Case Report

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Lichenoid Drug Reaction Developing During the Treatment of Recurrent Chronic Hepatitis C

Nüks Kronik Hepatit C Tedavisi Sırasında Gelişen Likenoid İlaç Reaksiyonu

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ABSTRACT

Lichenoid drug reaction is a cutaneous reaction that resembles lichen planus. Lichenoid eruptions are classified as type IV delayed hypersensitivity reactions. Although rarely, interferons may also play a role in their etiology. In this case, we present a female patient who received pegylated-interferon-alpha 2b (PEG-IFN-α2b)/ribavirin therapy for recurrent chronic hepatitis C virus (HCV) infections, and who developed a lichenoid drug reaction during the fifth month of her treatment. Administration of a topical steroid and antihistamine treatment for a period of one month allowed the patients' symptoms to be treated, and a permanent viral response to be achieved, without discontinuing the PEG-IFN-α2b/ribavirin therapy, xerosis and eczematous skin lesions that occur during the treatment of chronic HCV infection can be managed with moisturizers and topical steroids. We believe that an awareness of this possibility among physicians would help preventing any unnecessary dose reductions or discontinuations during PEG-IFN-α2b/ribavirin combination therapies, and thus contribute to a higher rate of permanent viral response among patients. *(Viral Hepatitis Journal 2014; 20(1): 32-35)*

Key words: Chronic hepatitis C, treatment,lichenoid drug eruption

ÖZET

Likenoid ilaç reaksiyonu, liken planusa benzeyen kutanöz ilaç reaksiyonudur. Likenoid erüpsiyonlar Tip IV gecikmiş hipersensitivite reaksiyonlarıdır. Etiyolojisinde interferonlar nadir de olsa rol oynamaktadır. Bu çalışmada, nüks kronik hepatit C virüs (HCV) enfeksiyonu tanısı ile pegile-interferon-alfa2b (PEG-IFN-α2b)/ribavirin tedavisi alan ve tedavisinin beşinci ayında likenoid ilaç reaksiyonu gelişen bir kadın hasta sunulmuştur. PEG-IFN-α2b/ribavirin tedavisini kesmeye gerek kalmadan, bir ay süre ile topikal steroid ve antihistaminik tedavi ile şikâyetleri iyileşen hastada kalıcı viral yanıt elde edilmiştir. Kronik HCV enfeksiyonu tedavisi esnasında ortaya çıkan kserozis ve ekzematöz lezyonlar nemlendirici ve topikal steroidler ile kontrol altına alınabilir. Bu durumun hekim tarafından bilinmesinin, gereksiz doz azaltılması veya kesilmesini önleyerek, hastaların kalıcı viral yanıtını artıracağını düşünmekteyiz. *(Viral Hepatit Dergisi 2014; 20(1): 32-35)*

Anahtar Kelimeler: Kronik hepatit C, tedavi, likenoid ilaç erüpsiyonu

Introduction

Hepatitis C virus (HCV) infection is one of the leading causes of liver diseases. The standard treatment for these infections is the pegylated-interferon-alpha (PEG-IFN-α) and ribavirin combination therapy (1). One of the most important challenges encountered with interferon-alpha (IFN-α)-based therapies is the numerous side effects associated with both IFN-α and ribavirin. Flu-like symptoms, hematological, neuropsychiatric and dermatological toxicity, and the development of various autoimmune disorders represent the most commonly observed side effects (2). HCV infections may also lead to extrahepatic symptoms involving multiple organs (3). Various concomitant conditions, such as endocrinopathies and skin disorders, are also observed during HCV infections. Numerous viral, genetic or environmental factors may be involved in the skin disorders associated with HCV infection (3). In many cases, the exact mechanisms through which HCV infections trigger and exacerbate skin symptoms cannot be identified; such cases require further and more comprehensive examinations for the determination

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of potential factors (3). IFN-α is a biological medication that is used in the treatment of viral hepatitis infections, and which can potentially lead to serious side effects in various organs such as the skin (3). Predicting potential skin reactions to IFN-α therapy is generally not possible, and it is important to assess the persistence of such skin reactions following the discontinuation of the IFN-α treatment (3).

PEG-IFN-α is similar to IFN-α in terms of effectiveness and side effects; however, PEG-IFN-α use is more advantageous in that it has a longer duration of effect and lower biological activity. PEG-IFN-α was demonstrated as being more effective in the treatment of chronic HCV infection than standard IFN-α therapy (4).

In this case report, we present a female patient who received PEG-IFN-α2b and ribavirin therapy for chronic hepatitis C, and who developed a lichenoid drug reaction during the fifth month of treatment.

Case

A 62-years-old female patient receiving subcutaneous (sc) PEG-IFN-α2b 100 µg/week and ribavirin 1000 mg/day oral tablet (tb) combination therapy was admitted to our clinic for eruptive and pruritic skin lesions in the sacral region (Figure 1) that developed in the fifth month of her treatment. The patient's past medical and family history was unremarkable.

The patient described that she began receiving PEG-IFN-α2a 180 µg/week plus ribavirin 1000 mg/day for chronic HCV infection six months ago, and that she did not develop any dermatological complaints during this treatment. Dermatological examination of the patient revealed purple-colored, lichenified papular lesions in the sacral region (Figure 1). No pathological findings were identified during the systematic examination of the patient. The following values were determined during the patient's laboratory tests: white blood cell count: 2500/mm^3; neutrophil count: 1280/mm^3, hemoglobin: 12.03 g/dL; hematocrit: 33.41%; and platelet count: 113.00/mm^3. The patient's biochemistry values and coagulation tests were normal. The histopathological examination of the punch biopsy obtained from the sacral region showed findings consistent with a lichenoid drug reaction. Detailed histopathological examination revealed an epidermis with hyperkeratosis, hypergranulosis and irregular acanthosis (Figure 2); an underlying diffuse inflammation that effaced the dermoepidermal junction; apoptotic bodies in the epidermis; and eosinophils within the lymphohistiocytic cellular infiltration (Figure 3).

In accordance with the recommendations of the dermatology department, the patient was treated with a topical steroid and a systemic antihistamine for a period of one month. In the examinations/controls performed one month after beginning this treatment, it was observed that the lesions had completely healed. Discontinuation of the PEG-IFN-α2b and ribavirin combination therapy was not necessary. The patient completed her 48 weeks treatment for chronic HCV; by the end of the treatment, the patient tested negative for HCV-RNA. The patient continues to attend follow-up visits.

Figure 1. Lichenified papular lesions in the sacral region.

Discussion

The effectiveness and reliability of PEG-IFN-α/ribavirin therapy for chronic HCV infections is well-evidenced, however, the widespread use of the PEG-IFN-α/ribavirin therapy for HCV infections has led to a significant increase in the number of skin symptoms reported among chronic HCV patients (1). IFN-α is a cytokine with antiviral, antineoplastic and immunomodulator effects (1). Together with natural killer cells, interferons constitute the first immunological barrier against viral infections and tumors. IFN-α enhances CD8 cytotoxic T-cell response and increases the synthesis of immunoglobulins by stimulating the proliferation of B-cells (4,5). IFN-α therapy is known to trigger autoimmune disorders such as autoimmune thyroiditis, rheumatoid arthritis, sarcoidosis, and psoriasis; it is also known to elevate during treatment the levels of autoantibodies such as antinuclear antibodies (ANA), rheumatoid factor (RF), anti-smooth muscle antibodies (anti-SMA), and double-stranded deoxyribonucleic acid antibody (dsDNA) (5,6). Ribavirin is a generally well-tolerated drug, with photosensitivity being the most common dermatological side effect reported during monotherapy (1,7,8). As the side effect profile of the combination therapy is similar to that of IFN-α monotherapy, and since ribavirin is associated with relatively fewer side effects; it is generally accepted that the adverse effects observed during combination therapy are mostly caused by the IFN-α component (1). However, compared to the IFN-α monotherapy, the PEG-IFN-α/ribavirin therapy leads

Figure 2. Image showing an epidermis with hyperkeratosis, hypergranulosis and irregular acanthosis; and an underlying diffuse inflammation that effaced the dermoepidermal junction (HE x100).

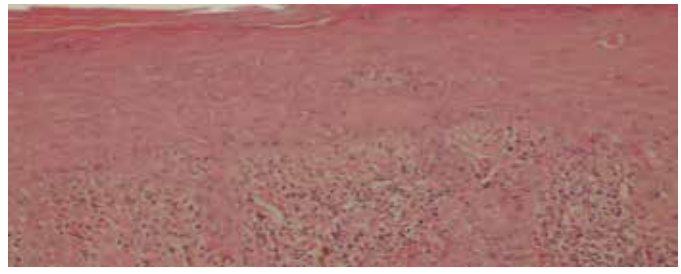

Figure 3. Imaging showing apoptotic bodies in the epidermis and eosinophils within the lymphohistiocytic cellular infiltration (HE x200).

to a higher incidence of cutaneous side effects. IFN-α-based treatments are associated with side effects involving the skin and other organs, and which necessitate the discontinuation of treatment in 6-7% of the cases; this ratio increases to 10-14% when PEG IFN-α is used instead (1). Depression is reported as the main reason for the discontinuation of classic interferon-based therapies. Dermatological side effects are not listed among the other common reasons for discontinuation (2). According to data from large-scale studies, serious dermatological side effects associated with classic interferon-based therapies necessitated the cessation of treatment in only 0.1% of patients. Hemolytic anemia is the leading cause of dose reductions during combination therapy. The occurrence of hemolytic anemia is mainly associated with the ribavirin component (9). Management of skin eruptions and pruritus caused by ribavirin therapy is generally challenging. Skin eruptions related to ribavirin generally occur on the trunk and upper back. Such eruptions are maculopapular and pruritic (2). While Aspinall et al. reported that topical steroid administration to the lesions did not result in adequate response or healing, Lübber et al. determined that these lesions responded well to topical steroid treatment (2,10,11). The cutaneous side effects of IFN-α applications include injection site reactions, xerosis, seborrheic dermatitis, pruritus, vitiligo, alopecia, photoallergic eczema, and lichen planus (Table 1) (1).

Injection site reactions are the most commonly observed side effect, followed by dry skin and pruritus (1). Injection site reactions are observed in almost all patients receiving peginterferon therapy. In these reactions; the injection site generally appears red and slightly swollen, and can reach a diameter of 5 cm or more. The lesions may take weeks to heal, and patients are advised to receive injections from a different site on their body every week. In case the area of the injection site reaction expands, or in case there is pain and an increase in skin temperature at the site, the patient must be examined to determine whether a skin abscess has formed. If an abscess is identified, the abscess can be drained and oral antibiotics can be administered without discontinuing the peginterferon therapy (2). However, if a large abscess is present, it may be necessary to discontinue the peginterferon treatment for a certain period of time (2,10). Various reports suggest that IFN-α therapy for HCV infections induce lichen planus, or exacerbated pre-existing ones. The mechanism through which IFN-α treatment induces lichen planus development is unknown (2). Currently proposed mechanisms include the stimulation of keratinocyte surface antigen expression by IFN-α to ensure the elimination of viruses, which initiates the immunological reaction that causes lichen planus; the development of lichen planus as a result of an acquired hypersensitivity to IFN-α (as is the case with other lichen planus variants triggered by medication use); the conversion of the immune response against HCV infection into an autoimmune reaction directed towards the skin during IFN-α therapy; or the development of lichen planus as a result of a toxic reaction to IFN-α (1,3,12).

Table 1. Cutaneous side effects of interferons

Injection site reactions	Seborrheic dermatitis
Xerosis	Nummular eczema
Pruritus	Exacerbation of psoriasis
Lichen planus	Lichen aureus
Vitiligo	Diffuse hypertrichosis
Alopecia	Hyperpigmentation
Photoallergic eczema	Herpes zoster
Hypopigmented atrophic plaques	Alopecia universalis
Eosinophilic pustular folliculitis	Dermatitis herpetiformis
Systemic lupus erythematosus	Meyerson's nevus
Erythema on the face	Vogt-Koyagani-Harada Disease
Eczematous dermatitis	Sarcoidosis

Lichenoid drug reaction is a cutaneous drug reaction that resembles lichen planus. Lichenoid drug reactions are seldom observed. Lichenoid drug reactions are classified as type IV delayed hypersensitivity reactions. It is believed that drug molecules bind to epidermal proteins and render the epidermis antigenic by acting as haptens (13). Lichenoid eruptions usually occur months or years after the intake of the drug. The lesions typically appear as purple-colored, flat polygonal papules resembling classic lichen planus; however, unlike classic lichen planus, the drug-induced form exhibits symmetric and diffuse distribution across the body, rather than becoming distributed only on flexural surfaces.In addition, the lesions in lichenoid drug reactions exhibit marked polymorphism, and can exhibit atypical crust and scurf formation (13). Clinical identification is largely based on subjective criteria. A history of drug intake, and spontaneous recovery following the discontinuation of the drug are considered as being indicative of lichenoid drug reactions. Medications known to be associated with lichenoid drug reactions include gold-salts, non-steroid anti-inflammatory drugs (NSAID), angiotensin converting enzyme inhibitors, antimalarial drugs (quinine, quinidine), acyclovir, phenothiazine, sulphonamides, β-blockers, D-penicillamines and thiazide diuretics (13). IFN-α-2b and PEG-IFN-α also figure among the drugs described in case reports as being associated with lichenoid drug reactions (13). In the current case, lichenoid drug reaction symptoms occurred five months after the beginning of the drug treatment, and included purple-colored lichenified papules (Figure 1). Polymorphism was observed in our case, with atypical crusting being present on the lesions. Although the identification and cessation of the drug responsible for the reaction is described as the most important step for treatment, reports also emphasize that topical steroid creams can be used for symptomatic treatment (13). In the current case, a treatment involving topical steroids and systemic antihistamines were administered for a period of one month without discontinuing the PEG-IFN-α/ribavirin therapy. We observed that the lesions healed completely as a result of this treatment.

The xerosis and eczematous lesions that occur during the treatment of chronic HCV infections can be usually managed with moisturizers and topical steroids. In the current case, the topical steroid and systemic antihistamine treatment administered for one month following the onset of the lichenoid drug reaction

effectively treated the drug-induced reaction. The patient completed her 48 weeks of chronic HCV infection treatment, and a permanent viral response was achieved. We believe that an awareness of this option among physicians would help preclude any unnecessary dose reductions or discontinuations during PEG-IFN-α2b/ribavirin combination therapies, and thus contribute to a higher rate of permanent viral response among patients.

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