both cases ([table 1](#)).

Discussion

Understanding the immunological adverse events in chronic hepatitis C is a complex phenomenon. The genotypic variability of the treatment response and host immunological status plays an important role in this complexity [11]. It was observed in the previous case reports that autoimmune manifestations are more common in patients with stronger immune response. Th1 and Th2 cytokine ratio may be a major determinant affecting the outcome of the treatment. The Th2 cytokine profile (IL-4 and IL-10) correlates with the persistence of the disease [12] and less autoimmune manifestations.

Vitiligo and Interferon

We reviewed all case reports of vitiligo in hepatitis C patients and realized that vitiligo lesions appeared during the first 6 months of IFN- α or PEG-IFN- α therapy. In a US male veterans' study, a significant relationship between hepatitis C and vitiligo was reported [13], whereas in two other studies, it was shown that the seroprevalence of HCV in vitiligo patients was not significantly different from the controls [14, 15]. In all these case reports, severity of the vitiligo and virological response achieved were correlated. Sustained virological response (SVR) due to stronger immune response was associated strongly with appearance of more generalized vitiligo lesions. However, a direct association between chronic hepatitis C and vitiligo is still debatable.

It appears that the time of onset and the course of vitiligo in IFN- α and PEG-IFN- α -associated cases is variable. Hamadah et al. [16] reported 8 cases of noninjection site IFN-treatment-related vitiligo in chronic hepatitis C patients. Autoimmune disease history (Hashimoto's thyroiditis and primary hypothyroidism) was noted in 2 out of 8 patients [16]. In one case report, vitiligo vanished completely after cessation of IFN [5] while in others, skin lesions persisted even after a few months of withdrawal of IFN [6] or PEG-IFN- α 2a [17].

Interestingly, Taffaro et al. [18] reported a chronic hepatitis C patient whose old vitiligo lesions improved after initiation of PEG-IFN- α 2a and ribavirin therapy. It may be a result of immune modulation by PEG-IFN.

Vitiligo at injection site of IFN- α 2b has been reported in one case of hepatitis C who was previously diagnosed with vitiligo capitis [8]. What makes these case reports unique is that vitiligo originated at the injection site of PEG-IFN- α 2a in patients with no past medical history and has diffusely progressed in one patient (table 2).

PEG-IFN as an Etiological Factor for Vitiligo

The suggested etiopathogenesis behind drug-induced vitiligo is: (1) activation of cytotoxic T cells directed against melanocyte antigens, (2) damage to sympathetic nerves that are connected by chemical synapses to melanocytes with a resultant functional disturbance, and (3) a direct cytotoxic nature of the drug on melanocytes (apoptosis). Most of the mechanisms suggested are hypothetical with no direct or scientific evidence to establish the exact role of the implicated drug.

The mechanism of action of PEG-IFN, a well-known immune-modulator, may provide a clue for its role in the pathogenesis of vitiligo. Current knowledge supports the role of PEG-IFN- α therapy in accelerated lymphocyte attachment to endothelial cells with deposition of immune complexes and vasculitis [19, 20]. In our patients, we hypothesize that vitiligo at PEG-IFN- α 2a injection site could be due to PEG-IFN-induced cytotoxic T-cell-mediated immune response against melanocytes at the injection site, with a resultant local destruction of melanocytes. It is possible that PEG-IFN- α 2a might have triggered this process in chronic hepatitis C patients. Its role as a causative factor is also supported by similar findings in patients during the treatment of chronic myeloid leukemia, hepatitis B and C, and malignant melanoma [3–7].

Viral genotype and host immune status may explain the localization or the progression of vitiligo in our patients. In the patient with genotype 1a, early virologic response and early treatment response was achieved and maintained for a short span of time. The SVR was not achieved in this patient. We consider the cytokine profile in this strain of patients may be of the Th2 variety. Th2 cells secrete IL-4, IL-5, and IL-10, which help B cells produce neutralizing antibodies. The cytokines shift the body's attack mechanism towards increasing the humoral response while decreasing the cytotoxic component. With the body's immune response focusing on non-self targets, attack on melanocytes is suppressed and progression of vitiligo is prevented after treatment.

In our second patient with genotype 2b, SVR was achieved. We consider the higher Th1 activity in genotype 2b is more efficient at removing virally infected cells. Th1 produces IL-2, which encourages cytotoxic T cells to induce apoptosis in the infected cells, and IFN- γ , which stimulates macrophages to engulf the virally infected particle. The Th1 cytokines and stronger cell-mediated immune response may be the reason for a more intense form of vitiligo in this patient [21]. Due to its potential to reveal the future course of this adverse event, monitoring cytokines may be considered for research purposes.

PEG-IFN-Related Dermatological Side Effects

A list of dermatological side effects related to PEG-IFN has been reported which include necrosis, psoriasis, hyperpigmentation and vasculitis at the injection site, xerosis, pruritus, urticaria, and reversible hair loss, sudden onset of psoriasis or flaring of preexisting psoriasis, pityriasis rosea, lichen planus, eosinophilic fasciitis and vitiligo [2].

Drugs Causing Vitiligo

Drug-induced vitiligo is frequently reported [22–25]; some culprit drugs are listed in [table 3](#). Suggested mechanisms of action in the causation of vitiligo are hypothetical.

Vitiligo and Other Autoimmune Diseases

Vitiligo is associated with a substantial number of other autoimmune conditions [26–39]. In both children and adults, the most common autoimmune disorder known to be associated with non-segmental vitiligo is autoimmune thyroiditis [40, 41]. Skin diseases and malignancies have been reported in association with vitiligo [33–39]. The rare association of segmental subtype of vitiligo with autoimmune diseases further supports its neural etiology [42].

Conclusion

Vitiligo with chronic hepatitis C treatment, certain other drug treatment, and its associated autoimmune diseases were briefly reviewed ([table 4](#)). PEG-IFN-associated immune modulation explained its autoimmune triggering role in our HCV and vitiligo

patients. Host immune status provided a clue for the localization or progression of the depigmentation.

PEG-IFN- α 2a demonstrated a significant benefit in the treatment of chronic hepatitis C. Its antiviral benefits and adverse effects are both mediated via the induction of cytokines. In the era of the widespread use of PEG-IFN- α 2a as the treatment for chronic hepatitis C, clinicians should be aware of these diverse pigmentary changes and subsequent disfigurement associated with its use. Furthermore, clinicians should keep in mind that not all individuals treated with PEG-IFN- α 2a will experience melanocyte destruction. More research is indeed needed to explain the rare pathogenesis of injection and surrounding site vitiligo since the course of the dermatological disease is unpredictable.

Table 1. HCV subtype and response upon treatment

Time line	Case 1 (Genotype 1a)	Case 2 (Genotype 2b)
0 weeks	Treatment started	Treatment started
12 weeks	VL* – undetectable	VL – undetectable
16 weeks	Vitiligo at injection site	NA
20 weeks	Vitiligo at injection site	Vitiligo at injection site
24 weeks	Vitiligo at injection site	Vitiligo at injection and surrounding site
	VL – not reported	VL – undetectable
48 weeks	Vitiligo at injection site	Vitiligo at injection and surrounding site
	VL – undetectable	VL – not reported
6 months	Vitiligo at injection site	More diffuse Vitiligo
	VL – detectable	VL – undetectable
Host immune response	Weak	Strong

* Viral load.

Table 2. Case reports on PEG-IFN- α related vitiligo

PEG-IFN	Report	Past history of vitiligo	Effect of treatment discontinuation	History of autoimmune disorder
Injection site local ¹				
2a	Present report (case 1)	No	Stable	No
2b	Anbar et al., 2008 [8]	Yes	Stable	No
Injection site diffuse ²				
2a	Present report (case 2)	No	More diffuse	No
2b	Never reported	NA	NA	NA
Generalized vitiligo				
2a	Nouri et al., 1997 [43]	No	More diffuse	No
	Krzysztof et al., 2006 [17]	Yes	Stable	No
	Seckin et al., 2004 [3]	No	More diffuse	No
	Simsek et al., 1996 [5]	No	Regression	No
2b	Bernstein et al., 1995 [6]	No	Stable	No
	Patricia et al., 2006 [7]	No	Stable	No

¹ Local = Injection site vitiligo remained local.

² Diffuse = Injection site vitiligo spread to whole body.

Table 3. Drugs causing vitiligo

Group	Drugs
Anticonvulsants	Carbamazepine, valproic acid, clonazepam, phenytoin
Antimalarials	Chloroquine, quinine
Antiparkinson's drugs	Tolcapone, levodopa
Drugs for alopecia	Diphencyprone, squaric acid dibutylester
Biological drugs	Interleukin-2, interleukin-4, interferon α and β , infliximab, imiqimod, imatinib
Other drugs	Fluphenazine, clofazimine, dopamine, hydroquinone monobenzyether ester, ganciclovir, β -blockers, lispro insulin

Table 4. Vitiligo and other autoimmune diseases

Associations	Case reports
Autoimmune thyroiditis	Autoimmune hepatitis
Autoimmune gastritis	Primary biliary cirrhosis
Alopecia areata	Behçet's disease
Diabetes mellitus	Celiac disease
Rheumatoid arthritis	Myasthenia gravis
Pernicious anemia	Sjögren's syndrome
Addison's disease	Autoimmune nephritis
Hashimoto's thyroiditis	Pachydermoperiostosis
Vogt-Koyanagi-Harada Syndrome	Neurofibromatosis type 1
Loss of hair pigmentation	Hematopoietic cell transplantation
Polyglandular autoimmune syndrome	Dermatitis herpetiformis



Fig. 1. Localized vitiligo (case 1) at the injection site. **a** Left arm. **b** Right arm.



Fig. 2. Generalized vitiligo (case 2) on treatment.

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