

## Widespread Dystrophic-Anagen Alopecia and Drug Eruption due to Usage of PEG-IFN $\alpha$ -2a /Ribavirin Combination Therapy

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### Abstract

Chronic hepatitis C infection (CHC) is acknowledged as a major health problem all over the world. The World Health Organization estimates that 3-4 million individuals are infected each year worldwide, with a global 170 million chronic HCV carriers at risk of developing liver cirrhosis and/or liver cancer.

The most experienced treatment for chronic hepatitis C is pegylated interferon (PEGINF) and ribavirin (RBV) combination therapy. A variety of conditions ranging from endocrinopathies to different skin diseases have been described in only HCV infections and/or associated with IFN based therapy.

The skin lesion during anti-HCV therapy rate is 24-28%, according to randomized controlled clinical trials. The incidence of cutaneous eruptions has been estimated to be 13% to 23%. Alopecia is a frequent adverse effect of interferon and ribavirin treatment in 19% of patients treated with combination therapy. Several types of alopecia exist; telogen effluvium, localized alopecia at the injection site AA (Alopeciae Areata) and AU (Alopeciae Universalis) have been described. Telogen effluvium (TE) is characterized by an excessive loss of telogen hair. It occurs in about 30% of patients who are treated with IFN. Anagen effluvium (AE) is the non-reported case in literature in terms of the PEG-IFN and RBV combination therapy for chronic HCV infection induced anagen alopecia. Herein, we are present a case of dystrophic TE which was attributed to the INF/ribavirin combination therapy, and interpretation of the case according to hertrichogram findings. To the best of our literature search, our patient is the first case in terms of extensively interpreted with both clinical and trichogram features of a PEG-INF/ribavirin induced alopecia.

**Keywords:** Alopecia; Drug eruption; Interferon therapy; Chronic hepatitis C

### Introduction

Chronic hepatitis C infection (CHC) is acknowledged as a major health problem all over the world. The World Health Organization estimates that 3–4 million individuals are infected each year worldwide, with 170 million chronic HCV carriers at risk of developing liver cirrhosis and/or liver cancer globally [1]. The most experienced treatment for chronic hepatitis (CHC) is pegylated-interferon (PEG-INF) and ribavirin (RBV) combination therapy. The most common side effects of many medications are drug-induced cutaneous eruptions. The overall cutaneous drug reaction rate of 2.2% was found in collected data regarding adverse events from 15,438 consecutive medical inpatients for The Boston Collaborative Drug Surveillance Program [2]. Various types of dermatologic manifestations such as injection site reactions, psoriasis, eczematous drug reactions, alopecia, sarcoidosis, lupus, fixed drug eruptions, pigmentary changes, and lichenoid eruptions have been reported due to HCV infection and during antiHCV therapy. The incidence of skin lesions during antiHCV therapy is 24–28%, according to randomized controlled clinical trials [1,2]. The incidence of cutaneous eruptions

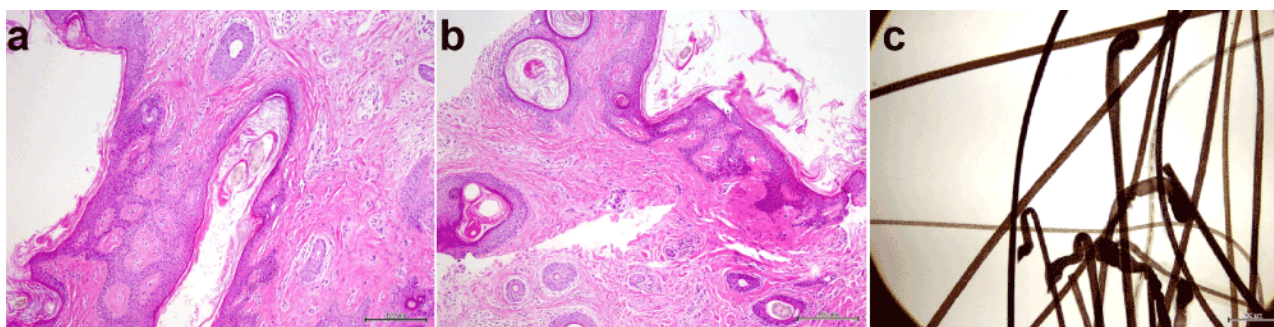
has been estimated to be 13% to 23% [2]. Lots of hair disorders, including reversible hair discoloration, hypertrichosis, straight hair and effluvium (alopecia), and diffuse thinning of the hair, hair curling, repigmentation of hair, trichomegaly of the eyelashes have often been described during IFN therapy [3-5]. Alopecia is a frequent adverse effect of interferon and ribavirin treatment in 19% of patients treated with combination therapy. It seems that the incidence of alopecia increases with the duration of treatment and usually is noticed in up to 36% of treated patients in pivotal clinical trials [6]. Among the clinical types of alopecia, telogen effluvium (TE), localized alopecia (LA) at the injection site, alopecia areata (AA) and alopecia universalis (AU) have been described [5,7-10]. TE is characterized by an excessive loss of telogen hair. It occurs in about 30% of patients who are treated with IFN [5,8,11]. LA is characterized by the local loss of hair at the injection site. It develops secondary to the inflammation at the injection site. AA is characterized by circumscribed, noninflammatory and nonscarring alopecic patches on the scalp [5,8,11]. AU, which is defined as complete hair loss extending to the whole skin, is a severe form of AA [7]. Anagen effluvium (AE) is a prominent adverse effect of antineoplastic agents, which cause acute damage of rapidly dividing hair matrix cells. The best known of these agents are antimetabolites, alkylating agents, and mitotic inhibitors such as adriamycin, cyclophosphamid, etoposide [12-14].

Herein, we present a case of dystrophic TE which was attributed to the INF/ribavirin combination therapy, and interpretation of the case according to her trichogram findings.

**Case:** A fifty-year old woman was admitted to our outpatient clinic due to chronic hepatitis C infection and her widespread diffuse alopecia. According to the patient's history, she had been admitted to another hospital to treat chronic hepatitis C infection in August 2013 and was diagnosed as having chronic HCV infection proven by positive anti-HCV antibody, HCV-RNA 1465147 IU/mL and HCV genotype was 1b. She had aspartate aminotransferase (AST): 57 U/L, alanine aminotransferase levels (ALT): 58 U/L. Previously she had hypertensive heart disease and asthma. She has no other known medical conditions, has no history of eczema or atopy, and is not taking any other drugs. After the diagnosis, a PEG-IFN  $\alpha$ -2a/ribavirin (RBV) combination therapy was started (180 mg of PEG-IFN  $\alpha$ -2a subcutaneously once a week in combination with RBV 1200 mg/daily, and a 48-week course of therapy). Three months after beginning the therapy, 5-12 mm in size, yellowish-pink, erythematous-squamous papules on the whole trunk and the face, multiple purpuric macules on the anterior surfaces of her lower legs, and wide alopecic plaques especially on the vertex of the scalp appeared. Separate excisional biopsies were performed on each of two different eruptive lesions. In the histological examination of erythematous papules, a slight

orthokeratosis, mild lymphocytic exocytosis, and a few apoptotic keratinocytes were shown. In the papillary dermis there was a mild edema and mononuclear inflammatory infiltration including perivascular eosinophils. Purpuric macules showed only a few apoptotic keratinocytes and perivascular eosinophilic infiltration with extravasated erythrocytes in the papillary dermis. With the histopathological findings the skin lesions were diagnosed as drug side effects dependent on PEG-INF and RBV then therapy was stopped. Three months after the cessation of the drug, the therapy was resumed. Similar skin eruptions recurred. The therapy was stopped once again.

In February 2014 the patient was admitted to our outpatient clinic to restart therapy. In the dermatological examination, a diffuse alopecia was shown on the whole scalp. There was no erythema, desquamation or enduration on the surface of the scalp. The hair pull test was negative for all alopecic areas. The exclamation mark hairs were absent. The clinical appearance of the hair loss showed a diffuse shedding. The shafts of the hairs were thinner and were faded. In the histopathological examination of an excisional biopsy specimen follicular density was spared on the infundibular level. While some of the follicles were empty, the others were shown as catagen follicles. Eosinophil-rich mononuclear infiltration was seen in the perifollicular areas (Figure 1a and 1b).



**Figure 1:** Histopathological appearance of the scalp and trichological appearance of the hairs: Follicular density was spared on the infundibular level. While some of the follicles were empty, the others were shown as catagen follicles (a. 100XHE, b. 200XHE). The ratio of catagen/anagen, and count of the dystrophic hairs were increased (Telogen 60%, anagen 30%, catagen 6%, and dystrophic hairs 4%) in trichological examination (c.40X).

For a trichological examination, following three days without shampooing and brushing, 3 contingents of 40 hairs were removed with tweezers, in three points on the scalp (frontal, vertex, and occipital). The proximal extremity of the hair was placed in between a slide and a coverslip and analyzed with a binocular optical microscope with a low (x20 and 40) and high (x100) magnifications. In the trichogram, the ratio of catagen/anagen was significantly increased, and the ratio of anagen/telogen (A/T) was decreased. The telogen, catagen and dystrophic hairs were found to increase of approximately four-fold, three-fold and two-fold, respectively (Telogen 60%, anagen 30%, catagen 6%, and dystrophic hairs 4%) (Figure 1c).

Laboratory examination at the time of the beginning therapy in our hospital showed a decrease in white blood cell count (3,300/ $\mu$ L), red

blood cell count (460 $\times$ 10<sup>6</sup>  $\mu$ L), hemoglobin (13 g/dL), and platelets (62,000/ $\mu$ L), as well as elevations in AST (48 IU/L) and ALT (32 IU/L). She had HCV-RNA negative IU/mL. The other etiological examinations did not reveal other pathologies. With the clinicopathological findings the patient was diagnosed as dystrophic-telogen effluvium (DTE) that developed as a drug side effect of PEG-INF/ribavirin combination therapy. After the restart of the therapy the previous skin eruption did not recur, and the shedding stopped in a 15-day period, and scalp hairs began to grow. The regrowth of the hairs in the 4th month of therapy was satisfactory (Figure 2). The patient is still under follow-up. During a 6 month follow-up period neither the skin rash nor the alopecia recurred.



**Figure 2:** Clinical appearance of the alopecic lesions. a,b,c,d: three weeks after the Starting of INF  $\alpha$ -2a/ribavirin therapy. e,f,g,h: Satisfactory regrowth of the hairs at the 4<sup>th</sup> month of therapy.

## Discussion

Various types of skin rash have been reported due to HCV infection, as well as antiHCV treatment. Some skin rashes improve with antiHCV treatment, whereas others worsen, necessitating the discontinuation of the treatment and the initiation of therapy targeted toward the rash itself [1].

On the other hand, an adverse drug reaction is a noxious or/and unintended effect of a medication that has been administered in standard doses by the appropriate route for the purpose of prophylaxis, diagnosis or treatment. The adverse drug reactions may be immediate, accelerated (occurring within three days) or late (occurring three or more days after using the drug). Cutaneous reactions are usually late reactions. In general, the mechanisms of drug reactions remain unknown. It is believed only 10% of drug-induced rashes are the result of true allergic mechanism [2]. As a rule, any drug that is administered systemically can cause cutaneous side effects. Skin lesions may vary in severity from localized rash to diffuse skin involvement. Most drug eruptions are accounted for simple exanthems and urticaria, 95% and 5% of skin reactions, respectively. Adverse cutaneous drug eruptions may be part of a systemic reaction that can be life-threatening, approximately 2% of all adverse cutaneous reactions. If a drug skin reaction has bullae, erosions, purpura or exfoliative dermatitis it is a serious cutaneous reaction that can be life-threatening [2].

Interferon (IFN), a family of secretory glycoproteins, is an immune modulating agent that is used in the treatment of viral infections, tumors, and inflammatory conditions including multiple sclerosis. The three main types of IFNs are classified according to their nucleic acid

sequence: alpha, beta, and gamma. A wide range of diseases with recombinant IFNs and/or natural IFNs have been observed, and about 5-12% of side effects related to IFN treatment involve adverse skin reactions, either localized at the injection site or generalized skin reactions. IFN- $\alpha$  (subtypes: 2a, 2b, pegylated or not), mainly is used in the treatment of hepatitis C and B, AIDS, leukemia, or malignant tumor. Cutaneous reactions reported in the literature include localized reactions and generalized effects. [15,16]. The development of diffuse skin eruptions during the early course of antiHCV therapy has been reported in Europe and Asia [1]. There was a rare case of immediate-type reaction to IFN $\alpha$ -2b in a patient with melanoma, which led to discontinuation of adjuvant therapy with IFN $\alpha$ -2b in the literature [17]. Moreover, some other side effects have been reported due to IFN therapy, including immune and non-immune mediated. The non-immunological mediated side effects include lichen planus, dry skin, excessive sweating, acne, nail disorders, epidermal necrolysis, and skin discoloration and the immune-mediated include psoriasis, pemphigus, vitiligo, and alopecia [18].

On the other hand, the exact mechanism of ribavirin-induced skin reactions during the early stage of antiHCV therapy is unknown. They may be due to histaminelike side effects of ribavirin. Ribavirin has been found to cause itching, nasal stuffiness, recurrent bronchitis, and asthma like symptoms. These histaminelike side effects occur in 10-20% of patients and are usually mild to moderate in severity. Skin lesions may vary in severity from localized rash to diffuse skin eruption [1]. Furthermore, there have been some reports of drug eruption or alopecia caused by ribavirin and PEG-IFN- $\alpha$ 2b or IFN- $\alpha$  combination therapy [1,2,5,7].

In our case had squamous and maculopapular skin eruptions on the whole trunk and the face and multiple purpuric macules on the anterior surfaces of her lower legs portended a severe reaction. PEG-IFN/RBV combination therapy tried twice times and it had to cease for frightened of life threatening complications. The drug eruptions and diffuse effluvium occurred after three months of therapy in other words that is a late reaction.

Alopecia caused by drugs is a usually reversible diffuse nonscarring hair loss that occurs within days to weeks of starting a new medication or changing the dose. The hair loss may be "patterned" as seen in male pattern (androgenetic) or female pattern alopecia. The scalp is the most common site affected, but all body hair including eyebrows and eyelashes may be lost with chemotherapy. Development of hair loss and the severity depend both on the drug and individual predisposition. Some drugs cause hair loss in most patients receiving an appropriate dose. Other drugs are only occasionally responsible for hair loss [19]. On the other hand, scalp hair grows in cycles, with each hair follicle undergoing 10 to 30 cycles in its lifetime. Diffuse hair shedding is the result of a disruption of one phase of the hair cycle, ie, anagen (active hair growth), catagen (involution), or telogen (resting). The anagen phase can last 2 to 8 years, the catagen phase lasts 4 to 6 weeks, and the telogen phase lasts 2 to 3 months. The exogen phase (the release of dead hair) coincides with the end of the telogen phase. Normally, each hair follicle cycles independently, so that while some hairs are growing, others are resting and others are shedding. Thus, the density of the scalp hair and the total number of scalp hairs remain stable. Most people have about 100,000 scalp hairs, and normally 10% to 15% of these are in the telogen phase. Shedding of 100 to 150 telogen hairs per day is normal [20]. Toxic and drug-induced hair loss can be telogen, dystrophic-telogen and anagen (or dystrophic-anagen [DAE]) effluvium according to the type of toxicity of the molecule on the hair cycle [18,21]. There are some infrequently alopecia cases depended on interferon treatment, and have been reported in 19% of patients treated with combination of interferon/ribavirin [2]. These reports typically indicated a diffuse thinning of the hair. Except for the diffuse thinning, some other hair-side effects of this combination therapy have been reported as AA, AU, trichomegaly of the eyelashes and eyebrows, generalized hypertrichosis, hair curling and hair repigmentation [2]. However, in these reports, the alopecic lesions were identified and discussed only according to their clinical shapes of the lesions. None of them has been described the alopecic lesions according to their trichological and histopathological characteristics. Because of our patient had no other reasons of hair shedding (iron, vitamin B12, folic acid, hypothyroidism, hyperthyroidism, autoimmune thyroid disease, other autoimmune disease and severe febrile illness), and their alopecic lesions started simultaneously with the cutaneous eruption (nonspecific squamous and maculo-papular, and purpuric) we thought that the diffuse effluvium of the patient depended on this combination therapy. Additionally, previous histopathological report of the skin rash of the patient supported our presumptive diagnosis (drug side effect). Because of the hair loss of the patient were appeared as a diffuse shedding clinically, we thought that the alopecia could be a TE.

TE is shedding of resting or bulb hairs and may occur as a result of serious drug eruption such as Stevens Johnson syndrom/toxic epidermal necrolysis or drug hypersensitivity syndrome, in which case hair falls out a few weeks to months after the acute illness and slowly regrows again [19]. In the condition of a "TE" the percentage of telogen hairs is abnormally high compared to the percentage of anagen hairs. The A/T ratio (is normally superior to 5 (80-85/15-20) is

decreased. The percentage of dystrophic hairs is normal, and the percentage of catagens sometimes increases [18,22]. The diameter of the hair shaft is decreased. This is the formula observed in reactional telogen effluvium (vitamin or iron deficiency, high fever, some drugs, etc...). Another condition of TE is "dystrophic telogen effluvium". In this condition, similar to the TE, the ratio of A/T is decreased. The percentage of telogens and dystrophic hairs is increased compared to anagen hairs. This formula is mainly observed in androgeno-genetic alopecia (adrogenetic alopecia [AGA]). Additionally, in the AGA, miniaturizations of >20 % of hairs (heterogeneity of the diameters) in androgenic areas (frontal and vertex) are seen [18-22]. In our case, because of the appearance of the alopecia was diffuse, the diameter of the hair shafts decreased, decreased of A/T ratio, and increase of the dystrophic hairs, the diagnosis was made as DTE. Although the formula of the trichogram also complied with an AGA, due to the absence of follicular miniaturization and no any predilection of alopecic areas, the diagnosis was excluded.

On the other hand, because of the clinical shape or pattern of the shedding did not similar an AA, negativity of the hair pull test, absence of exclamation mark hairs, absence of prominent lymphocytes and presence of eosinophil's in the per follicular infiltrate, the diagnoses of "AA" or its expanded form (AU) were excluded [18-22].

Anagen (or dystrophic anagen) effluvium is due to the premature termination of anagen hair growth or anagen arrest, after an acute, severe metabolic insult. It is most often iatrogenic, caused by treatment with cytotoxic drugs or radiation [19,21]. There are some key words that indicate an anagen hair loss. The loss the result of interruption of the anagen hair cycle, presents as abrupt hair shedding with severe diffuse scalp alopecia. A serious insult to the hair follicles can cause up to an 80% loss of scalp hair. The time course for anagen effluvium is usually rapid compared with telogen effluvium, occurring within days to weeks of the insult to the hair follicles. The hairpull test is positive for dystrophic anagen hairs with tapered ends. If the insult ceases, hair growth restarts again within weeks. In the trichogram, internal and external epithelial shafts are intact and visible on the entire length of the hair root of a healthy anagen hair. They are translucent and surrounded by a fibrous shaft. They are located on either side of a large bulb including a dark matrix covered by a lighter area and a keratogenic area. On the other hand, in a normal catagen hair the bulb has lost its pigmentation. The keratogenic area has disappeared. The persistence of epithelial shafts gives it a "golf club" aspect. Moreover, in the "DAE" the growth of anagen hairs has ended prematurely due to the absence of mitoses within the matrix. The distal part of the hair therefore takes on a characteristic pointed, discoloured aspect with no matrix or shaft. The number of dystrophic anagen hairs can normally be observed under 2%. In the AE, the percentage of dystrophic hairs is increased compared to the percentage of normal anagen hairs due to the acute alteration of the functioning of the matrix. The percentage of telogens usually remains normal [18-22]. In our case, even though significantly decreased of the anagen hairs, because of the ratio of A/T was significantly decreased, the ratio of catagen/anagen was relatively increased and the hair-pull test was negative, we also ruled out a diagnoses of AE or DAE in accordance with the general diagnostic rules.

On the other hand, in the trichogram of our patient, the follicles in the catagen phase were increased. Because of the average duration of the catagen follicles is 3 weeks and the normal ratio of them is 1 to 2 % [18,21], we thought that there was a prolonged catagen phase. On the other hand, because of the average duration of the anagen follicles is 3

years and the normal ratio of them is 80 to 85 % [18,21,23] and the anagen follicles of the patient were significantly decreased, we think that the reason of this could be due to the acute toxic effect of drug(s) only on the cells showing rapid mitosis. Thus, a great number of anagen follicles may have been influenced of antimetabolic effect(s) of drug(s) or these follicles may have been entered catagen phase earlier and concurrently. Because of both the mentioned reasons and hair growth of our patient restarted when the therapy ceased again within weeks, although the proportion of telogen and dystrophic hairs were increased compared to the anagens, we think that it would not be wrong to say “there was also a partial AE or DAE “in our case, at least in a portion of this process.

Additionally, another reason of this prolonged catagen phase could be due to the insensitivity these catagen follicles to drug(s) or adaptation to antimetabolic effects of drug(s). Because of the decrease in the occurrence of alopecic response after the repeated using of drug(s), we anticipate that whereas the “acute anagen toxicity” is more valid in the initial phase, the “insensitivity or adaptation to the drug(s) of prolonged (or long-lasting) catagen follicles” is valid in the following or late phases of this type effluvium. Indeed, the first side effect was cutaneous rash that developed away from interferon injection sites. Interestingly, the rash improved with the discontinuation of PEG-INF/ribavirin therapy for several days, but the patient experienced a recurrence of the rash and a diffuse alopecia after rechallenging the combination PEG-INF/ribavirin therapy. However in the last administration of this combination, neither cutaneous rash nor alopecia did not recur. Even we do not know true mechanisms of these different side effects yet; this interesting process supports an adaptation or desensitization to the drug(s).

If any complication occurs against the drugs during INF therapy, usually the recommendation is to stop the therapy, but this issue is controversial for IFN therapy due to CHC infections. There were some cases where their complications worsened under the therapy and the other cases improved. In the cases of taken of PEG-IFN- $\alpha$ 2b or IFN- $\alpha$  combination therapy, most of them were not severe and improved only with a topical steroid and oral anti-allergic drug, without the need for discontinuation of the antiviral treatment. Severe cases required a discontinuation of the antiviral treatment; a steroid was administered in very severe cases. In our case, both alopecia and cutaneous eruption improved under the therapy in this case. Therefore, if the skin lesions worsen despite the measures discussed above, we recommend discontinuing PEG-INF/ribavirin until the skin findings (eruptions or alopecia) resolves and then reintroducing therapy again. Skin testing was poorly informative and not predictive of relapse. In all previously reported cases from other continents, it was unclear whether interferon or ribavirin was the contributing factor for the side effects.

In conclusion, even if some cases of alopecia were reported in literature, no DTE (and partially DAE) case associated with this combination therapy has been reported previously. To the best of our literature search, our patient is the first case in terms of extensively interpreted with both clinical and trichogram features of a PEG-INF/ribavirin induced alopecia.

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